RIZAYEV J.A., MUHAMADIYEVA L.A., MAMATKULOVA D.H.,
TURAYEVA N.O., RUSTAMOVA G.R.,

PEDIATRICS. MEDICAL GENETICS

Textbook for students
faculty of denistry

MINISTRY OF HIGHER AND SECONDARY SPECIAL EDUCATION OF THE REPUBLIC OF UZBEKISTAN

MINISTRY OF HEALTH CARE OF THE REPUBLIC OF UZBEKISTAN

SAMARKAND STATE MEDICAL UNIVERSITY

RIZAYEV JASUR ALIMDJANOVICH

MUHAMADIYEVA LOLA ATAMURODOVNA

MAMATKULOVA DILRABO HAMIDOVNA

TURAYEVA NAFISA OMANOVNA

RUSTAMOVA GULNOZA RUSTAMOVNA

PEDIATRICS. MEDICAL GENETICS

Textbook for students faculty of denistry

SAMARKAND – 2025

UDC: 616-053.2:575(075.8)

BBC: 57.33ya73+28.04ya73 /P 36

RIZAYEV JASUR ALIMDJANOVICH, MUHAMADIYEVA LOLA ATAMURADOVNA, MAMATKULOVA DILRABO HAMIDOVNA, TURAYEVA NAFISA OMANOVNA, RUSTAMOVA GULNOZA RUSTAMOVNA, PEDIATRICS. MEDICAL GENETICS, TEXTBOOK FOR STUDENTS FACULTY OF DENISTRY SAMARKAND 2025\ 176-P ARTEX NASHR

Developers:

RIZAYEV JASUR ALIMDJANOVICH - *doctor of medical sciences, professor*

MUKHAMADIYEVA LOLA ATAMURODOVNA - *Doctor of Medical Sciences, associate professor*

MAMATKULOVA DILRABO HAMIDOVNA - *candidate of medical sciences, associate professor*

TURAYEVA NAFISA OMANOVNA - *PhD, associate professor*

RUSTAMOVA GULNOZA RUSTAMOVNA- *PhD, associate professor*

Reviewers:

NAVRUZOVA SHAKAR ISTAMOVNA - *doctorof medical sciences, professor*

SAMIYEVA GULNOZA UTKUROVNA – *Doctor of Medical Sciences, professor*

ISBN: 978-9910-8467-1-7

2181

Modern training of specialists in the field of dentistry requires not only a deep understanding of the clinical aspects of the future profession, but also a solid grasp of the fundamental principles of related medical disciplines. Among these, pediatrics and clinical genetics hold a particularly important place, as knowledge in these areas is essential for a comprehensive understanding of the patterns of child growth and development, the identification and prevention of hereditary diseases, and the assessment of factors influencing the formation of dental health.

This textbook is devoted to key issues in pediatrics and medical genetics and has been prepared in accordance with the model curriculum developed for students of the dentistry faculties of medical universities. It presents up-to-date information on methods of anthropometric examination of children, indicators of growth and development, principles of rational feeding of infants and young children, as well as the most common diseases of early childhood that are of practical significance for the dentist.

The individual sections of the textbook cover the fundamentals of genetic testing, the molecular mechanisms of heredity, the influence of environmental factors on genetic processes, hereditary diseases, and the basic principles of medical genetic counseling. The material is presented with consideration of the need to form in students a holistic understanding of the biological foundations of health and disease.

The textbook is intended for students of higher medical educational institutions studying in fields and specialties related to dentistry and other areas of medical science.

LIST OF ABBREVIATIONS

ADA-adenosine deaminase

AFP - alpha-fetoprotein

KZLP - low density lipoprotein

MFK - multifactorial diseases

TTG - thyroid stimulating hormone

PCR - polymerase chain reaction

UTT - ultrasound examinations

EDS - Ehlers - Danlo syndrome

FKU - phenylketonuria

TGM - medical genetic counseling

FISH - fluorescent hybridization

IMT - Chromosome Microarray Analysis

INTRODUCTION

Pediatrics is derived from the Greek words *paid* — child, and *iatria* — treatment. It studiesthe anatomical and physiological characteristics of the child's body from the moment of its development as a fetus to adolescence, as well as the specific features of the development and course of diseases occurring during this period, and provides guidelines for performing practical skills in treatment and care. Thus, pediatrics is a field of medical practice focused exclusively on children. At the same time, pediatrics is a challenging specialty that requires strict responsibility, patience, and perseverance from future healthcare professionals. This is because a child, especially under the age of 5–6 years, is unable to clearly and coherently describe the changes occurring in their body during growth and development.

Secondly, most changes in the child can only be detected through careful observation, deep knowledge, and proper interpretation, which allows the healthcare provider to determine the necessary assistance. Failure to reach the correct conclusion in time and provide timely caremay endanger the child's life.

The theoretical and practical development of modern medicine is characterized by the widespread use of genetic methods. This is due to several factors.
First, as knowledge about the developmental patterns of human organs has expanded, it has become clear that in the postnatal period—under the influence of the external environment—the genetic factors inherited from parents through germ cells play a significant role.

Second, modern changes in the structure of human pathology demonstrate the growing importance of genetic predisposition factors.

Third, studies of the etiology and pathogenesis of multifactorial diseases (such as ischemic heart disease, gastric and duodenal ulcer disease, diabetes, etc.) have shown that their development is associated with the presence of genetic factors.

Fourth, pathology is known to arise from the interaction between an organism and a pathogenic factor. Since every person has unique genetic characteristics, this interaction is highly individual.

Scientific medicine not only studies general bodily reactions but also examines the specific manifestations unique to each individual, enabling significant progress in the diagnosis, treatment, and prevention of hereditary diseases. While preparing this textbook, the authors, based on the curricula of medical institutions, provided information about child growth parameters, proper feeding of young children, common diseases of early childhood, as well as the basics of clinical genetics, genetic methods, and genetic pathology.

CHAPTER I

1.1. Evaluation of Child's Growth and Development

Assessing a child's growth provides important information about their nutrition and health. There are several ways to measure a child's growth, including weight-for-age, weight-for-height, and height-for-age. Initially, the weight-for-age index was used in most countries to assess a child's growth and nutritional status. However, as an indicator of nutritional status, this method has drawbacks. A child with a low body weight for a given age may be stunted and still have a relatively normal body weight for their height (depending on body structure).

According to WHO growth assessment standards, the weight-for-height ratio is recommended as the standard for assessing the nutritional status of children. It is also recommended to use separate standards for boys and girls.

The level of physical development in a child depends on many factors:

- **Genetic factors:** more than 100 genes control the synthesis of growth hormones and growth factors.
- **Hormonal factors:** growth hormone (GH), and other hormones (thyroid, sex hormones, insulin).
- **Other factors:** nutritional factors, climatic and geographical conditions, lifestyle, and diseases.

The following methods are used to assess physical development:

- **Somatoscopic:** visual assessment of body constitution and proportionality.
- **Somatometric (anthropometric):** measurement and evaluation of the main parameters of physical development — body weight, height, head and chest circumference.
- **Functional assessment:** determining lung capacity using physiometric devices and measuring muscle strength using a dynamometer.

1.2. Methods of Anthropometric Examination in Children

Height Measurement

The height of newborns and children under 2 years of age is measured using a horizontal stadiometer. The child is placed on the device so that their head touches the fixed board. The head should be positioned so that the lower margin of the orbit is in the same vertical plane as the upper margin of the external auditory canal. While gently pressing on the child's knees to straighten the legs, the movable board is aligned with the heels. The child's height equals the distance between the fixed and movable boards of the stadiometer.

The height of children older than 2 years is measured using a vertical stadiometer. The child stands with their back against the stadiometer, with the heels, buttocks, shoulder blades, and the back of the neck touching the vertical surface. The head should be positioned so that the lower margin of the orbit and the upper margin of the external auditory canal lie in the same horizontal plane. The movable headboard is lowered until it touches the top of the child's head.

(Figure 1)

Figure 1.

Measuring Circumferences

Head circumference is measured using a measuring tape. The tape should pass across the eyebrows and around the occipital prominence at the back of the head, and it should be pulled slightly to obtain an accurate measurement.

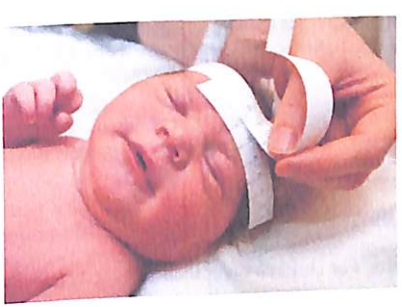
Measurement of Chest Circumference

Chest circumference is measured three times: when the child is breathing in a calm state, at the peak of inhalation, and during maximal exhalation. The measuring tape is placed from the back across the lower angles of the scapulae, with the tape positioned horizontally on both sides, and in front it passes across the most prominent point of the chest.

(Figures 2, 3).

Figure 2

Figure 3



Body Weight Measurement

The body weight of infants and young children is measured using a special electronic scale designed for children. It is recommended that the scale used for children weighing up to 10 kg has an accuracy of 1 gram (see Figure 4).

Figure4

The body weight of older children is measured on an empty stomach with an accuracy of up to 50 grams on a medical scale.

Height measurement

The height of newborn babies is 48-52 cm. Table 3-2 shows the average height of children under 1 year of age. (Table 1)

Table 1.

Height of children under 1 year old

Child's age in months	Height, sm	
	1 month	in the quarter
0-3	3	9
4-6	2,5	7,5
7-9	1,5-2	4,5-6
10-12	1	3

Height Growth

During the first year, a child's height increases by an average of 25 cm. By the end of the first year, the height is typically 75–77 cm. In the second year, it grows by 12–13 cm, and in the third year, by 7–8 cm.

The following method can be used to estimate the height of children older than 1 year: at age 4, the height of a child is approximately twice that of a newborn, averaging 100 cm. For children younger than 4 years, height can be calculated as:

Height=100−8×(4−n)\text{Height} = 100 - 8 \times (4 - n)Height=100−8×(4−n)

where nnn is the child's age in years. For children older than 4 years, height can be estimated using:

Height=100+6×(n−4)\text{Height} = 100 + 6 \times (n - 4)Height=100+6×(n−4)

At age 8, a child's height is approximately 130 cm. By age 12, height increases to roughly three times that of a newborn, averaging 150 cm. Growth accelerates during puberty: in girls between 10–12 years, and in boys between 13.5–15.5 years.

During this period, the body length increases by 8–10 cm per year on average. Individual and constitutional characteristics play a decisive role in growth. Growth is typically completedby age 16–17 in girls and 18–19 in boys.

Head Circumference Assessment

The head circumference of newborns ranges from 34 to 36 cm. Average head circumferenœ at different ages is presented in Table 2:

- At 1 year: 46 cm
- At 5 years: 50 cm
- At 10 years: 55 cm

The growth of head circumference during the first year of life is also shown in Table 2.

Table2.

Growth of head circumference in the 1st yearof a child's life

Age in months	Growth of head circumference	
	1 month	1 in aquarter
0-3	2	6
4-6	1	3
7-12	0,5	1,5

Ratio of Chest Circumference to Head Circumference

The head circumference of a newborn (34–36 cm) is 1–2 cm larger than the chest circumference (32–34 cm). By 3–4 months of age, these parameters become approximately equal. At the end of the first year, the chest circumference exceeds the head circumference by 1–2 cm. After the first year, the chest circumference continues to exceed the head circumference by 2 cm, with variations depending on the child's age.

Assessment of Body Weight

The weight of a full-term newborn is typically 3200–3500 g. Within the first 3–4 days, body weight decreases by 5–6% — a physiological weight loss. By the 7th–10th day of life, this deficit is restored, after which continuous weight gain occurs.

Daily weight gain:

- During the first 3 months: 23–30 g/day
- From 4 to 6 months: 20–25 g/day

Average monthly weight gain:

- During the first 6 months: 800 g/month
- During the second 6 months: 400 g/month

The approximate calculation of normal weight in the first six months of life can be based on the following formula: the weight of a 6-month-old child is considered 8200 g, and 800 g is subtracted for each preceding month of age.

A healthy child gains an average of 4300 g during the first 6 months

Approximate Calculation of Standard Weight in the Second Half of the First Year

The approximate calculation of standard weight in the second half of the first year of life can be determined using the following formula: the weight of a 6-month-old child is 8200 g, and 400 g is added for each subsequent month up to 12 months.

Later, the child's body weight increases on average as follows:

- In the 2nd year of life: 2.5 kg
- In the 3rd year of life: 2 kg
- From 3 to 10 years old: 2 kg per year
- From 10 to 15 years old: 3–4 kg per year

The following formula can be used to estimate the body weight of children aged 2–11 years:

Body weight (kg)=10.5+2n\text{Body weight (kg)} = 10.5 + 2nBody weight (kg)=10.5+2n

where nnn is the child's age in years, and 10.5 kg is the average weight of a 1-year-old child.

The average weight of children older than 3 years can also be determined using growth tables:

- A 7-year-old child is 125 cm tall and weighs 25 kg
- For every 5 cm deviation from the standard height, subtract 2 kg if shorter or add 3–3.5 kg if taller, depending on age

Thus, the growth of a child's weight follows these general principles:

- By the end of the first year, the child's weight triples compared to birth weight
- At the age of 6–7 years, the child's weight doubles compared to birth weight
- At the age of 11–12 years, the child's weight triples compared to birth weight

---

1.3. Assessment of Anthropometric Indicators

Anthropometric indicators are evaluated using the following methods:

- Parametric (sigma) method
- Non-parametric (centile) method
- Regression analysis method
- Using TVI detection

Parametric Method
This method is based on calculating the arithmetic mean (M) of the indicators, their standard deviation (σ), and the mean square relative to age- and gender-matched groups. The following assessment categories are used:

- I — Average (M ± σ)
- II — Below average (M − 1σ to M − 2σ)
- III — Low (M − 2σ to M − 3σ)
- IV — Medium to high (M + 1σ to M + 2σ)
- V — High (M + 2σ to M + 3σ)
- VI — Very high/very low (higher/lower than 3σ)

The doctor's conclusion should note that harmonious growth and deviations from the sigmoid curve should not exceed 1σ. The parametric method is useful for detecting growth disorders in children.

Non-parametric Method
This method uses centile tables to determine the range of a child's indicators (height, weight, chest circumference). After evaluating these parameters, the child's physical development is categorized based on the centile corridor:

- 0–2 — Harmonious development
- 3 — Disharmonious development
- 4–7 — Extremely disharmonious development

Body Mass Index (BMI)

The Body Mass Index (BMI), also known as the Quetelet index, is the most widely used indicator of harmonious development. It is calculated using the formula:

BMI=weight (kg)height (m)2\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}BMI=height (m)2weight (kg)

BMI reference values for different ages are presented in Table 3.

Table3.

Indicators of body mass index for different ages.

Age	Boys and girls	Boys	Girls
6-8	16		
9-10	17		
11	18		
2	19		
3-16		20	
17		21	
13-14			20
15-17			21

– 2 conditional signs areadded tothe necessaryindicatorof excess body weight. For example, overweight in 6-8-year-old children starts from 18 (16+2), for 9-10-year-old children from 19 (17+2), etc.

– Excessweight is evaluated with "1", in othercases with "2".

- – The equality assessment of the child's physical development is carried out by analyzing the consecutive measurements determined in certain periods.
  – Up to 1 year (monthly)
  – Up to 3 years old (once per quarter)
  – 3–7 years old (twice a year)
  – 7–17 years old (once a year)
- **Weight according to age**
  Weight according to age reflects the child's body weight in relation to their age on a given day. Follow-up measurements can show whether the child is gaining (or not gaining) weight over time, so this is a measure of growth. This indicator is used to assess whether a child is underweight, but it is not used to diagnose a child as overweight or obese.
- Because it is relatively easy to measure weight, this indicator is widely used. However, in situations where it is not possible to accurately determine the child's age, this method cannot be completely trusted. Low body weight for a given age (thinness) is the first sign of undernutrition (malnutrition), reflecting the alimentary health status of the population, including children. Underweight for age is the result of not gaining or losing weight.
- Rapid weight gain, sudden cessation of growth, and acute or chronic malnutrition may indicate the presence of disease (malnutrition, diarrhea, acute respiratory infections, measles, etc.). It should be noted that when nutrition is disturbed, body weight changes before other parameters, and it takes much longer for height to slow down and stop. Therefore, it is very important to monitor the child's body weight, especially during infancy. Examples of weight-for-age charts for boys and girls are included in Appendix 2.
- **Explanation:** If the child has swelling in both legs, the fluid in the body increases the child's weight; in fact, the child may be due to being underweight. It is necessary to note the presence of swelling in the child's height chart. A child with a tumor is automatically classified as malnourished and should be referred for specialized care.
- **Body length / Weight for height**
  One of the main indicators of the state of nutrition of children at an early age is the prevalence of underweight (thinness) in relation to a given height. This indicator shows the child's feeding status at the same time. Low body weight for a given height is the result of either not increasing or decreasing body weight. Rapid weight gain, sudden cessation of weight gain, and severe malnutrition may also be observed.
- Body weight for height is a more accurate indicator than body weight for a given age. Based on this, it is more reliable in identifying children who need alimentary treatment and rehabilitation. This indicator is called the weight-height index (WHI) and is calculated based on the following formula:
- **WHI = Child's body weight (kg) / Body length/height (m^2)**
- The weight-height index shows the ratio of body weight in kilograms to body length in square meters (for children under 2 years old) or standing height (for children older than 2 years). This indicator is especially useful in situations where the child's age is unknown (for example, in a refugee camp).
- The child's weight–body length/height diagram allows identifying children with different levels of protein-energy deficiency (thinness), underweight, and short stature. However, these charts also help identify children who are overweight or obese, and who have a high weight–body-length/height ratio.
- **Height/Length for age**
  Another key indicator of early childhood nutritional status is stunting (low height for age). Stunting is caused by a delay in the development of the bone system. In general, it reflects a chronic process and is used as an indicator of chronic malnutrition. Growth retardation can often occur within a short period of time, from a few months to about 2 years after birth. This corresponds to the time of giving the child additional food.

- **Shoulder circumference**
  A shoulder circumference of less than 115 mm in young children is an indicator of severe malnutrition.

II.CHAPTER. FEEDING CHILDREN.

2.1. Natural, Artificial and Mixed Feeding of Children

Benefits of Breastfeeding

Breast milk is the best food for breastfed children. It contains all the necessary nutrients for the child during the first six months of life. Breastfeeding has many benefits for both the baby and the mother. Nutrients in breast milk are sufficient to meet the needs of the child. It is more easily digested by the body than cow's milk or milk formula. Cow's milk allergy is more common in formula-fed children than in breastfed children, as allergens are not observed in breast milk.

Growth and development factors in breast milk help the lining of the baby's intestine to mature and make it more resistant to proteins. Allergic reactions can be prevented by reducing the absorption of proteins. The amount of protein and salts in the breast milk of a premature baby is higher than that of a full-term baby, which serves to cover the increased needs of premature babies. Most of the protein in breast milk is whey protein, which is easier to digest than casein, abundant in cow's milk.

Fats in breast milk are rich in easily digestible fatty acids. Breast milk facilitates the absorption of minerals such as zinc and iron. Mother's milk contains eight times more linolenic acid than cow's milk. Linolenic acid is necessary for normal growth and development of children. Mother's milk contains less protein and fewer minerals than cow's milk, but it is sufficient to meet the baby's needs. Since excesses of these substances are removed through the kidneys, the burden on the kidneys is less in breastfed babies.

During lactation, the amount of fat in breast milk varies. Its amount increases at the end of breastfeeding, creating a feeling of satiety in the baby. This property is hypothesized to prevent overeating and obesity. Breast milk has a higher cholesterol content than cow's milk or artificial milk, which speeds up the enzyme system to prevent fat accumulation.

Due to the large amount of lactose in breast milk, the absorption of calcium in the intestine improves. Lactose also helps the growth of bacteria that produce lactic acid in the intestine and contributes to the formation of intestinal flora. Breast milk is also rich in enzymes like amylase and lipase, which ease digestion. Mother's milk contains more vitamins A and C than cow's milk.

There is ample evidence in the literature that exclusive breastfeeding during the first six months of life reduces morbidity and mortality in children.

Improving the Functioning of the Immune System

Most of the protective effect of breastfeeding against infectious diseases is passive. The protective factors of immunity in breast milk protect the surface of the mucous layer of the gastrointestinal tract and respiratory tract, reducing the risk of infection. At the same time, there is information that breast milk has an active effect on the child's immune system.

At four months of age, a breastfed baby's thyroid gland is twice as large as a formula-fed baby's, and breastfed babies respond better to some vaccines than formula-fed babies. There is also

evidence that protective function against infections is maintained for many years after the cessation of breastfeeding. The factor responsible for improving the child's own immune system in breast milk is unknown, but it is likely that V-lymphocytes, T-lymphocytes, anti-idiotypic antibodies, cytokines, and growth factors play such a role.

Chronic Diseases

Studies on the effects of breastfeeding on chronic diseases in children are limited to retrospective studies. There is evidence of an inverse relationship between insulin-dependent diabetes and breastfeeding. Insulin-dependent diabetes is an autoimmune disease, but breastfeeding has a positive effect on the child's immune system. Introduction of cow's milk proteins at an early age (up to 4 months) can also increase the risk of early development of insulin-dependent diabetes.

Some data support the hypothesis that breastfeeding can protect against Crohn's disease, non-specific ulcerative colitis, and leukemia. According to research, the results of assessment of the child's reception activity are on average 2–3 degrees higher in children who are breastfed compared to those fed with artificial milk.

Benefits for the Mother

Breastfeeding has both short-term and long-term benefits for the mother. The risk of postpartum hemorrhage can be reduced by latching the baby to the breast immediately after birth. There is growing evidence that breastfeeding mothers have a lower risk of developing breast and ovarian cancer.

Exclusive Breastfeeding for 6 Months

A 1984 analysis of available studies found that the risk of death from diarrhea at 0–6 months was higher in partially breastfed children than in exclusively breastfed children. Exclusive breastfeeding during the first six months meets the energy and nutritional needs of most children. No other food or liquid is needed. Breast milk consists of 87–93% water, which is enough to satisfy the child's thirst. Giving additional fluids may reduce breast milk intake. Nevertheless, many give water and tea to babies from the first weeks of life. Such a practice can lead to a twofold increase in the risk of developing diarrhea.

One of the benefits of exclusive breastfeeding is to prevent early return to fertility and to quickly regain pre-pregnancy weight. In women who breastfeed frequently and without exception during the first six months after delivery, the risk of pregnancy in the case of preserved amenorrhea is reduced by 2%.

Supplementary Feeding from 6 Months

If additional food is not given at this age or is given incorrectly, it can have a negative effect on the growth and development of the baby. In many countries, the period of complementary feeding is 6–23 months. This is the period when the child stops growing, there is a deficiency of micronutrients, and the occurrence of infectious diseases increases. Even after introducing complementary foods, breastfeeding remains an important source of nutrients. It supplies about half of the energy needed by a child under one year of age and a third of the energy needed by a child in the second year.

Breastfeeding continues to provide higher-quality nutrients and strengthens protective factors compared to complementary foods. Therefore, it is recommended to continue breastfeeding with complementary foods until the age of 2 years or more. Complementary food must be

nutritionally adequate, safe, and properly administered to meet the child's energy and nutrient needs. Nevertheless, problems such as excessive dilution of complementary feeding products, failure to feed the baby often and in sufficient quantity, and low-quality products often occur.

The method of feeding, like the food itself, affects the complementary feeding process, so both mothers and caregivers need support and advice on how to introduce complementary foods correctly.

2.2. Physiological Basis of Breastfeeding

Composition of Breast Milk

Breast milk contains all the nutrients necessary for the first six months of a baby's life, including fats, carbohydrates, proteins, vitamins, micronutrients, and water. It is easily digested and efficiently utilized. In addition, breast milk contains biologically active components that strengthen the immune system, protecting the infant against infections, and other factors that aid digestion and nutrient absorption.

Fats:
Breast milk contains approximately 3.5–4.2 g of fat per 100 ml, providing about half of the energy content of milk. Fat is present in small droplets, and its concentration increases during feeding. As a result, milk becomes richer in fat and creamy-white in color by the end of a feeding session. In the first days of life, colostrum is low in fat and has a light yellow-gray color. Breast milk contains long-chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and arachidonic acid (ARA), which are essential for the development of the infant's nervous system. While DHA and ARA are added to some infant formulas, they are not as effective as naturally occurring breast milk components.

Carbohydrates:
The primary carbohydrate in breast milk is lactose, which accounts for approximately 40% of milk calories. One hundred grams of breast milk contains about 7 g of lactose, more than other types of milk, providing a key source of energy. Lactose is efficiently digested and absorbed (>90%) in the small intestine under the action of lactase. Undigested lactose reaches the large intestine, where it is fermented by bacteria to form short-chain fatty acids and lactate. This process contributes to nutrient absorption, energy use, and lowers intestinal pH, improving calcium absorption. Lactose also promotes the growth of beneficial bacteria such as lactobacilli, supporting a favorable gut microbiota that protects against gastroenteritis. Oligosaccharidesin breast milk provide protection against viruses, bacteria, and their toxins, while supporting the growth of probiotic strains such as bifidobacteria.

Proteins:
Breast milk proteins differ in both quantity and quality from those in animal milk. The protein content is lower (0.9 g per 100 ml) than in animal milk, preventing overload of the infant's immature kidneys with nitrogenous waste. Casein in breast milk is easily digested, while α-lactalbumin and lactoferrin provide essential amino acids. Cow's milk contains β-lactoglobulin, which is absent in breast milk and cannot be digested by infants.

Vitamins and Minerals:
Even women with low nutritional status produce breast milk sufficient for normal infant development. However, optimal micronutrient content depends on the mother's diet. Micronutrients can be divided into two groups:

- **Affected by maternal nutrition:** Thiamine, zinc, riboflavin, iron, vitamin B6, folate, vitamin B12, calcium, vitamin D, vitamin A, iodine, selenium. Low maternal intake can negatively impact the infant's development, but concentrations can be restored by improving maternal diet.
- **Less affected by maternal nutrition:** Water-soluble vitamins depend on maternal dietary intake, while fat-soluble vitamins are less dependent. Even when maternal intake is insufficient, breast milk generally contains adequate amounts for the infant, except for vitamin D, which may require supplementation or sunlight exposure. Iron and zinc are present in small amounts but are efficiently absorbed.

Clinical micronutrient deficiencies are rare in exclusively breastfed infants during the first six months. If maternal micronutrient intake is adequate during pregnancy and lactation, additional supplements for the infant are generally unnecessary.

Anti-infective Factors:
Breast milk contains antimicrobial agents that strengthen the infant's immune system and protect the digestive and respiratory tracts against infection. Key components include:

- **Secretory immunoglobulin A (sIgA):** Protects intestinal epithelium from antigens and enhances immunity.
- **Lactoferrin:** Binds iron, reducing bacterial growth and the risk of gastrointestinal infections (e.g., *Escherichia coli*, *Staphylococcus spp.*).
- **Lysozyme:** Antibacterial enzyme that lyses bacterial cell walls.
- **Bifidus factor:** Promotes growth of beneficial bifidobacteria in the large intestine.
- **Macrophages and lymphocytes:** Produce immunoglobulins, phagocytose bacteria, and support immune defense.
- **Protease inhibitors, complement, interferon, antioxidants, and fatty acids (DHA, ARA):** Contribute to immune protection, antiviral activity, tissue development, and free radical protection.

These protective factors remain in breast milk beyond the first year, providing continued defense against infections. Breastfeeding reduces the risk of gastrointestinal and respiratory infections, otitis media, bacteremia, meningitis, and urinary tract infections. Formula-fed infants are more susceptible to infections, including necrotizing enterocolitis in neonatal intensive care settings. Partial breastfeeding still confers some protective effects.

Colostrum and Mature Milk

Colostrum is a special form of milk produced during the first 2–3 days after birth. It is secreted in small quantities—about 40–50 ml on the first day—but contains all the essential components a newborn needs. Colostrum is rich in leukocytes and antibodies, particularly immunoglobulins, and has higher percentages of protein, minerals, and fat-soluble vitamins (A, E, and K) compared to later milk. Vitamin A is crucial for eye protection and the integrity of epithelial surfaces, giving colostrum its yellow color.

Colostrum provides immune protection to the newborn against environmental microorganisms. Epidermal growth factor in colostrum helps prepare the intestinal mucosa for efficient nutrient absorption. During this period, exclusive breastfeeding is highly recommended, and other foods should be avoided. Feeding prior to the first breastfeed is called **pre-lactation feeding**.

Milk production increases significantly by the 2nd–4th day after birth, causing the breasts to feel full—a stage referred to as **"milk coming in"**. By the third day, a newborn typically consumes

300–400 ml of milk in 24 hours, increasing to 500–800 ml by the fifth day. Milk produced from day 7 to 14 is called **transitional milk**, and after two weeks it is referred to as **mature milk**

Animal Milk and Supplementary Feeding

Animal milk (e.g., cow or goat) differs from human breast milk in both nutrient quantity and quality. Infants under 6 months should only receive animal milk under exceptional circumstances and for a short period. To make it suitable for consumption, water, sugar, and micronutrients must be added. Even then, animal milk can never fully replace breast milk and lacks its antibacterial and biologically active components.

After 9 months, infants can be given boiled undiluted milk. **Infant formula** is usually produced from cow's milk or soy products, with nutrients adapted to resemble breast milk. However, differences in fat and protein composition remain, and antibacterial and bioactive components are absent. Powdered formula is not sterile and may contain pathogenic bacteria such as *Enterobacter sakazakii*, which can cause life-threatening infections. Soy-based formulas contain phytoestrogens, which may affect hormonal development, potentially reducing fertility in boys and causing precocious puberty in girls.

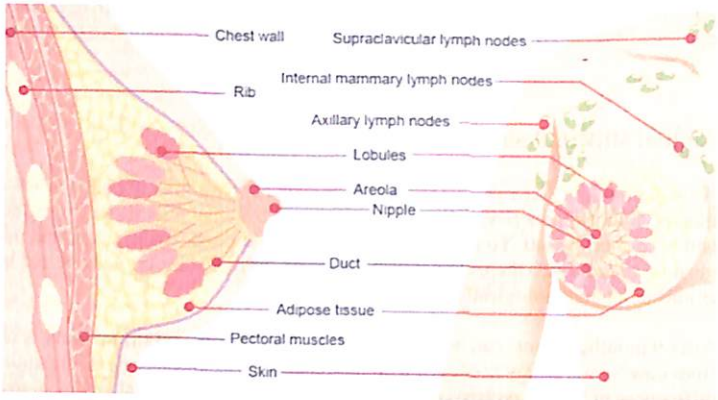
Breast Anatomy

The breast consists of the **nipple, areola, breast tissue, blood and lymphatic vessels, and nerve fibers**.

Breast tissue contains **alveoli**—small sacs that secrete milk—and **ducts** that transport milkout. Between feedings, milk collects in the alveoli and ducts. The alveoli are surrounded by myoepithelial (muscular) tissue that contracts to push milk through the ducts.

Nipple and areola:
The nipple has an average of nine milk ducts opening on its surface, along with muscle and nerve fibers. **Montgomery glands**, located on the areola, secrete an oily fluid that protects the nipple and areola and produces a specific maternal scent that helps the infant locate the breast. During breastfeeding, under the influence of the oxytocin reflex, milk is ejected from the alveoli into the ducts and toward the nipple.

Figure 3



Hormonal control of milk production

There are two types of hormones that directly affect breastfeeding:prolactin and oxytocin.A number of other hormones, such as estrogen, are indirectly involved in the lactation process.When the baby sucks, sensory impulses pass from the nipple to the brain.In response to this, prolactin is produced from the anterior part of the pituitary gland, and oxytocin from the posterior part and released into the blood. Prolactin serves for milk secretion by alveolar cells.The level of prolactin in the blood rises sharply during pregnancy, and by influencing the growth and development of breast tissue, it helps prepare for milk production. But during this period, milk does not come, because progesterone and estrogen, which are pregnancy hormones, block this action of prolactin.After childbirth, the level of progesterone and estrogen decreases sharply, milk begins to be secreted under the influence of prolactin. Prolactin is at its highest level for about 30 minutes after breastfeeding, so its main effect is to prepare milk for the next feeding.During the entire period of breastfeeding, the more the child sucks and stimulates the nipple, the more prolactin and milk production is observed under its influence. This is especially important during the period of lactation, if the mother stops breastfeeding - milk will not be produced. Prolactin is produced after the mother has finished breastfeeding in order to prepare for the next breastfeeding. Prolactin is secreted mainly at night, so breastfeeding at night is useful for continuous milk production in the mother's body.Prolactin calms the mother and makes her feel drowsy, so she is usually well rested even if she nurses at night. During lactation, other hormones are released by the pituitary gland in the mother's body, including gonadotropin-releasing hormone (LG), follicle-stimulating luteinizing hormone, which suppresses ovulation and menstruation.In this way, frequent breastfeeding helps prevent future pregnancies.Nighttime breastfeeding enhances the effectiveness of this feature and plays an important role in ensuring it. Oxytocin causes contraction of the myoepithelial cells surrounding the alveoli.This forces the milk collected in the alveoli to flow and fill the ducts.Oxytocin is produced in the mother's body during or before breastfeeding to force the milk to flow. The oxytocin reflex is also called the milk ejection reflex. Oxytocin is produced faster than prolactin.Under its

influence, the milk in the breast flows out of the milk ducts and helps the child suck the breast easily. Oxytocin starts working in the mother's body when she is preparing to breastfeed and when the baby is sucking.The reflex depends on the mother's senses such as touch, smell, sight, and when the mother hears the child crying or is full of love for the child, oxytocin starts to work in full.If the mother has a serious illness or is in a depressed mood, the oxytocin reflex is suppressed and her milk supply may suddenly decrease. If a nursing mother is supported, helped to feel better, and continues to breastfeed, the supply will be restored and improved.Understanding the oxytocin reflex is important because it helps you understand why mother and baby need to be together and why they need to be physically close. Oxytocin causes the uterus to contract after birth and helps reduce bleeding. During the first few days of a nursing baby, the contraction of the mother's uterus can cause severe pain. Signs of an Active Oxytocin Reflex Mothers may recognize signs of an active oxytocin reflex:

- pain in thechest during andbeforebreastfeeding;
- milk when a mother thinks of her child or hears her cry, it begins to flow from the chest;
- milk flows from the second breast when the child is feeding;
- when the child stops sucking, milk starts to come out of the breast;
- slow anddeepsuckingandswallowingof milk intothechild's mouth shows that it is flowing;
- pain in the uterus or bleeding from the uterus;
- thirst during breastfeeding.

Thepresenceof oneor moreof theabove signs indicatesthatthereflex is working. Even in theabsenceof these signs, this reflex is present, that is, theabsenceof signs does not determinetheactivityof thereflex.The signs may not beobvious andthemothermay not noticethem.

Psychological effects of oxytocin.

Oxytocinalsohasimportantpsychologicaleffects, and in animalstudies it hasbeen found that it affectsthematernalinstinct. In humans, oxytocininducescalmnessandreducesstress. It can strengthen the feeling of closeness and love between mother and child, and also help to develop this feeling. The pleasant touch of mother and child's bodies increases the release of oxytocin and prolactin, which develops physical closeness between mother and child after childbirth, and helps maintain emotional closeness during breastfeeding.

Feedback inhibitor of lactation. Milk production is controlled in the breast by a substance in breast milk known as feedback inhibitor of lactation, or TLI (polypeptide). Sometimes there is no milk in one breast, but there is no milk in the other breast.This is because local control of milk production is carried out independently in each breast.If the milk collected in the second breast during breastfeeding is not given to the child, the inhibitor stops the release of milk in order to protect against the negative effects caused by overfilling the breast. If breast milk is given to the child, the inhibitor is also removed and milk secretion is restored. If the baby is unable to suckle, the milk can be removed by expressing. TLI allows you to regulate the amount of milk produced depending on how much milk the baby sucks and how much milk the baby needs. This mechanism is

especially important for continuous regulation after lactation is established.At this stage, prolactin is needed for uncontrolled production of milk.

Children's reflexes. A child's reflexes play an important role in successful breastfeeding.The main reflexes are core, sucking and swallowing reflexes.If something touches the child's lips or tongue, he turns his face to this side in search of the reason for this and opens his mouth and starts rolling his tongue 5 up and down.This is a core reflex that appears from about the 32nd week of pregnancy. When something touches the child's palate, he begins toask (suck).This is the sucking reflex. When the baby fills his mouth with milk, he starts to swallow. This is the swallowing reflex.Premature babies can latch on to the nipple from about 28 weeks of gestational age and begin to suckle a little from about 31 weeks. Coordination of sucking, swallowing and breathing appears between 32 and 35 weeks of pregnancy. Babies at this age can only suckle for a short time, but during this time they can also eat complementary foods from a bowl.Most babies can be fully breastfed from 36 weeks of gestation. In order to support the mother and child in starting and continuing breastfeeding without exception, it is necessary to have information about these reflexes, because the level of maturity of these reflexes may indicate whether it is possible to breastfeed the child directly or to temporarily use another method of feeding.

Rules for keeping the child at the breast

In order for the child to take milk without difficulty, it is necessary to stimulate the nipple and ensure the milk is released from it, and to ensure that the milk comes in sufficient quantity, the child should be held at the breast.Because the baby does not take the breast in the mouth properly, it cannot suck well, and this causes a number of problems.signs of proper latching:

- a large areaof the areolaand the underlying tissue in the child's mouth (along with big flutes) will be;
- breast tissue creates a long "nipple" shape, but theactualnipple is only one third of it;
- the child's tongue is located between the lower gums and the milk sinus and forward

it will be slightly protruding (in fact, thechild'stongue surrounds the "nipple").

it will bethere, but it is not visible in thepicture);

- the child sucks the breast, not the nipple.

When the baby is sucking, pressing the nipple to the hard palate, the wave-like movements of the tongue muscles move back and forth around the tongue and squeeze the milk from the milk sinuses into the baby's oral cavity, and then the baby begins to swallow the milk. While sucking, the baby tries to spread the breast tissue and hold it in his mouth.The oxytocin reflex causes breast milk to come out of the tubes, and the baby uses tongue movements to squeeze the milk out of the tubes. If the baby is properly latched to the breast, his mouth and tongue will not rub against the skin of the nipple and the areolaand will not injure them.Breastfeeding is comfortable and often pleasant for the mother. The mother does not feel pain. Incorrect Breastfeeding shows what happens when a baby is not properly latched onto the breast. It is necessary to note the following:

■ in the child's mouth there is only the nipple, not the underlying tissues or tubes;

■ the child's tongue is deep inside the mouth and does not press the milk sinus.

Improper breastfeeding can be uncomfortable and painful for the mother, and can cause nipple redness, cracks, and damage to the skin of the nipple and areola.Improper latching is the most common cause of nipple inflammation, which can lead to poor milk absorption and insufficient milk production. Signs of correct and incorrect methods of holding a child to the breast. The four main external signs of correct and incorrect breast holding are shown. Depending on these signs, it can be determined that the mother and the child need counseling.Four signs of proper latching:

■ most of the areola is over the child's upper lip, not the lower lip visible;

■ thechild's mouth is wideopen;

■ thelower lip of thechild turns outward;

■ the child's chin is touching or relatively touching the chest.

These signs indicate that the baby is close to the breast and opens its mouth to cover most of the breast.The first sign shows that the baby is grasping the breast and nipple from below, allowing the breast to be drawn to the baby's palate and the tongue to get under the nipple tissue to press on the milk ducts. The presence of all four signs indicates that the child is properly latched on to the breast. In addition, breastfeeding should be comfortable for the mother. Symptoms of improper breastfeeding:

■most of the areola is over the child's lower lip, not the upper lip is visible - or else it is thesame from aboveandbelow;

■ thechild's mouth is not wideopen;

■ thelower lip of thechild is turned down or turnedinward;

■ thechild'schin is away from thebreast.

If any of these symptoms are observed or breastfeeding is painful and uncomfortable, it is necessary toapply the practice of holding the breast correctly to the child.If the baby is too close to the breast during the breastfeeding assessment, it will be difficult to see how the lower lip is positioned. Some women have a large areola, and the child's mouth may not cover it completely. That is, most of the areola can be outside the child's mouth, this symptom is not a reliable sign that the breast is attached incorrectly.If the circumference of the nipple is the same above and below the child's mouth, or if a large part of the areola is visible from the lower lip of the child, then this sign is a more reliable sign that the child is not attached to the breast than the overall size of the areola.

Correct sucking reflex

If the baby is properly latched to the breast, he can suck properly (effectively). Signs of a correct sucking reflex indicate that milk is being released into the baby's mouth.The child is slow and deep for a second, and then you can see and hear him swallow.Sometimes she stops sucking for a few seconds, allowing the nipples to refill with milk.When the baby starts sucking again, he may suck a few times quickly to get the milk flowing, and then start sucking slowly and

deeply. During breastfeeding, the baby's lungs are rounded. After breastfeeding, sucking slows down as the number of deep suckings decreases and the pause between them lengthens.By this time, the amount of milk will decrease, but it is necessary to continue breastfeeding, taking intoaccount that the milk that comes at the end is rich in fats. After the child is full, he usually lets goof the breast on his own. The nipple may appear stretched for a second or two, but it will quickly return to its original shape. Signs of an Incorrect Sucking Reflex A baby who is latched on incorrectly may not be able to latch well. He may not be able to swallow quickly, his lungs may be drawn in during sucking, which means that the milk is not coming into the baby's mouth properly.When the baby stops sucking, the nipple appears pulled back and slightly flattened with creases at the top or bottom, indicating damage to the nipple from improper latching. Consequences of Incorrect Sucking Reflex. If the baby is not sucking properly, he will not be able to suck in enough milk, and as a result:

- swelling of the breasts due to insufficient milk removal, blockageof the milk ductsor mastitismayoccur;
- that the child consumes less breast milk and its weight decreases can cause;
- the child can pull himself from the breast and suckle;
- the child sucks for a long time or toooften because he is not satisfied possible;
- too long breastfeeding leads to prolonged stimulation of the nipple and which can result in overproduction of milk.

Reasons for Incorrect Breastfeeding. It is known that the mechanism of breastfeeding is different from bottle feeding, so feeding a baby from a bottle before breastfeeding can cause reasons for incorrect breastfeeding. Factors such as flat or flat nipples, or the fact that the baby is too small and weak, can also be the reason for the wrong attachment of the baby to the breast.However, the most important reasons are the inexperience of the mother and the lack of competent medical advice from the medical personnel whoare watching her.Most mothers need professional help in the first days after giving birth to ensure that the baby is properly latched on to the breast and that it is feeding well. In this case, medical workers are required to have the necessary skills to provide such assistance.

The position of the mother and the child to latch the baby correctly.

To latch the baby correctly, the baby and its mother must be in the correct position.There are different cases for them, but in any case, the basic rules must be followed. Position of the mother. The mother can be in a sitting, lying or standing position, depending on her preference.But he should be completely relaxed and not be disturbed, especially the lower back should not be tense. In the sitting position, aback support is needed, and it should beable to hold thechild without leaningforward. Position of the child. During breastfeeding, the child can be in different positions in relation to the mother - on the chest, on the stomach, under the arm or next to the body. There are four basic rules that must be followed regardless of the situation of the mother and the child in relation to the mother:

- thechild'sheadand body should be in oneline. Thechild should befacingthemother'sbreast. His nose should beoppositethenipple.He will

befarenoughaway from themother toseeherface.This is the most convenient position for thebaby tosucklewell, because in most womenthenipple is slightly downward.

- the child's body should be close to the mother, that is, close to her breast allows it to be and absorb well.
- the mother should hold the child's whole body.The child can be lying on the bed, held by a pillow, or on the mother's lap or in her arms. The mother should not hold the baby only by the head, shoulders or the lower part of the body. Following these rules is especially important in the first two months of a baby's life.

eed for complementary foods increases with age, particularly for energy and nutrients such as iron, and plays an important role in the development of neuromuscular skills. Breastfed children are not physiologically ready to eat adult food directly after breastfeeding. Therefore, transitional foods from specially adapted family meals are introduced to bridge this gap. This period continues until the child is about **one year old**, when they can eat regular family food.

Introducing foods with different textures and consistencies helps develop motor skills such as chewing. Timely introduction of appropriately selected complementary foods during periods of rapid growth supports the child's health, improves nutrient intake, and contributes to overall physical development. Breast milk should remain the primary source of nutrition throughout the period of complementary feeding, with additional foods introduced around **6 months of age**.

What is Complementary Feeding?

Complementary feeding is the provision of nutrients and liquids in addition to breast milk to nursing children. Complementary foods can be divided into the following categories:

1. **Transitional foods** – specially formulated nutritional products designed to meet the physiological and nutritional needs of breastfed children.
2. **Family table or homemade foods** – foods given to young children that are also consumed by other family members, adapted to suit the child's age and needs.

Exclusive breastfeeding is recommended for the first six months of life. After this period, a **transitional period** begins, during which breastfed children are gradually introduced to additional foods while continuing to breastfeed. By around one year of age, children are generally physiologically ready to eat family table foods, which then fully replace breast milk.

Importance of Transitional Feeding

The introduction of transitional foods is a critical stage in a child's development. The diet changes from a single food source—breast milk, with fat as the main energy source—to a variety of foods necessary to meet nutritional needs. This transition is closely linked to rapid growth, physiological maturation, and overall development.

Incorrect principles or methods of feeding during this period can increase the risk of:

- Physical development disorders (e.g., wasting and stunting)
- Nutrient deficiencies, especially iron
- Long-term negative consequences for health and mental development

Health workers play a key role in supporting families by improving knowledge and practices regarding the preparation and introduction of complementary foods, ensuring the child's nutrition supports optimal growth and development.

Effect of Additional Food on the Child's Physiological Development and Maturation

Adaptation to the consumption of solid ("hot") food requires the maturation of the neuromuscular, digestive, renal, and protective systems.

Neuromuscular Control
The development of neuromuscular control affects the timing of solid feeding and the infant's ability to eat it. Many feeding reflexes at different stages of development make feeding different foods easier or harder. For example, from the moment a child is born, breastfeeding with breast milk is facilitated by both the reflex to find the breast and the reflexes of sucking and swallowing, whereas giving solid food is hindered by the vomiting reflex.

Breastfed babies under four months of age do not have the neuromuscular control to bite food, move it to the back of the mouth, and swallow. Head control and spinal support are not yet developed, so it is difficult for babies to hold their bodies firmly in order to suck and swallow semi-solid food.

By about five months, babies begin to put objects in their mouths, and at this time the development of the "chewing reflex" allows them to eat some harder foods, regardless of whether they have teeth. By about eight months, most babies can sit up independently, the first teeth appear, and the relatively thick tongue is flexible enough to swallow a bite of food. Soon after that, children develop the first skills of eating independently, such as drinking water while holding a bowl in both hands, and they will be able to eat food at the family table.

It is important to encourage children to acquire feeding skills such as chewing and bringing food to the mouth at the appropriate stages. If these skills are not mastered in time, behavioral and eating problems may develop later.

Periods of Additional Meals
The optimal age for starting transition food can be determined by comparing the advantages and disadvantages of different periods. In order to support the child's growth and maintain the prevention of deficiencies, it is necessary to assess the extent to which breast milk can provide enough energy and nutrients, and at the same time, what the risk is of infectious and allergic diseases caused by the consumption of contaminated nutrients and "foreign" proteins.

Additional important aspects to consider include the child's physiological development and maturation, various developmental indicators of food readiness, as well as maternal factors such as the composition of the mother's diet, the effect of reduced breastfeeding on maternal fertility and childcare availability, and principles and practices of early childhood care.

There are certain disadvantages of starting complementary foods long before the due date, namely:

- Breast milk can be displaced by additional food, which leads to a decrease in breast milk production, meaning that the child does not receive enough energy and nutrients.

- Breastfed children may ingest disease-causing microbes that may be found in foods and liquids, which increases the risk of dyspeptic diseases, resulting in malnutrition.
- Due to the immaturity of the intestine, the risk of dyspeptic diseases and allergies increases, and as a result, malnutrition occurs.
- Fertility in mothers is restored relatively quickly because the decrease in lactation shortens the ovulatory period.

Problems also arise if complementary food is started much later than the due date, namely:

- Lack of energy and nutrients from breast milk alone can lead to stunted growth and malnutrition.
- Deficiency of micronutrients, especially iron and zinc, may occur as a result of breast milk not being able to meet the needs of the child.
- Motor skills such as chewing and positive acceptance of new tastes and textures of food may not be fully developed or may lag behind in development.

Therefore, it is appropriate to start giving additional food on time, at the appropriate stages of the child's development. In addition, the optimal period is the full period of 6 months of the child's age.

Composition of Additional Food Products

When choosing products for complementary food, it is important to consider the effect of breast milk and complementary food with different energy densities that meet the energy needs during the feeding interval, while also taking into account the limited amount of food due to the small size of the stomach. The main food should not be too thick for a nursing child to consume, nor too liquid, so that the density of energy and nutrients is not reduced. At the same time, other factors affecting the amount of food—such as taste, aroma, and practical digestibility of each nutrient (biological compatibility and nutrient density)—should be considered.

Energy Density

The main factors influencing how well an infant can meet its energy and nutrient needs are the consistency and density (energy content per unit volume) of complementary foods and the frequency of feedings. Starch is the main source of energy in most cases, but during the process of heating it in water, the starch grains thicken (coagulate) and form a voluminous, thick, sticky porridge. Due to these properties, it is difficult for nursing children to swallow and digest such porridge. In addition, the low calorie and nutrient density means that a nursing baby would need to eat a large volume to meet its needs. Due to the small size of the child's stomach and the limited number of meals per day, this is usually not possible.

Mixing thick porridge with liquid to make it easier to swallow further reduces its energy density. Complementary food usually has low energy density and protein content, and although a liquid consistency makes it easier to consume, the amount needed to meet a child's energy and nutrient needs is often greater than the child can take.

Adding a small amount of vegetable oil makes the food soft and easy to eat, even when cold However, the addition of large amounts of sugar or fat, although it increases the energy content of the food, also increases viscosity (thickness) and therefore makes the food too heavy to eat in large quantities.

Thus, complementary feeding food should be rich in energy, protein, and micronutrients, while having a consistency that allows easy digestion.

Nutrient density and bioavailability. The amount of nutrients available to support the physical and mental development of a breastfed child, as well as their amount in breast milk and transitional food, depends on their biological compatibility. Biological compatibility is the degree of absorption of nutrients and their participation in the use for the purpose of metabolism, and the density of nutrients is the energy unit of this or that nutrient, for example, 100 kDj of energy per 100 g of food. There are significant differences in nutrient density and micronutrient bioavailability between animal and plant products.Animal products are generally higher in certain nutrients, such as vitamins A, D, and E, riboflavin, vitamin V12, calcium, and zinc, per energy unit. Some animal products (such as liver, meat, fish, and poultry) are high in iron, while others (such as milk and dairy products) are low in iron.On the other hand, while the density of thiamin, vitamin V6, folic acid and vitamin C is high in plant products, the amount of iron is much higher in products such as legumes and oats. In general, minerals from plant products are less absorbed by the body and participate in metabolism (biocompatibility) than minerals from animal products. Micronutrients with low bioavailability in plant foods include iron, zinc, calcium, and β-carotene in leafy produce and some vegetables.In addition, if the fat content in the diet is low, β-carotene, vitamin Aand other fat-soluble vitamins are difficult toabsorb. A diet with high biological compatibility of nutrients is diverse, and this diet includes a large amount of legumes and products rich in vitamin C, and a small amount of meat, fish and poultry.A diet with low bioavailability of nutrients consists mainly of cereals, legumes and root-fruit products, with very little meat, fish or products rich in vitamin C. Variety, taste and aroma. To meet the energy and nutrient needs of growing children, it is necessary to provide a wide variety of products with high nutritional value.In addition, children's appetite can improve if they are given a variety of foods. Although the structure of food changes every time, the amount of energy received by the child's body is coordinated in subsequent meals, that is, the total amount of energy consumed in one day does not change. Nevertheless, the amount of energy consumption may vary slightly on some days. When children are offered a variety of products, they choose food made from the products they like the most, and as a result, a balanced diet is formed. Organoleptic properties such as taste, smell, appearance and texture can affect the child's eating of transition food.The tongue's taste buds distinguish four primary tastes: sweet, bitter, salty, and sour.Sense of taste protects the child from eating harmful things and can help regulate the amount of food that they eat. Although children do not necessarily learn to like sweet or salty foods, research has shown that most children's food choices are greatly influenced by product learning and hands-on experience.Humans have a taste preference from birth only for sweet, and even babies love sweets.In children, the formation of a repetition of this or that taste effect can cause problems.Avoiding sweet foods and all other foods can limit the variety of foods and nutrients a child eats. Children eat more in a varied diet than in a uniform diet. During complementary feeding, children should be given the opportunity to try new products several times, which is important for the formation of a healthy system of positive food intake. It is necessary to taste different food at least 8-10 times, there are assumptions that the level of positive acceptance of this

or that food by the child will increase after taking it 12-15 times.So, parents should be reassured by explaining that it is normal for their child to refuse to eat.Products should be offered to the child several times, because the child will later start eating the products that he initially refuses. If the first refusal is considered permanent, the child may not be given the product again, thereby preventing the child from trying new foods and experiencing new tastes. The process of introducing additional food depends on whether the child can learn to enjoy the new food.Breastfed babies can adopt solid foods more quickly than formula-fed babies because they are used to the different tastes and smells of breast milk.

Basic principles of complementary feeding. After 6 months, it becomes difficult to cover the nutritional needs of the child exclusively with breast milk.Also, most babies are ready toaccept other products around six months. In poor sanitary conditions, introducing complementary foods after six months can reduce children's risk of foodborne illness.But since children at this age begin toactively explore the environment, even if they are not given additional food, the risk of microbial infection from the ground and other objects increases. Thus, 6 months is the optimal age to start giving complementary foods. The risk of undernutrition increases when complementary foods are introduced.This is often due to the nutritional quality of complementary foods being inadequate, too early or too late, too little or too long. Early cessation of breastfeeding or infrequent breastfeeding can also cause malnutrition in children older than 6 months.

Principles of feeding.

PRINCIPLE 1.Breastfeed without exception from birth to 6 months, from 6 months (180 days) continue breastfeeding and give additional food.Exclusive breastfeeding for 6 months provides a number of advantages to the child and the mother.The most important of them is a protective factor against gastrointestinal infections, which occur not only in developing countries, but also in developed countries. According to WHO's child growth assessment standards, exclusively breastfed children grow faster during the first 6 months of life than other children. Rules for starting to give additional food to breastfed children

1. Breastfeed without exception from birth to 6 months, continue breastfeeding from 6 months (180 days) and give additional food.

2. Continue frequent breastfeeding until age 2 and beyond.

3. Feed according to the child's response, using the principles of psychological support.

4. Follow hygiene and pay attention to safe preparation of products.

5. From six months, continue to breastfeed frequently, start feeding the baby less often, in small amounts, and increase the amount of food as the baby grows.

6. Asthechild grows up, increasetheconsistencyandvarietyof food according to his needsandpossibilities.

7. As the child grows, increase the amount of additional food.

8. Feed your baby a variety of nutrient-rich foods to meet his or her needs.

9. If necessary, use vitamin-fortified complementary food or vitamin-mineral supplements for babies.

10. After 6 months, increase fluid intake and breastfeed frequently when baby is sick, and encourage baby to eat soft foods he likes.After an illness, encourage him to eat more than usual and adjust the amount of food according to the age of the child. Typically, by 6 months, a baby weighs twice its birth weight and becomes more active.In order to meet energy and nutritional needs, exclusive breastfeeding is not enough, and it is necessary to start giving additional food. Around the age of 6 months, the baby is ready to master other products.The digestive system is developed enough to digest starches, proteins and fats outside of milk. Very young children can dislodge foods with their tongues, but between 6 and 9 months, babies keep solid, mushy food in their mouths relatively easily.

PRINCIPLE 2.Continue to breastfeed frequently up to two years of age and beyond, depending on the child's demand. Breastfeeding with complementary foods should continue until 2 years of age and beyond, while the child should be allowed to suckle as often as desired.Breast milk can provide more than half of a child's energy needs between 6-12 months, and a third of energy and other high-quality nutrients between 12-24 months.Breast milk continues to provide more protective factors and higher quality nutrients than complementary foods.Breast milk is the most important source of energy and nutrients when a child is sick, and it also reduces mortality among malnourished children.In addition, as mentioned in Chapter 1, breast milk reduces the risk of acute and chronic diseases.With the introduction of additional food, the child's desire for breast milk decreases, and therefore it is necessary toactively encourage its feeding.

PRINCIPLE 3.Apply feeding based on the child's response, using the principles of social and psychological support. The acceptability of complementary food depends not only on what to feed, but alsoon how, when, where and by whom it is fed. Feeding according to the child's attitude is:

- Feed the baby yourself and help older children feed themselves.
- Feed slowly and patiently, encourage the child to eat, but do not force.
- Use different combinations, tastes, textures, and incentives if the child is refusing to eat many foods.
- If thechildlosesinterest in food quickly, reducedistractions.
- Remember that feeding time is a time of teaching and affection.

According to the results of many studies, in the study of behavior, the random method of feeding prevails in some peoples.When it comes to eating, children are left to their own devices, and encouragement to eat is rare.In such conditions, an active method of feeding helps to improve the diet.The term "relational nutrition" is used to describe care using the principles of social and psychological care. The child should have his own plate so that the caregiver knows and monitors whether the child is eating enough.Depending on the type of food, you can use a spoon or clean hands to feed the child.The container should be suitable for the child's age.In many countries, a small spoon is used when a child starts eating solid food. A large spoon or fork can then be used. The best time to give additional food is when the child is ready to eat, that is, when the stomach is hungry and the mother can devote more time to her child. The first half of the day is preferable.Additional food can be given after breastfeeding to prevent depletion of breast milk.

PRINCIPLE 4.Follow hygiene and prepare products safely. Addition increases the microbial contamination of food, which is the main cause of gastrointestinal diseases, which are especially common in children aged 6 to 12 months. Safe preparation and storage of complementary foods can prevent microbial contamination while reducing the risk of diarrhea. The use of feeding bottles with suction cups is more likely to cause infection than the use of cups, so it is best to use them as little as possible. All items used for feeding babies and small children, such as bowls, plates and spoons, should be thoroughly washed.In many countries, it is customary to eat with your hands, and sometimes you can put hard pieces of food in the hands of children, called "food eaten with your hands".In that case, the hands of both the caregiver and the child should be thoroughly washed with soap before eating. Bacteria spread quickly in warm temperatures, and spread slowly when food is stored in a cold place.Many of the bacteria that occur in warm climates increase the risk of disease.If it is not possible to store the food in the refrigerator, it should be eaten shortly after preparation (no more than 2 hours) before bacteria start to multiply. Basic recommendations on food safety:

- Observe cleanliness;
- Store raw and boiled products separately;
- Process the products thoroughly at the required heat;
- Keep food at optimal temperature;
- Safe water and semi-finished according to sanitary standards

use the products.

PRINCIPLE 5.From 6 months, start feeding the baby in small amounts, and as the baby grows, increase the amount of food while continuing to breastfeed frequently. The total value of food is usually measured by the energy indicator, that is, by the amount of kilocalories (kcal) needed by the child, for the sake of convenience. But other nutrients are also considered important, and they are either a part of the main food products, or are additional to them. It can be understood that breast milk covers all the needs of a child up to six months, but after 6 months there is a lack of energy that must be covered by additional food. In addition to breast milk, the necessary energy is 200 kcal per day for children of 6-8 months, 300 kcal per day for children of 9-11 months, and 550 kcal per day for children of 12-23 months.The amount of food needed to cover the deficit increases as the child grows and consumes less breast milk. Table 4 shows the amount of food required in different age groups, the average amount of kilocalories needed by infants and young children at different ages, and the estimated amount of food that provides the required amount of energy in one day.As the child grows and develops, the amount of food increases.The table shows the average range for each age group.The amount of food needed depends on its energy density.It refers to the number of kilocalories in 1 ml or gram of food. There are about 700 kcal in 100 ml of breast milk or 0.7 kcal in 1 ml of milk.This value is variable in the supplement and is usually between 0.6 and 1.0 kcal per gram.Liquid and mixed products do not exceed approximately 0.3 kcal per gram. In order to have 1.0 kcal per gram of additional food, it should be fat or oil that is considered very dark and high in energy content. Complementary food should have a higher energy density than breast milk, that is, at least 0.8 kcal per 1 gram.suggests that the recommended

amount of food is 0.8-1.0 kcal per 1 gram of the product. If the extra food is high in calories, you will need to eat less of it to make up for the energy deficit. If the supplement is too diluted, more will be required to cover the need.When complementary foods are given, the baby is less eager for breast milk and the amount of milk he consumes decreases, thus the food displaces the breast milk. If complementary food is more diluted than breast milk, the amount of calories that the child receives will also decrease compared to breast milk without exception, and this can become an important cause of malnutrition. A child's appetite usually serves as a unit of measure in determining the amount of food that should be given.However, illness and malnutrition reduce appetite, and as a result, a child may eat less than he needs.A child recovering from illness or malnutrition may need additional support to ensure adequate nutrition.If the child's appetite improves after recovery, it is necessary to increase the amount of additional food given.

PRINCIPLE 6.As the child grows up, depending on his needs and possibilities, gradually increase the consistency and variety of food. The optimal consistency of food products for a baby or small child depends on the age and development of the neuromuscular system. From six months, the child can eat mashed, grated or semi-solid products.By eight months, the child can start eating foods that are usually held in the hand.By 12 months, most children can eat the same foods as other family members.Still, they need nutrient-dense food, but it's best toavoid allergens such as nuts. The extra food should be thick enough to fit on the tip of a spoon and not run. In general, darker and firmer products are more energy-dense and more nutrient-dense than liquid, watery, and soft products. When a child eats dense, solid foods, it's easy toadd more calories and a variety of nutrient-dense ingredients, including animal products.There is a sign that it is very important to start giving "sliced" ("pieced") food: if it is not given before the age of 10 months, problems with feeding may arise later. Continuing to give semi-solid foods can save time, but it is important to gradually increase the consistency of food for optimal baby development.

PRINCIPLE 7.As the child grows, increase the number of additional feedings. As the child grows up and needs more food every day, the number of feedings should be increased. The number of feedings a baby or toddler needs depends on:

- products necessary for the child to cover the energy deficit. The more food a child needs each day, the more meals he needs to meet his energy needs.
- theamountof food achildcaneat in one sitting.It dependson thesizeandsizeof thechild'sstomach, which is usually 30 milligramsperkilogramof weight.Thestomachvolumeof aneight-kilogramchild is 240 ml, which is equal toalargecup, and it would be wrong toexpectachild toeatmorethanthat.
- energy density of the food served.

The energy density of complementary food is higher than that of breast milk, i.e. at least 0.8 kcal per gram. If the energy density becomes low, then the amount of food should be increased (the number of meals may increase accordingly). A 6-8-month-old child who is breastfed should befed 2-3 timesaday, anda 9-23-month-old child should befed 3-4 timesaday.Dependingon thechild'sappetite, 1-2 short mealscanbegiven.A snack here refers toa meal that is

accepted between meals, usually eaten by the child independently, and is easy and simple to prepare.If it's roasted, it may have a higher energy density. The transition from twoadditional meals to three meals, from a small amount toa large amount, is carried out gradually between age groups, depending on the child's appetite and how he develops. If a child eats too little, he may not be getting enough food to meet his energy needs.If the baby eats too much, it can cause him to breastfeed less or stop breastfeeding altogether (weaning).In the first year of life, the displacement of breast milk (by complementary food) can lead toa decrease in the quality and quantity of nutrients that the child consumes.

PRINCIPLE 8. Feed a variety of nutrient-dense foods to meet needs. Complementary food provides enough energy, protein and micronutrients to compensate for the child's energy and nutrient deficits, so it meets all the needs of the child together with breast milk. Figure 9 shows the deficit of energy, protein, iron and vitamin A required for a child aged 12-23 months who is exclusively breastfed. The bottom (dark) panel of each column shows the percentage of a child's daily nutrient and energy needs that can be met with an average intake of 550 ml of breast milk. The upper (light colored) part shows the deficiency that needs to be filled with additional food. The biggest deficiency is iron deficiency, so it is advisable to have iron in the supplement, and if possible, it is important to eat animal products such as meat, poultry or fish. Legumes (peas, beans, lentils) and products rich in vitamin C, which help iron absorption, can be alternatives, but they cannot completely replace animal products.

Featuresof a good supplement:

- energy, protein and micronutrients (especially iron, zinc, calcium, A rich in vitamin C andfolicacid);
- not bitterandsalty;
- thechildeats it easily;
- the child likes him;
- available locally (store or market) and expensive it's not.

The main ingredients of the supplementary food are usually the main products produced and grown in the region.Pulses and vegetables are among the main products.Many other products can be added to the main product every day in order to provide various nutrients. They include:

- Animal products that are a source of protein, iron and zinc or fishLiver is aproductrich in vitaminAandfolicacid.Egg yolks are high in proteinandvitaminA, but lack iron.Thechild should eattheseproducts not only in liquid (soup) form, but also in solid form.
- Dairy products such as milk, cheese and yogurt are rich in calcium, protein, energy and B vitamins.
- Legumes – peas, beans, lentils and soybeans contain a lot of protein and some iron.Food sources of vitamin C include raw produce (such as tomatoes, citrus and other fruits, and green leafy vegetables) which, when given at the right time, help iron absorption.

Features of a good supplement:

- energy, protein and micronutrients (especially iron, zinc, calcium, A

rich in vitamin C and folic acid):

- not bitter and salty;
- the child eats it easily;
- the child likes him;
- available locally (store or market) and expensive

it's not.

The main ingredients of the supplementary food are usually the main products produced and grown in the region. Pulses and vegetables are among the main products. Many other products can be added to the main product every day in order to provide various nutrients. They include:

- Animal products that are a source of protein, iron and zinc or

fish Liver is a product rich in vitamin A and folic acid. Egg yolks are high in protein and vitamin A, but lack iron. The child should eat these products not only in liquid (soup) form, but also in solid form.

- Dairy products such as milk, cheese and yogurt are rich in calcium, protein, energy and B vitamins.

- Legumes – peas, beans, lentils and soybeans contain a lot of protein and some iron. Food sources of vitamin C include raw produce (such as tomatoes, citrus and other fruits, and green leafy vegetables) which, when given at the right time, help iron absorption.

- Fruits and orange vegetables like carrots, squash, and dark green leafy vegetables like spinach are rich in carotene, which is derived from vitamin A, and vitamin C.

- Oils and fats are a source of energy and certain essential fats that children need for growth.

Vegetarian (plant-based) complementary foods do not provide enough iron and zinc to meet all the needs of a child aged 6-23 months. In addition, it is necessary to consume animal products containing sufficient amounts of iron and zinc. In addition, fortified products or supplements can partially compensate for nutrient deficiencies. Oils, including fats, are also important because they increase the energy density of products and make them tastier. Also, oils help the absorption of vitamin A and other fat-soluble vitamins. Some oils provide the child's body with unequaled fatty acids. Fats should make up 30-45% of the total energy content of breast milk and complementary foods. The amount of fats should not be higher than the required standard value, otherwise, food containing proteins and other important substances such as iron and zinc may not be consumed in sufficient quantities. Sugar is a dense source of energy, but it lacks other nutrients.It can cause damage to children's teeth and can lead to overweight and obesity. It's best to limit sugary drinks like sugar and soda, as they can reduce your child's appetite for more nutritious foods. Tea and coffee are not recommended for small children due to the presence of compounds that can interfere with the absorption of iron. Families can also reduce concerns about allergic reactions if they limit certain foods from the diet of infants and nursing children. However, there are no clinical studies proving that a restricted diet is effective in preventing allergies. Therefore, from the age of six months, babies can eat a variety of products, including cow's milk, eggs and fish.

PRINCIPLE 9. Give babies vitamin-enriched complementary foods or vitamin-mineral supplements when necessary. Vitamin-deficient complementary foods - mostly plant-based - usually do not contain enough essential nutrients (especially iron, zinc and vitamin V6) to meet a child's needs. In some cases, the addition of animal products to such a diet can eliminate nutrient deficiencies, but it increases the overall cost of the product and is not suitable for low-income families. Difficulties in meeting these nutrient requirements are not unique to developing countries. If iron fortification programs were not so widespread, the average amount of iron consumed by infants in industrialized countries would not reach the required level. Therefore, in conditions where it is difficult or impossible to obtain animal products for many families, the demand for iron-enriched complementary foods, enriched with nutrients or lipid-based nutritional supplements, and vitaminized products is increasing.

PRINCIPLE 10. For children older than 6 months, increase fluid intake and breastfeeding during illness, encourage the child to eat soft foods that he likes. After an illness, encourage eating more than usual and bring it closer to age-appropriate norms. During the illness, the need for fluids often increases, so it is necessary to give the child more water and continue to breastfeed according to his needs. Often, the child's appetite decreases and the desire to suck increases, and breast milk can become the main source of both fluids and nutrients. The child should also be encouraged to eat more complementary foods, which will help the absorption of nutrients and help the child to recover faster. If the child is given products that he likes and soft and appetizing foods, the child will usually start eating more. At this time, the amount of food eaten by the child may be less than usual, so the caregiver should feed the child often, but in small amounts. A baby or young child's appetite improves during recovery, at which point the caregiver may need to feed more at each meal or increase the number of meals and snacks throughout the day.

Practical recommendations for providing additional food

Below are the main stages of the transition from breast milk to family meals in a short form. These stages are a continuous process, and the transition from one stage to another is relatively quick and smooth. It is also important to be able to distinguish between age-appropriately developing children's readiness to transition to complementary feeding, thus recognizing that the pace of introducing different complementary foods should be individualized. The following recommendations are aimed at ensuring that breastfed children receive adequate amounts of nutrients, that the biocompatibility and density of nutrients are as high as possible, and that appropriate behavioral skills are encouraged and that the child develops properly. First stage Skill development. The goal of this initial stage is to teach a breastfed baby to eat from a spoon. At first, food should be given in small amounts (about one or two tablespoons) and on the tip of a clean teaspoon. It may take some time for a child to be ready to pick up and swallow food from a spoon with their lips, and to learn how to transfer food to the back of their mouth. Some of the food may drip from the chin or fall out of the mouth. You need to be prepared for this from the beginning, know that this does not mean that the child does not like food. Fluids A baby should be breastfed as often as she wants without

exception. and breastmilk should remain the main source of fluids, nutrients, and energy. No other fluids are needed during this period. Transitional food. At the beginning of the transition period, the child should be given food consisting of one type of product, crushed and of a soft consistency, without the addition of sugar. salt or sharp spices. Positive examples include home-boiled and mashed rice made from grains other than wheat. mashed potatoes, and thick porridge made from traditional grains (oatmeal, vegetable or fruit purees). Breast milk (or formula) can be added to the puree to make it smoother. Meal Intervals. The skills of eating and enjoying new tastes can be achieved by eating one or two extra meals a day. In order to prevent breast milk from being displaced by additional food, it is better to give additional food after breastfeeding. Second stage: development of skills. After the child gets used to feeding from a spoon. it is possible to give foods of new taste and consistency to improve the variety of the diet and develop motor skills (Table 8). Factors that indicate a breastfed child's willingness to eat thicker purees include the child's ability to sit unsupported and transfer objects from one hand to the other. Fluids A baby should be breastfed as often as she wants without exception. and breastmilk should remain the main source of fluids, nutrients, and energy. During this period, the child can suck even less than during the breastfeeding period without exception. Transitional food. Well-boiled and mashed meat (especially liver), legumes, vegetables, fruits and various legumes can be started. To encourage positive acceptance of new products by children, it is possible to add a new taste to the familiar food they eat. for example, adding meat to mashed vegetables. Similarly, when introducing solid foods, a favorite food can be mixed with new, coarser-textured items (eg, small but significantly larger pieces of carrot). Instead of sugar, it is better to encourage eating spicy food, and it is recommended to have less sugar in the dessert. Interval of feeding. After a few weeks after starting to give complementary foods, it is necessary to start giving different products in small amounts two to three times a day. Stage Three: skill development. As children continue to develop, foods of a thicker consistency can be introduced to help them learn to chew and take small bites of food. With the development of fine motor skills and the appearance of teeth, nursing children begin to learn to take small pieces of food in their mouths and chew them. At this time, it is necessary to encourage the development of such skills by giving children food that can be eaten with their hands. Fluids. In order for the energy to be continuously supplied through breast milk, it is necessary to continue breastfeeding according to the child's desire. However, as the child grows, the energy and nutrients provided by the transition food become more important in meeting his nutritional needs. A small amount of cow's milk and other dairy products can be added to the food, and after 9 months, undiluted (unmodified) cow's milk can be given to children who are not breastfed. It is recommended to give liquids other than breast milk in a container (bowl, cup) with a spoon. Transitional food. Vegetables should be boiled until crushed, and meat should be passed through a meat grinder and mixed in the form of pieces. It is recommended to have a variety of food, and the composition of the products consumed during the day should include fruits and vegetables, legumes and a small amount of fish, yogurt, meat, liver, eggs or cheese. It is important to properly boil eggs to reduce the risk of

salmonella poisoning: foods containing raw eggs should not be given (see Chapter 12). It is advisable to offer food that can be eaten with your fingers, such as toast, carrots or fruit, at each meal. Bread can be spread with a moderate amount of oil, it is better not to eat products with added sugar, such as pastries and cakes. Intervals between meals. It is necessary to feed two to three times a day, and between them, you should give food products such as yogurt, raw or cooked apples, buttered bread. At this stage, children who are not breastfed or formula fed should eat at least five times a day. Fourth stage: development of skills. In the last months of complementary feeding, feeding the child should be mixed with their independent feeding. But while breastfeeding and early-age children are still developing their feeding skills, they cannot feed themselves enough to meet their needs, so caregivers play an important role in their nutrition. Fluids Breast milk should remain an important part of the baby's diet and should be the main fluid consumed during the second year of life (and beyond) whenever possible. From nine months, you can gradually increase the consumption of cow's milk and milk products made from it. Transitional food. As the child transitions to an adult diet, it is necessary to give finely chopped or crushed products, minced meat. At every meal, to teach the child to eat independently, it is necessary to give small pieces of fruit, vegetables, potatoes, toast, cheese and soft meat that can be eaten by hand. It is better to limit only foods made from fatty products. Feeding interval: Breastfed children should eat three meals a day and have two light snacks. By the age of one year, children usually start eating from table food and do not require separate meals. It is recommended not to add salt to a child's food, and reducing salt intake is beneficial for other members of the family as well. Children eat slowly and should be given extra time and attention. Breastfeeding and early-age children need to be encouraged when they are learning to eat, and those who feed them need to be patient. If the child is not left to eat independently from the family table, but if he is helped and encouraged enough, the amount of food consumed can increase somewhat. During meals, it is always necessary to monitor the feeding of nursing and early-aged children.

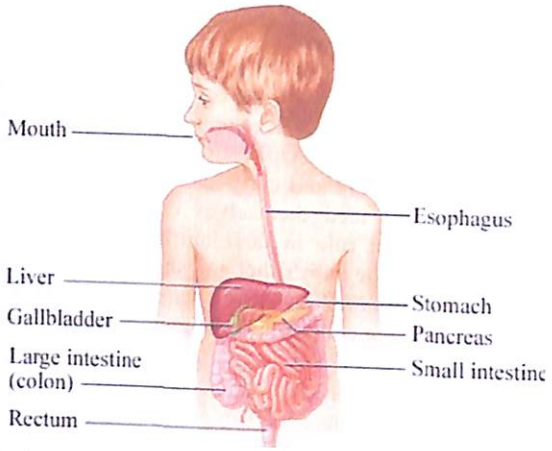
Normal gastrointestinal system. Semiotics of changes.

Functional disorders of the gastrointestinal system

The child's digestive organs have a number of morphological and physiological characteristics; these signs are clearly visible in children of early age. Their digestive system is mainly adapted for sucking and digesting breast milk.

Figure 5

Digestive organs in children

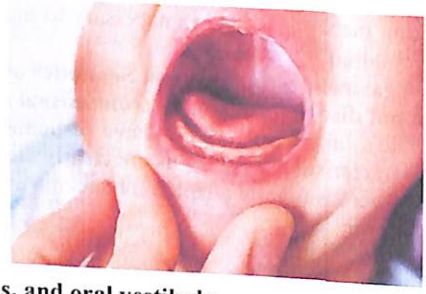


Oral cavity

The pediatric oral cavity is composed of the lips, buccal mucosa, alveolar ridges and teeth, hard palate, anterior tongue, and floor of the mouth. It has an important role in air exchange, food processing, swallowing, and phonation. The oral cavity is continuous posteriorly with the oropharynx, including the soft palate, tonsillar fossae, posterior pharyngeal wall, and base of the tongue.

Figure 6

Oral cavity



Lips, cheeks, and oral vestibule

When approaching the lips, recognizing the subtle surface landmarks allows for good functional as well as cosmetic outcomes. The lips form the anterior border of and opening into the oral cavity. The upper lip begins immediately inferior to the base of the nose and extends laterally on both the sides to the alar sulci. The philtrum is a vertical depression in the midline of the upper lip and it is bordered by 2 pillars, or philtral ridges.

Alveolar ridges and teeth

The maxillary and the mandibular alveolar ridges are the tooth bearing bony prominences of the respective bones. They contain alveoli, or tooth sockets, which are lined by cortical bone called lamina dura. The alveolar ridges and teeth are covered in a tightly adherent fibrous tissue and mucosa, which is referred to as gingiva.

In children, the teeth are an actively changing part of the anatomy. The deciduous teeth begin erupting at approximately 6-8 months of age

Palate

In the oral cavity, the palate forms the superior border, separating it from the nasal cavity and the nasopharynx. The structural relationships here are important during repair of cleft deformities. The hard palate forms the anterior two-thirds of the palate. It includes the horizontal processes of the palatine bones and the palatine processes of the maxillary bones. Embryologically, the hard palate is divided into the primary and the secondary palates.

Tongue

In infants, the relatively larger anterior tongue occupies almost the entirety of the oral cavity. As a child ages, the oral cavity grows, and the base of tongue descends into the hypopharynx, giving way to the adult proportions.5 The dorsal surface of the tongue is covered in foliate, fungiform, and circumvallate papillae, which contain the taste buds.

Salivary glands

Features of the salivary glands of a newborn baby:

- low secretarial activity;
- release of a small amount of thick viscous saliva (sealing of the oral cavity during sucking);
- saliva reaction is neutral or slightly acidic;
- amylase concentration is low.

Within 1.5-2 months, the functional activity of the salivary glands increases; In children of 3-4 months, saliva often comes out of the mouth. This is due to the lack of saliva secretion and swallowing (physiological saliva).

From the first days of life, saliva contains amylase, starch and other enzymes necessary for the breakdown of glycogen. In the first year of life, the content and activity of these enzymes increase significantly in newborns.

Larynx

In small infants, the larynx has special anatomical relations. In newborns, larynx has smaller dimensions in comparison to the body than it is the case in adults. At this age larynx is characterized by a high position because it lies on the level of the 4th cervical vertebrae, and descends in the childhood period. The axis of respiratory system is parallel to digestive system axis, which enables contemporary breathing and swallowing in newborns. Significant anatomical characteristic of the larynx at this age is soft cartilaginous structure of the skeleton and relatively narrow larynx lumen. In small infants the larlarynx is a narrow gate in the area of vocal cords. It is 7–9 mm wide, and conal subglottis in sucklings is 5.5–6 mm

wide. If it is narrowed to 4 mm because of edema, breathing is almost impossible. Softness of the cartilaginous skeleton additionally favors deformity of the larynx and trachea. Infants' laryngeal tissue is in its entirety softer than in adults. The upper end of the larynx is cone-shaped, the cricoid cartilage is inclined backward, vocal cords are shorter, and epiglottis is narrower. In fact, epiglottis hangs above the larynx. Epiglottis often has the shape of the Greek letter omega, but later on it assumes

the normal shape of a leaf or a triangle. In a human being, the larynx has a special function as a phonatory organ, not just as a respiratory tube.

The larynx of babies is funnel-shaped. The entrance to the larynx is located above the lower back edge of the palate and is connected to the oral cavity. Food moves from the sides of the throat, so the child can breathe and swallow without stopping sucking at the same time.

Esophagus.

The esophagus is the muscular tube that connects the throat to the stomach. The muscles in the esophagus contract to move food and liquid from the mouth through the throat and down to the stomach. At birth, the esophagus is formed, but its anatomical constrictions are not fully developed. The wall of the esophagus in a newborn baby is thin, the muscular membrane is not well developed. There are few glands in the mucous membrane of the esophagus in babies.

Sphincters

edit. The esophagus is surrounded at the top and bottom by two muscular rings, known respectively as the upper esophageal sphincter and the lower esophageal sphincter. These sphincters act to close the esophagus when food is not being swallowed. The upper esophageal sphincter is an anatomical sphincter, which is formed by the lower portion of the inferior pharyngeal constrictor, also known as the cricopharyngeal sphincter due to its relation with cricoid cartilage of the larynx anteriorly. However, the lower esophageal sphincter is not an anatomical but rather a functional sphincter, meaning that it acts as a sphincter but does not have a distinct thickening like other sphincters. The upper esophageal sphincter surrounds the upper part of the esophagus. It consists of skeletal muscle but is not under voluntary control. Opening of the upper esophageal sphincter is triggered by the swallowing reflex. The primary muscle of the upper esophageal sphincter is the cricopharyngeal part of the inferior pharyngeal constrictor. The lower esophageal sphincter, or gastroesophageal sphincter, surrounds the lower part of the esophagus at the junction between the esophagus and the stomach. It is also called the cardiac sphincter or cardioesophageal sphincter, named from the adjacent part of the stomach, the cardia. Dysfunction of the gastroesophageal sphincter causes gastroesophageal reflux, which causes heartburn, and, if it happens often enough, can lead to gastroesophageal reflux disease, with damage of the esophageal mucosa.

Stomach.

The stomach of a newborn baby is small and relatively underdeveloped in terms of functionality. It is positioned high in the abdomen but gradually descends as the child grows. In infants, the stomach is in a horizontal position; however, as

the child begins to walk, it gradually shifts to a more vertical orientation. The cardiac part of the newborn's stomach, along with the fundus and pyloric regions, is immature, while the pylorus is relatively wide. The entrance to the stomach is often located above the diaphragm, and the angle between the abdominal part of the esophagus and the adjacent wall of the stomach fundus is not well defined. Gubarev's fold (a mucous membrane that extends into the esophagus and helps prevent food reflux) is almost undeveloped at birth, maturing by 8–9 months of age. The cardiac sphincter is functionally weak, whereas the pyloric region is well developed at birth. These anatomical features can lead to the backflow of stomach contents into the esophagus, potentially causing peptic damage to its mucous membrane. Additionally, the tendency for regurgitation and vomiting in the first year of life is associated with the fixation of the esophagus by the diaphragmatic crura, as well as increased gastric pressure and impaired innervation. During the first weeks of life, the stomach is positioned lower, beneath the antral-pyloric region. Therefore, after feeding, infants should not be placed in a horizontal position to prevent aspiration. By the age of 7–11 years, the stomach takes on a shape similar to that of an adult.

The anatomical capacity of a newborn's stomach is 30–35 cm^3. However, its physiological capacity is smaller, measuring only 7–10 ml on the first day of life. By the fourth day after the initiation of enteral nutrition, it increases to 40–50 ml, and by the tenth day, it reaches 80 ml. Subsequently, the stomach's volume increases by approximately 25 ml per month. By the end of the first year of life, it reaches 250–300 ml, and by the age of three, it expands to 400–600 ml. A rapid increase in stomach volume begins after the age of seven, reaching 1300–1500 ml by the age of 10–12 years.

The muscular layer of the stomach in a newborn is not well developed. The mucous membrane, however, is thick and has prominent folds. In the first three months of life, the surface area of the mucous membrane triples, which aids in the digestion of milk. By the age of 15, it increases tenfold. At birth, the pancreas is morphologically and functionally underdeveloped, with the relative number of pancreatic cells being 2.5 times lower in newborns compared to adults. During the first year of life, the secretory apparatus of the stomach remains immature, and its functional abilities are limited. Infant gastric juice contains the same components as adult gastric juice, including hydrochloric acid, chymosin (which breaks down milk), pepsins (which break down proteins into amino acids and peptides), and lipase (which breaks down neutral fats into fatty acids and glycerol). During the first weeks of life, gastric juice has a very low concentration of hydrochloric acid and, consequently, low acidity. After the introduction of solid foods, hydrochloric acid production increases significantly, marking the transition from a lactotrophic diet to a more varied diet. As the pH level of gastric juice decreases, the activity of carbonic anhydrase, an enzyme involved in hydrogen ion formation, increases. In the first two months of life, the pH of the stomach is primarily determined by hydrogen ions from lactic acid, while later, it is regulated mainly by hydrochloric acid.

The synthesis of proteolytic enzymes starts during the antenatal period but their levels and activity are initially low in newborns, gradually increasing with

age. Notably, fetal pepsin is particularly active in protein hydrolysis for newborns. During the first year of life, infants exhibit higher levels of gastric lipase compared to adults, which aids in fat digestion in a neutral environment without the presence of bile acids. Newborns and breastfed infants have a lower concentration of hydrochloric acid and pepsin in their stomachs, which can decrease the protective function of gastric juice. However, this also helps preserve immunoglobulins (Ig) found in mother's milk, providing vital immune support. In the early months of life, stomach motor function is reduced, leading to slower peristalsis and an increased presence of gas. Infants may also experience increased tone in the stomach muscles of the pyloric region, occasionally resulting in pylorospasm. In older children, a condition known as cardiospasm can sometimes occur, affecting the lower esophagus.

Intestines

Small intestine. The relative length of the small intestine in a newborn baby is significant, measuring approximately 1 meter for every kilogram of body weight, compared to just 10 centimeters in adults. Due to the size of the liver and the underdevelopment of the small pelvis, the intestinal loops in infants are more compact than those in adults. The small intestine is the primary site for digestion and nutrient absorption. In infants, the duodenum has a looped shape, which later undergoes bending as the child grows. The duodenum in babies is quite mobile, but by the age of seven, the fatty tissue surrounding it becomes more fixed. Additionally, the mucosal folds of the duodenum are less pronounced in newborns than in older children, and the duodenal glands are smaller and less branched compared to those in adults. The duodenum plays a crucial role in regulating the entire digestive system by releasing hormones from the endocrine cells located in its mucosa. The small intestine comprises about two-fifths of its total length, while the ileum makes up about three-fifths (excluding the duodenum). The ileum terminates at the ileocecal valve, also known as the Baugin valve. In young children, this valve may exhibit relative weakness, which can allow intestinal contents from the cecum—rich in bacterial flora—to be pushed back, potentially leading to inflammatory conditions in its terminal section.

A child's small intestine contains a relatively large amount of gas, and this volume gradually decreases until around the age of seven, as adults typically do not have gas present in their small intestine. The mucous membrane of the small intestine is thin, richly vascularized, and exhibits increased permeability, particularly in infants during their first year of life.

Newborns possess both single and grouped lymphoid follicles within the mucosa, which initially are dispersed throughout the intestine but later become primarily concentrated in the ileal region as Peyer's patches. The lymphatic vessels in young children are numerous and wider than those found in adults. Importantly, lymphatic fluid from the small intestine bypasses the liver, allowing absorbed nutrients to enter the bloodstream directly.

In infants, the muscle layer of the intestinal wall, especially its inner layer, is underdeveloped. The overall contractile ability in newborns and young children is relatively weak but increases significantly during the first year of life. The small intestine is where the main stages of digestion and absorption occur, with

membrane digestion being the dominant process during breastfeeding. At birth, the secretory apparatus of the small intestine is generally well-formed. Even in newborns, enzymes such as enterokinase, alkaline phosphatase, lipase, amylase, maltase, and nuclease can be detected in intestinal juice, albeit at lower activity levels compared to adults. This enzymatic activity increases as the child grows. Specific features of protein assimilation in young children include a pronounced ability of intestinal epithelial cells to carry out pinocytosis. This process allows milk proteins to enter the bloodstream in a slightly modified form during the first weeks of life. However, this can lead to the development of antibodies against cow's milk proteins in some infants. In children over one year old, proteins are primarily hydrolyzed into amino acids. From the very first days of life, the enzymes throughout the small intestine exhibit sufficient hydrolytic activity. Maltase activity is notably high at birth and remains elevated into adulthood, while sucrose activity tends to increase somewhat later. Lactase activity experiences rapid growth in the final weeks of pregnancy, stays high during lactation, but typically decreases by 4-5 grams. The lowest levels of lactase activity are observed in adults. It's important to note that the β-lactose found in human milk is absorbed more slowly than the α-lactose in cow's milk, which means that some of it may reach the large intestine. This contributes to the development of a healthy gram-positive intestinal microflora in breastfed infants. However, fat digestion can be challenging for young children due to the relatively low activity of lipase.

Colon. The average length of the colon in a newborn is about 63 cm, and by the end of the first year of life, it increases to approximately 83 cm. After this period, the length of the large intestine typically matches the child's height. The colon is not fully developed at birth: the intestinal mesentery is poorly formed in newborns and only develops further during the child's second year of life. The anatomical features of the large intestine, including the haustra, become more defined later on, with haustra typically appearing around six months of age. By the age of six or seven, the colon, haustra, and mesentery reach their mature form. In newborns, a helminthic tumor may present as a conical shape, exhibiting considerable mobility due to the length of the stalk, and it can be located in various parts of the abdominal cavity, including the retrocecal area. The primary functions of the large intestine include water absorption and serving as a reservoir for waste evacuation. In the large intestine, the processes of decomposition and absorption of nutrients continue. This process is aided by enzymes from the small intestine and bacteria that reside within the large intestine, ultimately leading to the formation of feces. The mucous membrane of the large intestine in children is characterized by deepened crypts, a flat epithelial layer, and a rapid rate of cell proliferation.

The rectum of a newborn is cylindrical and lacks an ampulla, which develops during the early childhood years. The rectum also bends, with this curvature formed alongside the development of the tail and spinal curves. In infants, the rectum is relatively longer and more mobile due to the absence of developed fatty tissue. Additionally, the rectal muscles in newborns are not fully developed.

Functional characteristics of the intestines

The intestinal motility includes two main types of movements:

1. Pendulum-like movements: These occur in the small intestine and serve to mix its contents.

2. Peristaltic movements: These are responsible for directing the contents towards the large intestine.

In the large intestine, antiperistaltic actions help in thickening and forming stool. Young children tend to have more active motility, which facilitates more frequent bowel movements. For infants, the time it takes for food to pass through the intestine ranges from 4 to 18 hours, while for older children, it can take about a day. This high level of intestinal motility, along with insufficient tightening of intestinal loops, can increase the risk of inguinal hernia. Meconium, the primary stool present in the first hours of life, is a dark green, sticky mass with a pH of 6.0. It consists of desquamated epithelial cells, mucus, remnants of amniotic fluid, and bile pigments. By the 2nd to 3rd day, feces start to mix with meconium, and from the 5th day onward, they take on a more typical appearance. In the first month of life, infants may defecate after each feeding, averaging about 5 to 7 times a day. This decreases to about 3 to 6 times a day by the second month, and to 1 to 2 times a day by the age of 1. The stools of breast-fed infants are usually yellow, have an acidic reaction, and a sour smell. In contrast, the stools of formula-fed infants are darker, turbid, sometimes grayish, have a neutral or alkaline reaction, and a stronger smell. The golden yellow color of stools in young infants is primarily due to bilirubin, while green stools may indicate biliverdin presence. Defecation in children is primarily reflexive, but healthy children typically begin to gain voluntary control over their bowel movements by the end of the first year of life.

Microflora of the digestive system

The microflora of the digestive system plays several important roles:

1. Digestion assistance: It helps break down food and enhances the overall digestive process.

2. Pathogen prevention: Healthy gut bacteria inhibit the growth of pathogenic microorganisms, reducing the risk of infections in the intestine.

3. Vitamin synthesis: The microflora is involved in producing essential vitamins, such as some B vitamins and vitamin K.

4. Inactivation of active substances: It helps detoxify certain physiologically active substances and enzymes.

5. Influence on enterocyte renewal: The microflora affects the rate at which intestinal cells (enterocytes) are renewed and can influence the intestinal-hepatic circulation of bile acids. In the early stages of life, the intestines of fetuses and newborns are initially sterile, known as the aseptic period, lasting for the first 10 to 20 hours. Following this, the colonization period begins (2-4 days), during which the intestines start to be populated by microorganisms. The third stage, called stabilization of microflora, lasts from about 6 months to 2 years. The formation of intestinal biocenosis starts from the first day of life. For healthy full-term infants, the predominant bacterial flora from birth to about 7-9 days consists mainly of Bifidobacterium bifidum and Lactobacillus acidophilus. In breast-fed infants, B. bifidum typically dominates the intestinal microflora. In contrast, for

formula-fed infants. L. acidophilus, B. bifidum, enterococci, and normal E. coli are found in almost equal proportions. As children transition to adult nutrition, the composition of the microflora undergoes significant changes, adapting to accommodate a more varied diet. This evolution is crucial for developing a healthy gut microbiome and overall digestive health.

Pancreas.

In newborns, the pancreas is smaller and positioned higher than in adults. It's loosely attached to the back wall of the abdominal cavity, making it more mobile. The pancreas grows rapidly during the first three years of life and continues to develop through adulthood. In the early months after birth, the pancreas is not fully developed. It contains many blood vessels but has relatively little connective tissue. Interestingly, at birth, the endocrine component of the pancreas, which produces hormones like insulin, is more fully developed than the exocrine part, responsible for digestive enzyme production. Pancreatic juice plays a vital role in digestion, as it contains enzymes that hydrolyze proteins, fats, and carbohydrates. It also includes bicarbonates, which create an alkaline environment necessary for activating these enzymes. In newborns, the secretion of pancreatic juice is minimal and is stimulated by feeding. The activity of amylase (an enzyme that breaks down carbohydrates) and bicarbonate levels are low initially. As infants transition to a regular diet that includes a higher carbohydrate content, amylase activity increases significantly, peaking around 6 to 9 years of age. The activity of pancreatic lipase, crucial for breaking down dietary fats, is low in newborns. During the first months of life, other mechanisms, such as those in the salivary glands and stomach, play a significant role in digesting fats from breast milk. Moreover, the type of feeding has a substantial impact on pancreatic activity. In infants who are artificially fed, the enzymatic activity in duodenal juice can be 4 to 5 times higher than in those who are breast-fed. This highlights the differing demands placed on the pancreas based on dietary composition and feeding practices during early development.

Liver

The liver is a significant organ at birth, constituting a larger portion of the body weight compared to adults. Here are some key points about the liver in newborns and children:

1. Size and Weight: At birth, the liver makes up more than 4% of a newborn's body weight, whereas in adults, it's around 2%.

2. Protrusion: In newborns, the lower edge of the liver can extend beyond the ribs and may even touch the edge of the right iliac bone. For children aged 1 to 3 years, the liver edge can be palpated 1-3 cm below the medioclavicular line.

3. Growth and Development: After birth, although the liver continues to grow, its growth rate is slower than that of the body. By age 7, the liver typically does not extend beyond the subcostal arch and is usually not palpable at rest.

4. Liver Lobules: The formation of liver lobules starts during pregnancy, with clear distinctions by the time of birth. Their complete differentiation occurs in the postpartum period.

5. Susceptibility to Conditions: The liver is rich in blood volume, which makes it vulnerable to infections, intoxications, and circulatory disorders that can lead to rapid enlargement.

6. Hematopoietic Cells: In newborns, about 5% of the liver's volume consists of hematopoietic cells, but this percentage decreases quickly as they grow. By the age of 8, the liver's structure mirrors that of adult livers.

7. Fibrous Capsule: The fibrous capsule surrounding the liver is relatively thin in newborns and children.

Overall, the liver undergoes significant changes in size, structure, and function during the early years of life.

Liver function.

Bile production and metabolism in newborns and young children exhibit unique characteristics compared to adults. Here are some key points:

1. Prenatal Bile Production: Bile production starts during fetal development but tends to slow down shortly after birth.

2. Gallbladder Function: As children grow, their gallbladder becomes more efficient at collecting bile. This improvement helps in the overall digestion and processing of fats.

3. High Bile Acid Concentration: In the first year of life, particularly in the first days after birth, children have high concentrations of bile acids. This can lead to liver cholestasis or bile coagulation syndrome, where bile cannot flow properly.

4. Imbalance in Bile Acid Circulation: Newborns often experience an imbalance in liver bile acid circulation. This includes:

- Insufficient uptake of bile acids by hepatocytes (liver cells).
- Slowed bile flow from the liver to the gallbladder.
- A decreased synthesis of secondary bile acids and inadequate reabsorption in the intestine, leading to dyscholia.

5. Fatty Acid Composition: Children produce more atypical, less hydrophobic, and less toxic fatty acids than adults. This difference influences how bile interacts with fats.

6. Accumulation of Fatty Acids: The buildup of fatty acids in bile ducts can increase the permeability of intercellular junctions, which may lead to bile entering the bloodstream.

7. Bile Composition: In the initial months of life, bile has low levels of cholesterol and salts, which contributes to the rare occurrence of bile stones in newborns.

8. Fatty Acid Conjugation: In newborns, fatty acids are primarily conjugated with taurine, while in adults, they are usually conjugated with glycine. Taurine conjugates are more water-soluble and less toxic, facilitating easier elimination from the body.

9. Bile Composition: The bile of newborns has a relatively high content of taurocholic acid, which possesses bactericidal properties. This helps reduce the risk of bacterial inflammation in the bile ducts during the first year of life.

10. Immature Enzymatic Systems: At birth, the liver's enzymatic systems responsible for metabolizing various substances are not fully developed. While

artificial feeding can stimulate the maturation of these systems, it may also lead to imbalances in liver function.

11. Albumin Synthesis: After birth, newborns experience a decrease in albumin synthesis, which results in a lower albumin-globulin ratio in the blood. This change can affect various physiological processes, including maintaining proper osmotic pressure.

12. Bilirubin Metabolism: Newborns exhibit low activity of glucuronyl transferase, an enzyme necessary for converting bilirubin into a water-soluble form. This enzyme's low activity leads to higher levels of unconjugated bilirubin, which can contribute to conditions like jaundice.

13. Liver Function: The liver acts as a vital barrier, neutralizing both endogenous and exogenous harmful substances, including toxins absorbed from the intestines. However, this detoxification function is not fully developed in young children.

14. Gallbladder Anatomy: In newborns, the gallbladder is often positioned behind the liver, with variations in shape. Its size increases with age, typically doubling in length by the ages of 10-12 years.

15. Bile Secretion Rates: The rate of bile secretion in newborns is significantly lower—about six times less—than that of adults, which can impact digestion and fat absorption.

Methods of examination of the digestive system

Complaints

Stomach ache

Understanding manifestations of abdominal pain in young children requires careful observation and consideration of various factors. Here's a breakdown of key elements to assess:

General Discomfort

• Behavior: In younger children, abdominal pain often leads to general discomfort and crying.

• Expressions: Children may clutch their abdomen or assume a curled-up position.

Pain Characteristics in Older Children

• Rapid Satiety: Older children may express their discomfort as a feeling of fullness or that they can't eat much.

Clarifying Pain Character

1. Localization:

• In preschoolers, pain is often localized around the umbilical area.

2. Irradiation:

• Pain may radiate, but primarily it's focused on the site of the underlying issue.

3. Symptoms:

• Descriptions can include:

• Cramping: Sudden, severe episodes.

• Dullness: Persistent, less intense pain.

• Pulling: Discomfort that feels like a tugging sensation.

• Sharp: Sudden, severe pain that may indicate an urgent issue.

4. Periodicity:

• Children may experience alternating periods of pain followed by relief.

5. Seasonality:

• Some children may notice an increase in symptoms during the spring and autumn months.

6. Correlation with Food:

• Monitor how different foods and quantities affect the pain:

• Does it worsen after specific meals?

• Is there a pattern tied to particular food items?

7. Time of Appearance:

• Identifying when pain occurs can be vital:

• During a meal: Possible connection to food intolerance or allergies.

• 30-60 minutes post-meal: Could suggest issues with digestion.

• 1.5-3 hours after eating: May point to other gastrointestinal issues.

• 6-7 hours after a meal: Often indicates hunger-related pain.

• Nighttime pain (11 PM to 3 AM) that disappears after eating: Needs further exploration for possible causes.

Examination of the oral cavity.

Examination of the oral cavity should be carried out at the end of the study, as this may cause a negative reaction in the child. This includes examining the lips, oral mucosa, tongue, teeth, throat, and detecting bad breath. First, pay attention to the color of the lips, their moisture, cracks, herpes, ulcers in the corners of the mouth (angular cheilitis). Then check the mouth and throat. In a healthy child, the mucous membrane of the oral cavity and throat has a uniform pink color; white teeth; tongue wet, pink and clean. Tonsils usually do not protrude from the palate, and there is no bad breath. Rashes, aphthae (round erosion, yellowing or oozing), leukoplakia (keratization areas of the cheek mucosa), Velsky-Filatov-Koplik spots (with measles), inflammation of the gums (gingivitis), tongue damage (glossitis), infiltrates or ulcers in the corners of the mouth.

Examination of the abdominal cavity

Examination of the abdominal cavity is carried out in the horizontal and vertical position of the patient, paying attention to its shape, symmetry and size. Usually, the abdomen has a rounded symmetrical shape. In older children, the stomach is located slightly below the level of the chest, and in infants and young children, it is slightly above its level.

The shape and size of the abdomen depends on the physical condition of the patient (asthenic type abdomen is usually small, hypersthenic type abdomen is large). The degree of active participation of the abdominal muscles in the act of breathing is also evaluated. For this, the patient is asked to breathe in and out with the stomach. By irritating the abdominal cavity, the patient ensures proper breathing

Palpation

– Abdominal palpation is performed in two positions of the patient: horizontal and vertical.

– Superficial palpation

– Superficial palpation of the abdomen is carried out starting from the left groin area in symmetrical places to the left and right, rising to the epigastric region; or counterclockwise.

– Signs determined by superficial palpation.

– Pain (the area of pain projection indicates the pathological process of the relevant organ).

– The resistance of the muscles of the anterior abdominal wall indicates that the peritoneum is involved in the inflammatory process. In this case, the Shchetkin-Blumberg symptom (a sharp increase in pain with a sudden withdrawal of the palpation hand from the abdomen) should be checked.

– The condition of the "weak places" of the front wall of the abdomen (aponeurosis of the white line of the abdomen in the epigastric region, the umbilical ring, the external opening of the chovi canal); the presence of a hernia (in the form of protrusions of various sizes in the navel or the external opening of the inguinal canal; appears or enlarges when straining or coughing), the size of the hernia ring.

– Significant enlargement of abdominal organs (liver, spleen) or the appearance of a large tumor.

– Projection of the organs of the abdominal cavity on the front wall of the abdomen

– Left subcostal area: cardiac part of the stomach, tail of the pancreas, spleen, left turn of the colon, superior curvature of the left kidney.

– Epigastric region: stomach, duodenum, body of the pancreas, left lobe of the liver.

– Right subcostal region: right lobe of the liver, gall bladder, right bend of the large intestine, upper curvature of the right kidney.

– Left and right sides: the descending and ascending parts of the large intestine, respectively, the lower curvature of the left and right kidneys, part of the loops of the small intestine.

– umbilical region: loops of the small intestine, the transverse colon, the lower horizontal part of the duodenum, the greater curvature of the stomach, the head of the pancreas, the gates of the kidneys, the urinary tract.

– Left iliac region: sigmoid colon, left ureter.

– Suprabladder area: loops of small intestine, bladder.

– Right iliac region: cecum, terminal part of ileum, vermiform tumor, right bladder.

Deep palpation

– Deep palpation allows to conclude about some features of abdominal organs. In this case, the localization and size, shape, diameter, structure (soft, dense), nature of the surface (usually smooth, possible tuberosity), mobility and displacement (normal, different parts of the intestine are mobile), as well as pain and itching are determined. usually not).

– In healthy children, in most cases, it is possible to check the sigmoid, cecum and transverse intestine; The ascending and descending parts of the large intestine begin to be palpated at the same time. The sigmoid colon is examined in

the left iliac region as a smooth, moderately dense, toneless, slow and rarely peristaltic cord with a diameter of 2-3 cm.

– With a narrowing of the intestinal mesentery or sigmoid colon (dolichosigma), the intestine can be palpated more medially or laterally than usual. The cecum is in the form of a soft soft elastic cylinder with a diameter of 3-4 cm. It is slightly extended downwards (pear-shaped extension), where it ends blindly. When pressed, there is a noise. • In the right iliac region, sometimes the ileum can be palpated in the form of a cylinder of soft elastic consistency with a diameter of 1-1.5 cm; peristalsis is good and there is noise during palpation.

– In patients with a thin abdominal wall, mesenteric (mesenteric) lymph nodes expand during deep palpation of the umbilical region.

– It is difficult to palpate the great curvature of the stomach and pyloric section; other parts of the stomach cannot be palpated at all. To determine the lower border of the stomach, the method of determining the "shaking noise" (shum pleska) is used. Usually, in older children, the lower border of the stomach is 2-4 cm above the navel.

Palpation of the liver. Before palpation, localization of the lower edge of the liver is pre-percussion. In young children, in the right middle clavicular line, the edges of the liver are usually located 1-2 cm below the border of the rib cage, and in children older than 5-7 years, it is located at the level of the rib cage. Palpation of the lower edge of the liver reveals its consistency, shape and pain (normal - painless, slightly sharp.

– The gallbladder is usually not palpable. The projection of the gallbladder to the anterior wall of the abdomen corresponds to the point where the outer edge of the rectus muscle of the anterior abdominal wall intersects with the rib arch (point of the gallbladder).

– The ascending and descending parts of the large intestine are located on the right and left sides of the abdomen.

– The transverse colon is palpated in the umbilical region in the form of a cylinder, bent down, moderately dense, about 2.5 cm in diameter,

– The small intestine is usually not palpable because it is located deep in the abdominal cavity and is very mobile.

The pancreas can be palpated very rarely, so the pain points on the front wall of the abdomen are of diagnostic importance. The head of the pancreas is projected in the Shoffar-Rive zone, which has the shape of a rectangular triangle, located in the upper right quadrant of the umbilical region. One end of this triangle is at the navel, one of the legs is in the middle, and the hypotenuse is the inner third of the line connecting the navel with the right oblique arc and forming an angle of 45 ° with the midline. The caudal part of the pancreas is located in the bisector of the left upper quadrant of the abdomen, projected at the Mayo-Robson point.

A number of symptoms can indicate the pathology of the gallbladder.

- Kera's symptom - sharp pain when breathing at the point of the gallbladder during normal palpation of the gallbladder)

- Murphy's symptom (strong and sharp pain when breathing, when the doctor presses his fingers on the projection of the gallbladder, it causes the patient to stop breathing).

- Georgievsky's symptom - Mussi (phrenicus sign) - pain at the point of superficial location of the right diaphragmatic nerve.

• Palpation of the spleen is performed with the patient lying on his right side.

As a rule, it is impossible to palpate the spleen, because its front edge does not reach the edge of the rib arch by 3-4 cm, and it can be palpated when the spleen is enlarged (splenomegaly) at least 1.5-2 times.

Abdominal percussion

Percussion of the abdominal cavity is performed from the navel downward, as well as on the lateral surfaces of the abdomen, in both the supine and standing positions. Usually, the transition from a tympanic to a dull percussion sound on both sides occurs along the anterior axillary lines. A medial shift of this border indicates the accumulation of free fluid (ascites) in the abdominal cavity.

When the patient moves to a vertical position, the fluid shifts to the lower part of the abdominal cavity. Therefore, tympanitic sounds can be detected by percussion in the lateral areas of the abdomen, following a vertical line from the upper to the lower abdomen. In patients with severe ascites, a dull percussion sound is present in all parts of the abdomen, regardless of position. In such cases, additional factors should be considered, including the size and shape of the abdomen, changes in the anterior abdominal wall, and alterations in the appearance of the umbilical skin. In addition to percussion, the fluid wave test is used to confirm the presence of ascites.

The size of the liver is assessed through percussion, as its lower edge normally does not extend more than 3-4 cm below the costal margin. In cases of splenomegaly (enlarged spleen), the spleen is typically palpated at 1.5-2 times its normal size. Palpation of the spleen evaluates its shape, consistency, surface texture, mobility, and clarity of borders.

Liver size

Measurement of the liver is performed by percussion. In children older than 5-7 years, liver size is determined using M.G. Kurlov's method. According to this method, normal liver dimensions are:

9 cm along the right midclavicular line

8 cm along the midline

7 cm along the left costal arch

This method helps assess liver enlargement (hepatomegaly) and monitor liver health in pediatric patients.

Determination of the percussion dimensions of the spleen

Under normal conditions, the spleen does not produce a dull percussion sound but rather a moderately sharp tympanic tone. To assess spleen size, percussion is performed to determine its upper and lower borders along the mid-axillary line: The upper border of splenic dullness is typically located at the 9th rib. The lower border is usually at the 11th rib. The distance between these two points (splenic dullness) averages 4 cm in width.

The anterior and posterior borders of the spleen are determined by percussing: Anteriorly: Moving from the edge of the left costal margin toward the midline.

Posteriorly: Moving from the left posterior axillary line toward the spine until dullness is detected.

The distance between these points corresponds to the length of the spleen and helps evaluate splenic enlargement (splenomegaly).

Auscultation.

Abdominal auscultation typically allows for the detection of occasional intestinal motility sounds, such as gurgling. Instrumental studies utilized in the evaluation of abdominal conditions include ultrasound and various radiological methods. Among these, endoscopic techniques are particularly significant for assessing the digestive system. Procedures such as laparoscopy, sigmoidoscopy, and colonoscopy play vital roles in diagnosis and treatment.

Function methods.

Functional methods involve the evaluation of the secretory and acid-forming functions of the pancreas. Biochemical analyses of blood serum are crucial for assessing the functional state of the digestive system's organs. Key tests include the determination of bilirubin, transaminases, protein and its fractions, coagulation factors, cholesterol, total lipids and their fractions, as well as glycemic curves. These studies provide valuable insights into the overall health and functionality of the digestive system.

The main syndromes of gastrointestinal disorders in children of early age. Differential diagnostic signs of pylorospasm and pylorostenosis:

Pylorostenosis is a congenital anomaly of the stomach, characterized by narrowing of the pyloric part.

Pylorospasm is a disease that occurs in early children and is characterized by periodic spasms of the pyloric part of the stomach.

Table 4

Clinical signs	Pylorospasm	Pylorostenosis
Onset time of symptoms (vomiting)	Fromthe first day of baby's life	
Composition of vomit	Undigested milk	Kefir like milk
Time of vomitinf after breastfeeding	A few minutes after breastfeeding	After a long interval, possibly before the next feeding
Volume of vomit	Small amount of ingested food	Large amount of ingested food
Frequency of vomiting	2-4 times a day, not constant	1 – 2 times a day but constant
Vomiting reaction characteristics	Partial regurgitation	Projectile vomiting
Stool	Normal bowel movement, reflecated by defecation	Constipation

Urine outputand frequency	Unchanged or slightly reduced	Reduced to 3-4 times
General condition of the baby	Restless, cries before and during vomiting.	Mostly calm, occasional restlessness before vomiting
X-ray examination result	No sand clock symptom in the stomach, remains for 6-8 hours	Sand clock symptom in the stomach, persists for 24 hours or more
Ultrasound results	Normal	Pyloric wall hypertrophy > 4 mm

Malabsorption syndrome:

- "Malabsorption syndrome" (malabsorption) is a symptom complex, which includes maldigestion (maldigestion) and malabsorption (malabsorption) in the small intestine, with chronic diarrhea and severe eating disorders.
- A. Carbohydrate malabsorption
- lactase deficiency;
- sucrose-isomaltase deficiency;
- malabsorption of monosaccharides (glucose, galactose).
- B. Celiac disease - inability to digest gluten.
- Clinical manifestations:
- loss of appetite;
- abdominal enlargement;
- flatulence;
- stools are frequent (osmotic diarrhea), foamy, with a bitter-pungent smell.

Hirschsprung's disease is a congenital condition characterized by abnormal development of the large intestine due to a deficiency or absence of intramural nerve ganglia in the intestinal wall. This results in a lack of peristalsis in the affected segment of the intestine, leading to the retention of fecal matter.

Clinical Signs:

- Absence of meconium in newborns
- Difficulty with gas passage
- Abdominal distension
- Paradoxical diarrhea and vomiting in newborns

When gathering the medical history (anamnesis), it is important to consider the following:

- At what age did constipation first occur?
- Has the child been unable to defecate independently for several days?
- Has the child experienced diarrhea following a prolonged period of constipation?
- Were cleansing enemas administered, and if so, did they provide relief?

From the child's life history, it is essential to inquire about:

- Did the child pass meconium within 24 hours after birth?

• How has the child's physical development progressed? Was there any observed hypotrophy or other concerns?

Functional disorders of the gastrointestinal tract are prevalent issues in infants during their first month of life. In these cases, clinical symptoms are present, but there are no detectable organic changes in the gastrointestinal tract, such as structural abnormalities, inflammatory changes, infections, or tumors, nor are there metabolic alterations.

In functional disorders, issues with digestion, motility, absorption, and nutrient utilization can disrupt the intestinal microflora and impair immune system function. The underlying cause of these disorders is often related to a disruption in the nervous and humoral control of the gastrointestinal tract, even when the organ itself remains structurally intact.

According to the Rome III criteria established by an international working group in 2006, functional gastrointestinal disorders can be observed in children under the age of 2.

*G 1 Partial return of breast milk in infants
*G 2 Vomiting in infants
*G 3 Cyclic vomiting syndrome
*G 4 Newborn colic
*G 5 Functional diarrhea
*G 6 Painful and difficult defecation (dyshesia) in infants
*G 7 Functional constipation

Here's a polished version of your text regarding the functional gastrointestinal disorders in breast-fed children:

Partial regurgitation of breast milk, intestinal colic, and functional constipation are common in breast-fed infants, particularly those under 6 months of age. More than half of these children may experience some combination of symptoms, often with fewer than one isolated symptom. It is not uncommon for a single child to present multiple symptoms that contribute to functional gastrointestinal disorders. In infants born with hypoxia, various vegetative-visceral disturbances may arise, including hypertonic or hypotonic motility issues, disruptions in the activity of controlling executive peptides, simultaneous partial reflux (due to sphincter spasms), colic (characterized by motility disorders and increased gas production), and constipation (resulting from hypotonia or intestinal spasms). Additionally, genetic factors associated with nutrient absorption disorders and impaired enzymatic activation can exacerbate clinical symptoms in enterocytes, leading to alterations in intestinal microbiocenosis.

1. Connection with mother
2. Relationship with the child

1.The first group of reasons includes:

*obstetric anamnesis
*mother's emotional lability in stressful situations
*nutrition disorder of a nursing mother
*disruption of eating technique: eating more than the norm in natural and artificial feeding
* improper preparation of milk mixtures

*woman smoking

2. The reasons related to the child are as follows:

*anatomical and functional immaturity of the digestive system (abdominal esophagus shortness, sphincter deficiency, enzymatic deficiency, digestive system coordination failure).

*dysfunction of the gastrointestinal system as a result of immaturity of the intestinal central and peripheral nervous system

*intestinal microbiota formation

* the formation of sleep and wakefulness rhythm

Partial regurgitation of food into the oral cavity, colic, and fecal disorders can occur in infants due to factors such as lactase deficiency and gastrointestinal food allergies, often associated with vegetative visceral brain ischemia. Partial regurgitation refers to the situation where food from the stomach returns to the oral cavity without any forced action. Studies indicate that between 18% and 50% of infants under the age of 1 experience partial regurgitation. This phenomenon is particularly common during the first 4 to 5 months of life and may continue into the 6th to 7th month when supplementary foods, such as small porridges, are introduced into the diet. Regurgitation tends to decrease significantly when the child is positioned more vertically or sits upright, as this position facilitates the proper functioning of the gastrointestinal tract.

Experts assessed the degree of food regurgitation in the oral cavity on a five-point scale:

Table 5

A scale for assessing the intensity of partial regurgitation of food in the oral cavity (Y. Vandenplas et al., 1993)	
0 point	Partial regurgitation of food in the mouth
1 point	Regurgitation of food no more than 5 times a day and up to 3 ml in size
2 point	Return of food more than 5 times a day and more than 3 ml in volume
3 point	Half of the food given more than 5 times a day is half of the food given 1 time
4 point	Regurgitation of food in the oral cavity in the same volume for 30 minutes, and then after each meal
5 point	Partial regurgitation of food in the oral cavity is the return of half and full regurgitation of food

Protein energy deficiency, etiology, classification, diagnosis, clinic. Methods of treatment and prevention

Dystrophy, derived from the Greek words for "disruption" (dys) and "nutrition" (trope), refers to a nutritional disorder that can occur in early childhood. It manifests in three main types:

1. Hypotrophy: This type is characterized by decreased food intake, leading to insufficient nutrition and growth. Infants and young children with hypotrophy may not gain weight or grow at the expected rate for their age.

2. Obesity: In contrast to hypotrophy, obesity occurs due to an increased food intake that exceeds the body's energy requirements. This excessive caloric intake can result in excessive weight gain, which may lead to various health issues, including metabolic disorders.

3. Paratrophy: Paratrophy refers to an excess in body weight and height compared to normal growth standards. It can also describe an increase in body mass that exceeds the normal range by 10% of height.

Hypotrophy

Hypotrophy (from Greek hypo — under, below; trophe — nutrition) is a chronic nutritional disorder characterized by a deficiency in body weight. In Anglo-American literature, the term "hypotrophy" is often replaced with "malnutrition." The most common form of malnutrition is protein-energy malnutrition (PEM). Typically, children with this condition also experience deficiencies in vitamin intake (hypovitaminosis) as well as micronutrients. According to WHO data, in developing countries, up to 20-30% or more of young children suffer from protein-energy malnutrition or other types of nutritional deficiencies.

Etiology.

Hypotrophies are classified into two groups based on etiology: exogenous and endogenous.

Exogenous causes of hypotrophy

—Alimentary factors – quantitative malnutrition due to hypogalactia in the mother or difficulties in breastfeeding from the mother's side (flat or inverted nipples, "tight" mammary gland, etc.) or the child's side (regurgitation, vomiting, small lower jaw, "short" frenulum of the tongue, etc.). Qualitative malnutrition can also occur due to the use of an inappropriate formula for the child's age, late introduction of complementary foods, or a daily diet poor in animal proteins, fats, vitamins, iron, and trace elements.

—Infectious factors – intrauterine generalized infections (such as cytomegaly), intranatal infections, toxic-septic conditions, pyelonephritis, urinary tract infections, intestinal infections, etc. Hypotrophy is particularly often caused by infectious lesions of the gastrointestinal tract, leading to morphological changes in the intestinal mucosa (up to villous atrophy), suppression of disaccharidase activity (especially lactase), immunopathological damage to the intestinal wall, and dysbiosis. These factors contribute to prolonged diarrhea, maldigestion, and malabsorption. It is believed that in any mild infectious diseases, energy and nutrient requirements increase by 10%, while in moderate to severe cases, they rise by 50% compared to normal conditions.

—Toxic factors – the use of expired or poor-quality milk formulas during artificial feeding, hypervitaminosis D and A, poisoning (including drug intoxication), and other toxic influences.

—Anorexia – a consequence of psychogenic and other forms of deprivation when a child does not receive enough attention, affection, psychogenic developmental stimulation, outdoor walks, massage, or gymnastics.

Endogenous causes of hypotrophy.

1.Bronchopulmonary dysplasia – a chronic lung disease often resulting from prolonged mechanical ventilation and oxygen therapy in premature infants.

2.Congenital gastrointestinal tract malformations – complete or partial obstruction with persistent vomiting (pyloric stenosis, annular pancreas, dolichosigma, Hirschsprung's disease, etc.), as well as congenital heart defects.

3.Short bowel syndrome – a condition that occurs after extensive intestinal resections, leading to severe malabsorption.

4.Hereditary (primary) immunodeficiencies – mainly affecting the T-cell system, or secondary immunodeficiencies.

5.Primary malabsorption and maldigestion disorders – lactose, sucrose, glucose, and fructose intolerance, celiac disease, cystic fibrosis, exudative enteropathy, as well as secondary malabsorption caused by allergic intolerance to cow's or soy milk proteins, enteropathic acrodermatitis, etc.

6.Inherited metabolic disorders – galactosemia, fructosemia, maple syrup urine disease (leucinosis), xanthomatoses, Niemann-Pick disease, Tay-Sachs disease, and others.

7.Endocrine disorders – adrenogenital syndrome, hypothyroidism, pituitary dwarfism, and other hormonal imbalances affecting growth and metabolism.

8.Psychopathies and neuroses in adolescents – leading to anorexia due to psychological distress or eating disorders.

Pathogenesis.

In hypotrophy, the utilization of nutrients in the intestines and tissues is impaired. This leads to decreased enzymatic activity of the stomach, intestines, and pancreas. The intestines become dilated and elongated, resulting in constipation and dysbacteriosis. In cases of protein-energy deficiency, the functions of vital organs are disrupted, including the liver (protein-synthetic, carbohydrate, and protein metabolism), heart, kidneys, and lungs. This leads to anemia, which occurs due to deficiencies in protein, iron, copper, zinc, folic acid, pyridoxine, and other vitamins.

Metabolic disorders characteristic of hypotrophy:

Hypoproteinemia (low protein levels in the blood)

Hypoalbuminemia (low albumin levels)

Aminoaciduria (excessive loss of amino acids in urine)

Hypoglycemia (low blood sugar levels)

Acidosis (increased acidity in body fluids)

Hypokalemia (low potassium levels)

Hypocalcemia (low calcium levels)

Hypophosphatemia (low phosphate levels)

Disruptions in the exchange of sodium (Na) and potassium (K) occur due to adrenal gland dysfunction. Hypotrophy develops as a result of adrenal gland hypofunction, leading to electrolyte imbalances and metabolic disturbances.

1. Syndrome of Trophic Disorders. Thinning of the subcutaneous fat layer, leading to a visible reduction in body mass. Body mass deficit and disproportion in body structure, characterized by a decrease in Chulitskaya L. I. and F. F. Erisman indices. Reduced tissue turgor, indicating a decline in skin elasticity and hydration.

Signs of polyhypovitaminosis, including deficiencies of vitamins A, B1, B2, B6, D, P, and PP (niacin), which contribute to metabolic and structural disturbances in the body.

2. Syndrome of Digestive System Disorders

Decreased appetite and anorexia, resulting in insufficient nutrient intake.

Mood changes, often associated with nutritional deficiencies and metabolic imbalances. Constipation, caused by slowed intestinal motility due to malnutrition. Dysbacteriosis, which disrupts the balance of intestinal microflora, leading to digestive disturbances. Reduced tolerance to food, characterized by difficulties in digesting and absorbing nutrients.

3. Syndrome of Central Nervous System Dysfunction

Emotional tone disorders, including increased irritability or apathy. Low mobility, leading to reduced physical activity and muscle weakness.

Thermoregulation disturbances, resulting in an inability to maintain normal body temperature. Sleep disorders, which can manifest as difficulty falling asleep or maintaining restful sleep. Delayed psychomotor development, affecting motor skills, reflexes, and cognitive functions. Muscle hypo- and dystonia, characterized by decreased muscle tone and strength.

4. Syndrome of Hemopoiesis Disorders and Decreased Immunobiological Reactivity. Anemia, resulting from deficiencies in protein, iron, folic acid, vitamin B12, and other essential nutrients. Secondary immunodeficiency, making the body more susceptible to infections. Atypical course of infectious-inflammatory diseases, where infections present with prolonged or atypical symptoms due to weakened immune responses.

Classification

Depending on the severity, hypotrophy is divided into 3 levels: I, II, III. In the diagnosis, the etiology of hypotrophy, concomitant diseases, and complications should be noted. A distinction is made between primary and secondary (symptomatic) hypotrophy. Primary hypotrophy occurs as a result of lack of food, secondary hypotrophy is a complication of the main disease.

Clinic. Hypotrophy I degree– characterized by a decrease in subcutaneous fat in all parts of the body, especially in the abdomen. CHulitskaya index is equal to 10-15.

Tissues are turgid, muscle tone is reduced. There is a slight whitening of the skin and mucous membranes, a decrease in skin elasticity and turgor. The height of the child corresponds to the age, and the body mass is reduced by 11-20% compared to the norm. The general condition of the child is satisfactory. Psychomotor development is age-appropriate, but the child is restless, capricious, gets tired quickly, sleeps restlessly.

Hypotrophy II degree. The subcutaneous fat layer decreased in the abdomen, chest, and limbs, but was preserved in the face. CHulitskaya index is 1-10. The child's skin is pale, gray, and folds slightly. On the inner surface of the thigh, longitudinal, bag-like folds appear. Symptoms of polyhypovitaminosis (marbling of the skin, blistering and hyperpigmentation in the folds, brittleness of nails and hair, appearance of scratches in the corner of the mouth, etc.) develop. Tissue turgor is reduced. As a result of a decrease in muscle tone, the abdomen

becomes larger, causing intestinal atony and flatulence. In hypotrophy, rickets is manifested by muscle hypotonia, osteoporosis, osteomalacia, hypoplasia, craniotabes, softening of the large lichyldok area, late eruption of teeth, lordosis, kyphosis, scoliosis. Body mass decreased by 20-30%, height decreased compared to the norm. The child is lethargic, restless, capricious, indifferent to the external environment. The child's appetite and food tolerance have decreased. Sleep is disturbed, thermoregulation is disturbed, the child quickly cools down or overheats.

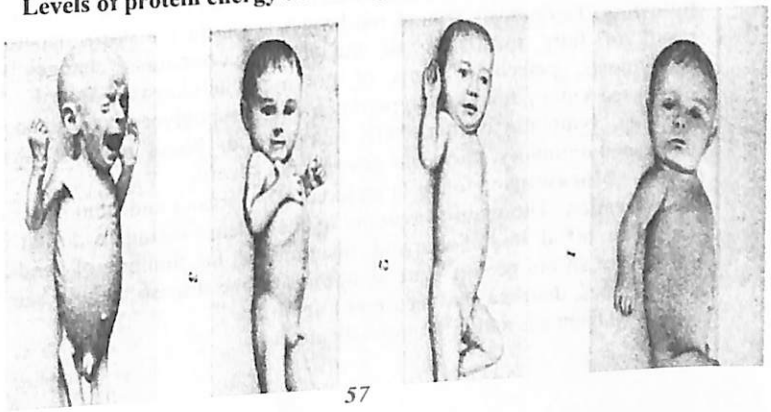
Many patients have otitis, pneumonia, pyelonephritis and other infectious diseases with few symptoms. At the level of hypotrophy II, patients' stools are variable: constipation alternates with dyspeptic stools.

Hypotrophy III degree (insanity, atrophy). In the III degree of primary hypotrophy, the appearance of the patient resembles a skinned skeleton. The subcutaneous fat layer is thin on the abdomen, chest, arms and legs, and on the face it is very reduced or completely absent. The skin is gray, dry, and the limbs are cold. Skin elasticity is lost and wrinkles are expressed on the face. CHulitskaya index is negative. Symptoms of hypovitaminosis (vitamins C, A, V) have developed in the skin and mucous membranes. The patient's mouth is large, and there are visible cuts in the corner of the mouth. Sometimes wet erythema is observed on the skin. The patient's face resembles the face of an old person (due to wrinkles). The stomach is large, full, the stools change, constipation alternates with diarrhea. Body temperature has dropped. The patient gets cold or warms up quickly. Body temperature rises without reason. As a result of weakening of immunological reactivity, otitis and other foci of infection (zotiljam, pyelonephritis, choleenteritis, etc.) develop and pass with mild symptoms. Hypoplasia and osteomalacia symptoms of rickets are observed in the patient. The patient's body mass is 30% or less than the norm. The height of the patient has also decreased.

In the III-level of secondary hypotrophy, the clinical picture of the disease is milder compared to primary hypotrophy, if the main disease is detected and treated quickly, the child's condition will improve.

7- figure

Levels of protein energy deficiency



1.healthy child
2. Hypotrophy I degree
3. Hypotrophy II degree
4. Hypotrophy III degree

Hypotrophy treatment options

Hypostatura (from the Greek hypo- low, statura-height) - the patient's height and body mass are uniformly reduced. CHulitskaya index decreased. Hypostasis is characteristic of patients born with brain and heart defects, encephalopathy, endocrine pathology, bronchopulmonary dysplasia. If the underlying disease is treated, for example, a congenital heart defect is surgically corrected, the patient's physical development will return to normal. Symptoms of polyhypovitaminosis, trophic disorders, dysproteinemia, aminoaciduria, etc. on the patient's skin. k. observed.

Kwashiorkor is a specific variant of hypotrophy in infants in tropical countries, but it is caused by a diet of plant products and a deficiency of animal protein. Protein deficiency can be caused by:

1. Decreased protein adsorption as a result of prolonged diarrhea
2. Proteinuria, infectious diseases, helminthiasis, burns, excessive loss of protein as a result of heavy bleeding
3. Excessive protein loss in chronic liver diseases.

The main symptoms of kwashiorkor are as follows:

1. Neuropsychological disorders (apathy, weakness, drowsiness, excessive crying, loss of appetite, retardation of psychomotor development).
2. Swelling (swelling occurs as a result of hypoproteinemia at the beginning of the disease, and later swelling is observed on the face and hands, leading to false obesity.
3. There is a decrease in muscle mass, muscle atrophy, tissue trophism.
4. Jismoniyrivojlanishdanorqadaqolish

These symptoms D. B. Djeliff. It is called Tetradasi.

In Kwashirkor, other sheep symptoms can be observed - changes in hair (weaving, thinning, fading), dermatitis (hypovitaminosis symptoms on the skin, anorexia, moon face, anemia, diarrhea). Rare symptoms of kwashiorkor include the following: Dermatosis (round red-brown areas on the skin), hepatomegaly (as a result of fatty infiltration of the liver), eczematous changes on the skin, ecchymosis, petechiae, signs of polyhypovitaminosis (A, V1, V2, Vs, D), decreased kidney function, hypoproteinemia, hypoglycemia, aminoaciduria, etc. k. Anemia, lymphocytopenia, SOE increased in blood analysis. As a result of decreased immunity, infectious diseases are severe.

Marasmus is found in children of preschool and school age and is caused by starvation. The main symptoms of the disease include a deficit of body mass (less than 60%), loss of skin and subcutaneous fat, thinning of hands, and the face looks like an old person. Rare symptoms of the disease include hair loss, vitamin deficiencies, diarrhea, and recurrent infections.

Diagnosis and differential diagnosis

The main indicator of the diagnosis of hypotrophy is the thickness of the subcutaneous fat layer.

Differential diagnosis. Hypotrophy should be differentiated from chondrodystrophy, bone spurs, vitamin D-resistant rickets, and vitamin D-dependent rickets.

Treatment

Treatment of patients with hypotrophy should be complex:

1. Identifying the cause of hypotrophy, eliminating it, and correcting it;
2. Diet therapy;
3. Organization of a rational regimen, education, massage, gymnastics;
4. Treatment of infectious ulcers, rickets, anemia, accompanying diseases;
5. Stimulating, symptomatic, enzyme-vitamin therapy.

Diet therapy is the basis of rational treatment in hypotrophy. The main principles of diet therapy in hypotrophy consist of a three-phase diet:

1. The period of identification of food tolerance;
2. Transition period;
3. Strong (optimal) feeding period.

The following important principles of diet therapy in hypotrophy include:

1. In the early stages of treatment, give easily digestible food products (mother's milk, sour milk, acidophilic mixtures, "Malyutka", "Malysh", "Biolakt", etc.);
2. Frequent meals (hypotrophy I-level-7 times, II-level-8 times, III-level-10 times);
3. Systematic control of eating (daily keeping, recording the amount of food eaten, the amount of liquid drunk, the amount of waste, diuresis);

The period of determining food tolerance-hypotrophy is 1-2 days in the I-level, 3-7 days in the II-level, 10-14 days in the III-level. From the first day of treatment, the amount of liquid should be given according to the actual mass of the child.

Table 7

Age	Daily water requirement, ml/kg of body weight
3 days	80-100
10 days	125-150
3 months	140-160
6 months	130-155
9 months	125-145
1 years old	120-135
2 years old	115-125
4 years old	100-110
6 years old	90-100
10 years old	70-85

On the first day of treatment, the daily volume of the mixture is given in relation to the body mass of 2/3 in hypotrophy level I, 1/2 in hypotrophy level II, and 1/3 in hypotrophy level III. Calorage is as follows: hypotrophy I - 100-105 kcal/kg; II- level - 75-80 kcal/kg; Level III-60 kcal/kg; amount of protein - 2g/kg per day in hypotrophy of I degree, II- degree - 1.5 g/kg, III- degree - 0.6-0.7 g/kg. The insufficient amount of fluid is given as enteral glucose, salt mixtures (oralit, regidron, citroglucosolone).

Restoration of the normal volume of circulating blood, correction of electrolyte metabolism, stimulation of protein synthesis are among the tasks of the first and second day in severe hypotrophy. Amino acid solutions (amino acid hydrolyzates), 5% albumin are used in parenteral nutrition. In the period of determining food tolerance, the amount of the basic mixture is increased by 10-20 ml per feeding every day.

In the transitional (intermediate) period, therapeutic mixtures (from 1/3 of the total volume) are added to the main mixture, that is, adapted mixtures containing more ingredients than mother's milk are added.

The size and composition of the meal is increased to the child's weight. To increase the amount of protein in the diet, protein mixtures and products (protein enpit, low-fat kefir, cottage cheese, egg yolk, etc.) are recommended.

The criteria for the effectiveness of diet therapy are the following: improvement of emotional state, normalization of appetite, improvement of skin and tissue turgor condition, increase of daily body weight by 20-30 g, normalization of L. I. Chulitskaya index, moderation of eating.

In the period of intensive nutrition, hypotrophy is recommended in the I-level - 140-160 kcal/kg per day, in the II-III level - 160-180 kcal/kg per day, the amount of protein is -3.5-4g/kg. The main criteria of the effectiveness of diet therapy are the following: nutrition and psychomotor status, improvement of metabolic indicators, daily body weight increase of 25-30 g/day.

If hypotrophy of the first degree is not complicated, it can be treated at home. Hypotrophy of the II and III degree is treated in an inpatient setting. The room should be clean, bright, room temperature should be 24-25 0 C. In case of hypotrophy, it is advisable to do massage and gymnastics.

Correction of intestinal dysbiosis: bifidumbacterin or bificol is used for 3 weeks to correct dysbacteriosis in hypotrophy.

Enzyme therapy - during the period of determination of food tolerance in hypotrophy, sheep enzymes are used: abomin, festal, mezim forte, creon, oshkozon juice, etc. If there is a large amount of neutral fat and fatty acids in the co-program, pancreatin, panzinorm, pancitrate are used.

Vitamin therapy - at the beginning of the disease, vitamins are prescribed parenterally, then per os. In the first days, vitamins C, V1, V6 are given. Vitamin A, RR, V 15, V5, E, folic acid, V12 are used in the 2-3 cycles of treatment.

Stimulating therapy - apilak, dibazol, pentoxyl, metatsil, pantocrine, ginseng is used. Immunoglobulin is used in severe hypotrophy with infection. For the purpose of stimulating therapy, 1 drop of 20% carnitine chloride per 1 kg of body weight is recommended (adding it to boiling water and drinking it).

Simptomatikterapiya:In order to treat anemia, iron preparations, folic acid are used, if the amount of hemoglobin is below 70 g/l, it is recommended to put an erythrocyte mass.

In the treatment of hypotrophy, the doctor must approach each child individually.

CONSEQUENCES: It depends on the elimination of the cause of hypotrophy, the presence of concomitant diseases and complications, the age of the patient, the nature of nutrition, environmental conditions, and the degree of hypotrophy.

PROPHYLAXIS

1. Natural feeding is important.
2. Early detection and rational treatment of hypogalactia.
3. Proper nutrition according to age.
4. Adequate vitaminization of food.
5. Prevention of rickets.
6. Organization of daily routine and care.
7. Early diagnosis and proper treatment of rickets, anemia, breathing, organs of the gastrointestinal system, kidneys, endocrine diseases.

Physiology of bone tissue

There are two types of bone tissue: lamellar (cortical), where collagen fibrils are aligned in the same direction, and woven (trabecular), where fibers are arranged in different directions. Cortical bone tissue forms the basis of human bones (80% of their mass), covers the outer surface of bones, bears the main load, and performs supporting and protective functions.

Embryogenesis: The formation of bone tissue begins in the second month of intrauterine life. Bone tissue develops from mesenchymal cells, in which ossification centers appear between weeks 5 and 7. By the time of birth, mesenchymal cells are usually absent. The process of ossification starts during the fetal period and involves the diaphyses of long bones, as well as some epiphyses (the upper and lower ends of the tibia, the upper end of the femur, and the cuboid bone). When the ossification centers (a total of 806) appear, the complete skeleton is formed.

Bone structure: Bone tissue is not a thin system of bone plates but a dense fibrous, reticular (mesh-like) structure. Bone canals are numerous, wide, and irregular in shape.

This version is grammatically correct and sounds natural in English. Let me know if you need any further adjustments!

The increase in bone length is especially noticeable between the ages of 2 and 3 years. Bone tissue has a remarkable regenerative capacity. For example, fractures of the clavicle, which may occur during childbirth, can heal within 5–6 days. Bones have a rich blood supply, with the terminal branches of blood vessels located within them. This contributes to the occurrence of hematogenous osteomyelitis, as infections can spread through the bloodstream and settle in the Haversian canals.

Bones contain a high percentage of water, especially in newborns—about 65%—which gradually decreases with age to approximately 20% per year. Young

children have fewer bones, and the mineral content increases as they grow. In the fetus, the mineral content reaches 39%, while by the age of 4, it increases to 47%.

Skull bones:

—A joint is formed where multiple bones connect.

—Two sutures are closed in premature babies.

—The small fontanelle remains open in 25% of newborns and may close as early as 2 months of age.

—The large fontanelle measures 2–2.5 cm in newborns and typically closes between 1 and 1.5 years of age.

Teeth:

- in the embryonic period, a derivative is formed from the 40th day
- the child is born without teeth (both milk teeth and permanent teeth are present)
- There is a definite period of teething
- milk teeth start to emerge at 6 months and end at 2 years.
- Their number is determined by the following formula: n-4, where the age of the nth child is in months (6-24 months old)
- The eruption of permanent teeth begins at the age of 5-6 and ends at the age of 11-12. Their number is determined by the following formula: 4n-20. where n-child is over 5 years old
- Wisdom teeth come out during puberty.

Muscular system

Embryogenesis of the Muscular System: Skeletal muscles develop from the mesoderm. In the third week of embryonic development, the dorsal portions of the mesoderm divide into somites, beginning at the cranial end. Segmentation then rapidly progresses in a craniocaudal direction, and by the sixth week, 39 pairs of somites are formed. Each somite differentiates into a sclerotome, a dermatome, and a myotome. Almost all striated (skeletal) muscles originate from myotomes.

In a four-week-old embryo, myotomes consist primarily of single-nucleated, round cells that later take on an elongated shape—these are known as myoblasts. Starting from the fifth week, myoblasts lose their ability to divide and synthesize DNA. Instead, they begin rapidly producing contractile proteins such as myosin and actin. These proteins form contractile filaments known as myofilaments.

By the eighth week of development, almost all of the embryo's muscles are anatomically differentiated. By the tenth week, muscle tendons are already formed. Smooth muscles develop from the mesoderm and differentiate from the mesenchyme surrounding the epithelial structures of various organs.

Dynamics of growth of muscle mass depending on the age of the child:

*23-24% in newborns

*8 years old 27-28%

*12 years 30%

*14-15 years old 32-33%

*17-18 years old 44%

Morphological features of the muscular system:

- 5 times thinner than adults
- has a well-developed interstitial tissue
- few myofibrils
- short, thin and pale
- has a small amount of contractile proteins - myzin and actin
-nuclei are round in shape
-low in fats, proteins, inorganic substances, rich in water

Innervation and Blood Supply of Muscle Units: The development of nerve endings in muscles begins long before birth, and their network continues to mature for a long time after birth. However, the proprioceptive apparatus develops at a much faster rate, surpassing the formation of motor nerve endings. By the time of birth, the neuromuscular junction has a well-developed capsule, bundles, scattered nerve fibers, and muscle spindles. With age, not only the structure but also the distribution of nerve endings in the muscles changes.

In the embryonic period and early childhood, muscle blood supply is already well developed. However, unlike in adults, the distribution of muscle vessels during this period is more diffuse or transient, whereas in adults, it becomes more structured. In general, the arterial supply to muscles is fully formed before birth.

3.1. Rickets in children

Rickets (Greek rhachis - spine) – is a childhood disease caused by metabolic disorders, primarily phosphate-calcium metabolism, leading to damage to various organs and systems, with the skeletal system being the most affected. There is not enough accurate information about the spread of the disease. According to statistics, 80% of children in England, 87.7% in the USA, 74.2% in Germany, and 80-90% in Russia have rickets.

Rickets is caused by a deficiency of vitamin D in the body, leading to a disruption of phosphorus-calcium metabolism. It is often associated with premature birth, general weakness, and artificial feeding. If a child is not properly cared for, does not spend enough time outdoors in fresh air and sunlight, or has an improper diet, vitamin D intake may be insufficient. Additionally, a lack of ultraviolet rays can impair the natural production of vitamin D in the skin, increasing the risk of rickets. Frequent illnesses and poor maternal nutrition during pregnancy can also contribute to the development of rickets.

Rickets leads to metabolic disorders and dysfunction of various organs and systems. In this disease, the metabolism of essential mineral salts, particularly phosphorus and calcium, is significantly disrupted. Calcium absorption in the intestines and its deposition in bones are altered, resulting in bone thinning, tissue softening, and dysfunction of the nervous system and internal organs.

The specific anatomical and physiological characteristics of bone structure in children depend on the formation of bone tissue. Children's bones differ from those of adults in that they contain more water and fewer minerals. This lower mineral content makes children's bones softer and more flexible compared to adult bones. When pressure is applied, a child's bone can change shape without breaking. Additionally, bone growth and repair in children differ from that of adults, allowing fractures to heal faster. Children's bones have a higher ability to withstand pressure while maintaining a degree of softness.

Rickets is most commonly seen in children under the age of two.

Etiology.

Causes and predisposing factors of primary vitamin D deficiency rickets:

1. Lack of Sunlight and Fresh Air: About 90% of endogenous vitamin D3 (cholecalciferol) is produced in the skin under the influence of sunlight. Studies have shown that for children over 1.5 years old, spending 1–2 hours in sunlight daily helps maintain a moderate level of calcitriol for a week.

2. Dietary Factors: The use of non-adapted formulas in artificial feeding, prolonged milk feeding (1 liter of breast milk contains 50–70 IU of vitamin D3, while cow's milk contains only 20–30 IU), and high phosphate content in cow's milk disrupt the calcium-phosphorus balance, preventing calcium absorption in the intestines.

Delayed introduction of complementary foods can also contribute to rickets. For example, 1 gram of egg yolk contains 140–390 IU of vitamin D3. Additionally, prolonged feeding with vegetable-based porridges without animal proteins can lead to rickets, as the child's body does not receive enough calcium, phosphorus, trace elements, vitamins, amino acids, and lipids. Furthermore, phytic acid in porridges and vegetables binds calcium in the intestines, reducing its absorption and inhibiting the uptake of vitamin D and its metabolites.

3. Perinatal Factors: Premature infants have a lower reserve of vitamin D, calcium (Ca), and phosphorus (P). The intensive transfer of Ca and P from the mother to the fetus through the placenta begins at 36 weeks of gestation. At 26 weeks, the transfer rate is approximately 100–120 mg/kg of Ca and 60 mg/kg of P per day. By 36 weeks, this increases to 120–150 mg/kg of Ca and 85 mg/kg of P per day.

Postnatal growth rates are higher in preterm infants, which increases their need for Ca, P, and vitamin D. The daily calcium requirement for full-term infants is 70–75 mg/kg, while in preterm infants, it can be as high as 200–225 mg/kg per day. In adults, this requirement drops to approximately 8 mg/kg. Similarly, the daily phosphorus requirement is 40 mg/kg for full-term infants and 110–150 mg/kg for preterm infants.

Secondary vitamin D deficiency causes of rickets include:

1. Malabsorption Syndrome – Conditions such as celiac disease, cystic fibrosis, and other pancreatic disorders impair fat absorption from food, which in turn reduces the absorption of fat-soluble vitamin D. Additionally, in exudative enteropathy and other chronic intestinal diseases, the synthesis of calcium-binding proteins and calcitriol is disrupted.

2. Chronic Liver and Kidney Diseases – These conditions reduce the formation of active metabolites of vitamin D3, leading to deficiencies.

3. Iatrogenic Factors – Long-term use of anticonvulsant drugs (e.g., phenobarbital, phenytoin) accelerates vitamin D metabolism, leading to endogenous deficiency. Prolonged use of diuretics and parenteral nutrition can cause not only calcium deficiency but also vitamin D deficiency.

4. Environmental Factors – Excessive amounts of strontium, mercury, zinc, and other metals in soil, water, and food can replace calcium in bones, contributing to the development of rickets, osteomalacia, and osteoporosis.

5. Psychosocial Factors and Lack of Physical Activity – In addition to perinatal encephalopathy, a lack of physical development activities in the family (such as massage and gymnastics) can lead to low muscle activity and reduced blood supply to bones.

6. Hereditary Anomalies of Vitamin D and Calcium-Phosphorus Metabolism – Genetic disorders affecting the metabolism of these essential nutrients can contribute to deficiencies and bone-related diseases.

7. Hereditary Metabolic Disorders – Conditions such as cystinuria and tyrosinemia can interfere with normal metabolic processes, leading to deficiencies.

8. Polyhypovitaminosis – A deficiency of multiple vitamins can further contribute to metabolic and developmental issues.

9. Chronic Infectious Diseases – Persistent infections can negatively impact overall metabolism and nutrient absorption, further exacerbating deficiencies.

The main functions of vitamin D:

1. Vitamin D – Enhances the synthesis of calcium-binding proteins in the intestines, ensuring the absorption of calcium (Ca) and phosphorus (P).

2. Bone Health – Stimulates bone mineralization by increasing citrate synthesis at the blood-bone interface.

3. Osteocalcin Synthesis – Promotes the production of osteocalcin (the main non-collagenous bone protein and a key marker of ossification) by osteoblasts.

4. Calcium Storage – Facilitates calcium accumulation in bones.

5. Blood pH Regulation – Helps maintain the acid-base balance of the blood.

6. Renal Function – Ensures the reabsorption of Ca and P in the renal tubules.

7. Immune Function – Exhibits immunomodulatory properties; in cases of vitamin D deficiency, phagocytosis, interleukin-1 and -2, and interferon synthesis decrease, weakening the immune response.

8. Muscle Function – Binds to muscle receptors, accelerates calcium transport into muscle cells, and enhances muscle contractility.

Pathogenesis of rickets

The state of hypovitaminosis D in the body reduces the synthesis of calcium-binding proteins in the intestines, impairs calcium absorption, decreases the ability of bones to fix calcium, and reduces the synthesis of citrates in tissues. As a result of hypocalcemia in the blood, the function of the parathyroid glands is disrupted, leading to increased production of parathyroid hormone. Parathyroid hormone promotes the release of calcium from bones into the bloodstream, enhances osteoclast activity, and suppresses osteoblast synthesis. Additionally, it inhibits the reabsorption of phosphates, bicarbonates, and amino acids in the renal tubules, increasing their excretion in the urine. This characteristic of parathyroid hormone leads to hypophosphatemia and metabolic acidosis in rickets. Hypophosphatemia causes a rapid release of phosphorus from organic compounds, primarily from the phosphatides of the myelin sheath in nerve fibers and nerve cells, as well as from adenosine phosphoric acid in muscle tissue. Demyelination first leads to increased excitability, followed by alternating inhibitory reactions. This results in impaired energy metabolism in muscle tissue and a decrease in muscle tone. This condition is accompanied by signs of increased excitability of the autonomic nervous system, including excessive sweating, sleep disturbances, sensations of flying and falling, and restlessness. In rickets, the level of alkaline phosphatase in the blood serum increases, but its significance is not yet fully understood. However, some scientists associate this increase with the release of phosphorus from organic compounds. Hyperparathyroidism and vitamin D deficiency lead to increased excretion of amino acids in the urine, a condition known as aminoaciduria. The structure of collagen protein, which forms the organic matrix of bones, is disrupted. A deficiency of the active metabolite of

vitamin D, along with imbalances in calcium, phosphorus, and citrate metabolism, leads to impaired osteogenesis. The leaching of calcium from bones results in osteoporosis. Bones gradually soften and bend under pressure, while bone calcification slows down. Calcium and phosphorus salts are not adequately deposited in osteoid tissue, and normal bone resorption is impaired. In the growth zone, osteoid cells divide irregularly and proliferate excessively, leading to the expansion of bone tissue at the epiphysis and growth points of tubular bones (osteoid tissue hyperplasia). At the same time, bones fail to grow properly, resulting in bone tissue hypoplasia.

Based on the above pathological conditions, changes in the bone system in rickets can be divided into 4 groups.

1. Symptoms of osteomalacia – softening of bones. In this condition the resorption of old bone cells occurs, leading to skull softening (craniotabes), softening of the periosteum, brachycephaly, as well as bending and softening of long bones, the spine, and ribs (Figure 8).

2. Symptoms of osteoid hyperplasia – these symptoms predominate in the subacute course of rickets. They include prominent forehead and crown, rickets bracelets, pearl strings, and rickets beads.. (Figure 9)

Figure 8

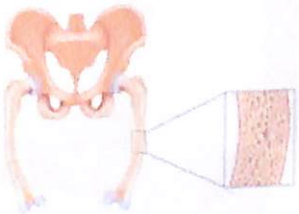
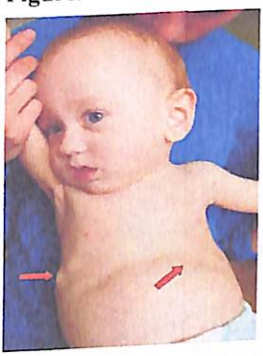


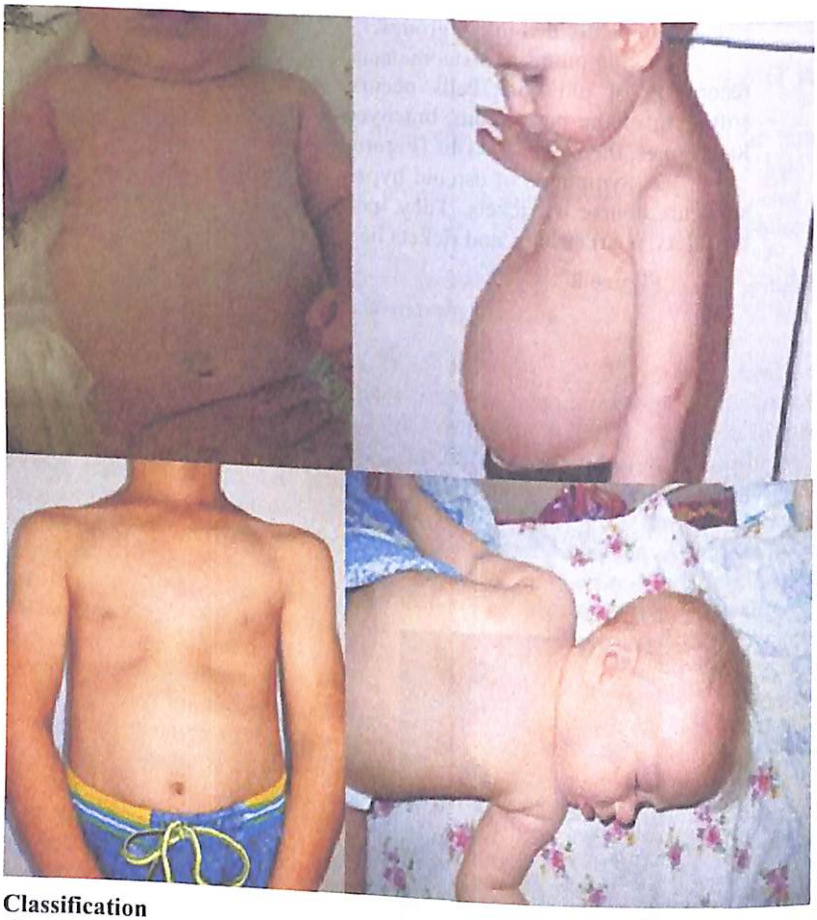
Figure9



3. Symptoms of bone tissue hypoplasia – shortened legs due to delayed growth of tubular bones, delayed eruption of primary and permanent teeth, late closure of the maxillary sinus, flat pelvis, underdeveloped lower jaw, and saddle nose.

4. Bone deformations caused by muscle hypotonia – curvature of the spine (lordosis, kyphosis, scoliosis) and chest deformities characterized by lower aperture curvature, such as pigeon chest (pectus carinatum) and funnel chest (pectus excavatum). (Fig. 10)

Figure 10



Classification

The classification of rickets was adopted in 1947 at the VI meeting of the All-Union of Pediatricians (S.O. Dulitsky). E.M. Additions were made by Lukyanova and co-authors in 1988 (Table 4).

Table 8

Classification of vitamin D deficiency rickets

Depeding on the period	Activity level	Passing	By type of crossing
Initial The peak period Recovery period -Period of residual complications	I - mild degree II- moderately severe level III- severe level	Sharp Acute under Relapsing rickets	Calcipenic type Phosphopenic type Calcium and phosphorus content type without obvious changes

Clinical picture

The clinic of the disease depends on the age of the child, the phase, period, duration and severity of the disease. The disease is often observed in late autumn and winter.

In the course of the disease, the following main periods are distinguished:

- Initial period.
- A period of climax.
- The period of convalescence.
- Period of residual complications.

The initial symptoms of rickets appear when a child is 1.5–2 months old, while in premature infants, they may appear as early as 3–4 weeks of age. The first symptoms are primarily characterized by functional changes in the nervous system:

The child sweats excessively without an apparent cause, leading to heat rash, skin tightness, itching of the nape, and hair loss.

The child becomes irritable and fussy for no apparent reason and experiences restless sleep.

The initial stage of rickets lasts from 2–3 weeks to 2–3 months. By the end of this period, changes in bone tissue become noticeable—particularly the softening of the edges of bones forming large joints.

If the disease is not diagnosed and treated in its early stage, it progresses to the second stage, during which changes affect multiple systems and organs, and bone-related symptoms become more pronounced.

Bone changes occur depending on the child's physical development and caregiving practices. For example, due to the softening and increased flexibility of the bones, prolonged positioning in the same posture, breastfeeding from only one side, or excessive time spent lying in a crib can cause deformations in the bones subjected to pressure.

The back of the head becomes flattened

Bumps appear on the forehead and crown bones

The skull may tilt in different directions

The chest takes on characteristic deformities, such as "pigeon chest" (pectus carinatum) or "cobbler's chest" (pectus excavatum)

"Rickets bracelets" – enlargements at the lower ends of the wrist bones

Narrowing of the small pelvis

O-shaped or X-shaped legs

Curvature of the spine, including kyphosis in the lower thoracic and lumbar regions, scoliosis (thoracic region), and lordosis (lumbar region)

Delayed and improper eruption of teeth

In addition to bone deformities, rickets also leads to decreased muscle and ligament tone, a hallmark sign of hypotonia.

During the peak stage of the disease, the symptoms worsen, and functional impairments appear in the respiratory and cardiovascular systems.

The convalescence period is marked by the gradual weakening of rickets symptoms, followed by recovery. The first improvements occur in the nervous system, bones begin to harden, teeth erupt, static and motor functions develop, and the liver and spleen return to normal size. Additionally, functional changes in internal organs gradually resolve.

Residual signs of rickets are typically observed in 2–3-year-old children who have experienced moderate or severe (Grade II or III) rickets. These signs may include changes in the shape of teeth and bones, occasional enlargement of the liver and spleen, and varying degrees of anemia.

Rickets is classified into three degrees based on the severity of clinical manifestations:

Grade I (mild) – minimal bone tissue changes

Grade II (moderate) – clearly developed symptoms

Grade III (severe) – now rarely observed

Rickets can follow acute, subacute, or recurrent courses.

It is not possible to diagnose rickets solely based on symptoms such as delayed growth, late eruption of the first teeth, or delayed motor development, as these signs may also be present in children with other unrelated pathological conditions.

Complications. If the disease is not diagnosed in time and appropriate specific and non-specific treatment measures are not taken, it can lead to severe and irreversible residual complications affecting the child's stature and bone system.

These complications include: Pathological conditions due to abnormal head positioning. Breathing problems caused by chest deformities. Pelvic bone deformities, particularly concerning for future mothers, which can lead to complications during childbirth. Excessive curvature of the legs (severe bowing or knock-knees)

The consequence. If rickets is detected in time and appropriate treatment is carried out, the outcome will end without complications. Only in some cases, cases of

the above-mentioned complications can be observed as a result of negligence of mothers.

Treatment and care. Treatment of rickets depends on the severity, course and duration of the disease, and the main methods of treatment include diet and hygiene, vitamin D and physiotherapeutic procedures.

Prevention of rickets: Prevention of rickets includes both non-specific and specific measures, each of which consists of prenatal and postnatal preventive strategies.

Non-Specific Prevention

Prenatal (Antenatal) Measures

Non-specific prevention before childbirth focuses on ensuring optimal conditions for the pregnant woman, including:

A nutrient-rich and diverse diet enriched with vitamins

Maintaining a balanced work-rest schedule

Following hygiene rules

Spending ample time outdoors for fresh air and sunlight

Postnatal Measures

After childbirth, the following basic non-specific preventive measures should be implemented:

1. Proper breastfeeding practices and timely introduction of vegetable or fruit purees
2. Prolonged outdoor exposure, maintaining hygiene in the child's environment, and following a daily routine suitable for the child's age
3. Refreshing treatments, such as air and light-air baths
4. Regular massage and physical exercises (gymnastics)
5. Protecting the child from infectious diseases as much as possible

ANATOMO-PHYSIOLOGICAL CHARACTERISTICS OF THE RESPIRATORY SYSTEM

Embryogenesis of respiratory organs

From the third week of embryonic development, the respiratory organs begin to form and continue developing for a long time after the child's birth. In the 3rd week of embryogenesis, a bulge appears in the neck region of the endodermal tube, which begins to grow rapidly. In the 4th week, it divides into the right and left parts—the future right and left lungs. Each of them, in turn, branches like a tree. The bronchial mucosa, muscles, and tendons are formed from the mesodermal mesenchyme. The skeleton of the trachea and bronchi begins to develop from the 10th week of fetal development. The canalicular phase (recanalization) lasts from 16 to 26 weeks. During this period, the formation of the bronchial cavity continues, along with the development and vascularization of the respiratory part of the lungs.

The final phase (alveolar)—the period of alveoli formation—begins in the 24th week. The formation of alveoli is not completed at birth and continues during the postnatal period. In children, the respiratory organs are relatively small and are not fully developed anatomically or histologically. Young children have relatively small noses, narrow nasal passages, and lack lower nasal passages. The nasal mucous membrane is thin, relatively dry, and rich in blood vessels. Due to the narrowness of

the nasal passages and their abundant blood supply, even slight inflammation can make nasal breathing difficult for infants. During the first six months of life, a child cannot breathe through the mouth because the upper airway is compressed by the tongue due to its relatively large size. In early childhood, the nasal passage (choanae) remains narrow, often causing prolonged nasal breathing difficulties.

Peculiarities of gas exchange according to age

Gas exchange in the fetus occurs through the placenta. Maternal blood flows through the uterine arteries into the lacunae between the villi. In turn, fetal blood reaches the placenta via the umbilical arteries, where capillary vessels extend into the lacunae between the widely branched villi. The barrier separating maternal and fetal blood is approximately 3.5 microns thick and consists of three layers. The partial pressure of oxygen (pO_2) in maternal blood is relatively low because it is mixed blood. As a result, the pO_2 in the blood entering the fetus through the umbilical vein averages around 60 mmHg (8 kPa). However, the low pO_2 in fetal blood is compensated by the high oxygen affinity of fetal hemoglobin. Additionally, an increased number of erythrocytes ensures an adequate oxygen supply, allowing up to 16–17 ml of oxygen per liter of blood. Furthermore, due to the unique characteristics of fetal circulation, oxygen-rich blood is preferentially directed to vital organs such as the brain and heart. Because of the lower oxygenation levels in other fetal organs, ATP is generated not only through oxidative metabolism but also anaerobically. This adaptation makes fetal tissues more resistant to hypoxia.

First breath. Low-amplitude respiratory movements are observed during fetal development. During childbirth, gas exchange through the placenta is disrupted, leading to hypoxia and hypercapnia. At this moment, the sensitivity of chemoreceptors suddenly increases, and the combined effect of hypoxia and hypercapnia stimulates respiratory activity. Approximately 40% of the fetal lungs are filled with cerebrospinal fluid (CSF), which is synthesized by alveolar cells. As the fetus passes through the birth canal, some of this fluid is squeezed out. However, the remaining fluid in the airways makes it difficult for the newborn to take its first breath, requiring significant effort to overcome surface tension. A crucial factor in initiating respiration is clamping the umbilical cord, which causes an increase in CO_2 levels in the newborn's blood. When CO_2 reaches a critical level, inspiratory neurons are stimulated through central chemoreceptors, triggering the first breath. During this process, the intrapleural pressure in a newborn can drop to -30 mmHg. Initially, the lungs do not fully expand uniformly, but the continuous absorption of residual fluid and the biosynthesis of surfactant help stabilize the alveoli. Full and uniform lung ventilation is typically achieved within a few days after birth. During aging, various changes occur in the respiratory system. In men, lung vital capacity decreases, anatomical and physiological dead space increases, breathing rate accelerates, lung elasticity diminishes, and the number of capillaries in the alveolar walls declines. As a result, gas diffusion in the lungs becomes less efficient, particularly during physical exertion. Maximum oxygen uptake is reduced, the alveolar-arterial O_2 gradient decreases, and arterial oxygen pressure declines, while CO_2 levels remain unchanged.

Anatomical-physiological characteristics of respiratory organs

The members of the respiratory system include:

- Nose;
-Additional spaces;
- Pharynx;
- Larynx;
-Bronchial tree;
- Lungs.

The main functions of the respiratory system:

- Supplying the body with oxygen;
- Release of carbon dioxide from the body;
- Distribution of air for gas exchange.

Air enters the body through the nose, larynx, trachea, bronchi, and lungs, where gas exchange occurs in the alveoli. The circulatory system ensures the distribution of oxygen to all body cells. In children of different ages, the respiratory organs have unique structural, functional, and physiological characteristics, which influence the course of broncho-pulmonary diseases. Understanding these features is essential for ensuring optimal respiratory development. In cases of pathological conditions, this knowledge enables the provision of appropriate care and treatment, as well as the development of effective preventive measures.

Morphological features of respiratory organs.

Characteristics of the upper respiratory tract.

In children of early age, the upper respiratory tract is morphologically incomplete.

Characteristics of the nose in children

The incomplete development of the facial part of the skull results in a small nose. Nasal passages are narrow, and infants do not have a fully formed lower nasal passage; its development is completed by the age of four. As the nasal passages widen, the choanae undergo intensive development. The nasal mucous membrane is thin, delicate, and rich in blood vessels. Due to the abundance of blood vessels and the narrowness of the nasal passages, even mild inflammation can cause rapid swelling, leading to nasal obstruction. As a result, infants may struggle to breathe through the nose, even with mild rhinitis, which can interfere with sucking and potentially lead to respiratory distress. The submucosal layer contains less cavernous tissue, making nosebleeds rare in early childhood. Cavernous tissue develops significantly between the ages of 8 and 9, which coincides with the onset of puberty. Consequently, nosebleeds are uncommon in children under one year of age.

The relatively wide nasolacrimal duct and the underdevelopment of its valves create conditions for infections to spread from the nose to the mucous membrane of the eye, increasing the risk of inflammation.

As atmospheric air passes through the nose, it is warmed, moistened, and filtered. The nasal cavity secretes 0.5–1 liter of mucus per day. Every 10 minutes, new mucus containing bactericidal substances (such as lysozyme and complement) and secretory immunoglobulin A flows through the nasopharynx, helping to protect against infections.

In premature infants, the paranasal sinuses are underdeveloped:

The maxillary sinus begins developing in the third month of fetal life, while the ethmoidal sinus develops by the sixth month. However, in newborns, these sinuses are small and not fully formed. On X-ray, they become visible at around three months of age. The complete formation of the sinuses and their pore-like structures is completed between the ages of 15 and 20.

The frontal and sphenoid sinuses are absent in early childhood. A small frontal sinus cavity begins to appear around the age of two, with development starting at age seven and completing by 15–20 years.

Clinical Significance: Due to the underdevelopment of the paranasal sinuses, young children are less likely to experience the spread of infections from the nose and nasopharynx to the frontal and sphenoid sinuses. Sinusitis, ethmoiditis, and frontal sinus infections are rare in infancy. Instead, young children more commonly develop sinusopathy, characterized by reduced air content in the sinuses following upper respiratory tract inflammation.

Distinctive features of larynx:

In young children, the auditory tube is short, wide, and positioned more horizontally compared to adults. The ear canal, which connects the outer ear to the middle ear, is also short, narrow, and relatively straight.

Clinical Significance: Due to these anatomical features, infections can easily spread from the nasopharynx to the middle ear. As a result, children are more prone to developing otitis media, especially during upper respiratory tract infections.

The pharyngeal lymphoid ring (Waldeyer's ring) consists of six tonsils and is underdeveloped in newborns; crypts and blood vessels in the tonsils are weakly developed. The tonsils become visible only by the end of the first year of a child's life. Between the ages of 4 and 10, the tonsils develop significantly and may undergo hypertrophy. During adolescence, they begin to undergo involution (atrophy).

Clinical significance:

Angina (acute tonsillitis) is not observed in children under one year of age. The tonsils act as a special filter for microbes, but frequent inflammatory processes in them can lead to the development of chronic infection foci, causing general intoxication and sensitization of the body.

The growth of adenoids (pharyngeal tonsils) is most commonly observed in children with constitutional anomalies, particularly in those with lymphatic-hypoplastic diathesis.

Clinical Significance:

In children, hypertrophy of the pharyngeal tonsils (adenoids) often occurs, leading to obstruction of the posterior nasal passages (choanae), making nasal breathing difficult. If the adenoids enlarge significantly (Grade 1.5–2 and beyond), surgical removal is recommended. Enlarged adenoids impair nasal breathing, forcing the child to breathe through the mouth. This results in air entering the lungs without being properly filtered and warmed, increasing susceptibility to respiratory infections.

Prolonged mouth breathing can lead to characteristic facial changes, known as "adenoid facies", which include:

A wide nasal bridge

A nasal voice (hyponasal speech)

Constantly open mouth
Snoring during sleep

Additionally, mouth breathing can negatively impact cognitive function, as reduced oxygen intake may impair concentration and learning. It can also affect posture and contribute to improper bite formation due to altered jaw development.

Anatomical and Functional Features of the Larynx in Children

Shaped like a water droplet
Narrow laryngeal space
Cartilages are delicate and soft
Relatively short in length
The mucous membrane is thin, delicate, and rich in blood vessels
The vocal fold is narrow in children under 6–7 years old
The vocal cords are short

In early childhood, the vocal folds are significantly narrower than in adults. Young children have shorter vocal cords, which results in higher-pitched voices. Around the age of 12, boys' vocal cords begin to lengthen more than those of girls, leading to deeper voices in males.

Clinical Significance: Due to these anatomical characteristics, even mild inflammation of the laryngeal mucosa can lead to stenotic changes (narrowing of the airway) in young children. This makes them more susceptible to laryngeal obstruction and respiratory distress, especially in conditions like croup. Additionally, high neuromuscular excitability in young children contributes to voice instability. Hoarseness is frequently observed after prolonged shouting, often not due to inflammation, but due to rapid fatigue caused by the relative weakness of the vocal cord muscles

Features of the lower respiratory tract

Characteristics of the Trachea in Children

Narrow lumen
Shaped like a water droplet
Thin mucous membrane, rich in blood vessels
Poorly developed mucous glands

In newborns, the upper border of the trachea is located at the level of the C4 vertebra and gradually descends to the level of C7 with age, similar to adults.

The trachea in newborns consists of 12–20 cartilage semi-rings, a number that remains constant throughout life.

The cartilaginous semi-rings are soft and pliable.

Elastic fibers in the semi-rings are underdeveloped.

In young children, the membranous (posterior) part of the trachea accounts for 1/3 of its circumference, while in older children, it is 1/5.

Clinical Significance: Due to the specific anatomical structure of the trachea, inflammation can rapidly lead to stenotic symptoms. This is commonly observed in:

Isolated tracheitis
Laryngotracheitis (combined with laryngeal inflammation)
Tracheobronchitis (combined with bronchial inflammation)

Additionally, the high mobility of the trachea makes it prone to displacement in unilateral pathological conditions such as exudate accumulation or tumors.

Specific structure of bronchi in children

By the time a child is born, the bronchial tree is fully formed, and the number of its branches remains unchanged throughout life. In newborns, the bifurcation of the trachea is located higher (at the level of the T3 vertebra), whereas in adults, it is at T5. The right bronchus is a direct continuation of the trachea and is positioned almost vertically. The left bronchus branches off at an approximately 90-degree angle. The bronchial walls are highly elastic, soft, and durable, allowing for easy movement. In newborns and infants (up to 1 month old), the inner layer of the bronchial wall is particularly well developed. The mucous membrane is thin and rich in blood vessels. The mucous glands in the bronchi are underdeveloped, resulting in relatively dry airways and insufficient humidification of inhaled air. The muscles and elastic tissue of the bronchi are weakly developed. Ciliary motility in the respiratory epithelium is reduced, affecting mucus clearance.

Clinical Significance:

Due to the vertical position of the right bronchus, foreign bodies enter it in 90% of cases. The immaturity of mucous glands makes the airways prone to dryness, reducing their ability to trap and expel pathogens. Weak bronchial muscles and ciliary function contribute to poor mucus clearance, increasing susceptibility to respiratory infections and bronchial obstruction.

Slowed bronchial motility reduces the drainage and cleansing function of the bronchial tree. Blockage of small bronchi with infected mucus can lead to lung tissue collapse (atelectasis) and subsequent damage. In young children, a weak cough reflex makes it difficult to clear mucus from the airways, increasing the risk of respiratory infections and airway obstruction.

SPECIFIC CHARACTERISTICS OF LUNGS IN CHILDREN:

Like adults, the left lung has two lobes (upper and lower), while the right lung has three lobes (upper, middle, and lower).

The segmental structure of the lungs is well developed at birth:

The right lung consists of 10 segments.

The left lung consists of 9 segments.

Segmental divisions:

The upper lobes (left and right) contain three segments (1st, 2nd, and 3rd).

The middle lobe of the right lung contains two segments (4th and 5th).

The lingular segment (equivalent to the middle lobe) of the left lung consists of two segments (4th and 5th).

The lower lobe of the right lung has five segments (6th, 7th, 8th, 9th, and 10th).

The lower lobe of the left lung has four segments (6th, 8th, 9th, and 10th).

Clinical Significance:

In children, pneumonia often develops in specific segments (2, 4, 5, 6, and 10) due to:

Differences in aeration (air distribution).

Variations in bronchial drainage activity.

Impaired mucus clearance, which increases susceptibility to infection.

Developmental Differences in Children's Lungs:

Lung development is uneven across different lobes.

In infants under 1 year, the upper lobe of the left lung is poorly developed.

In newborns, the middle and lower lobes of the right lung are of equal size.

By the age of 2 years, the proportion of lung lobes becomes similar to that of adults.

In newborns: The terminal bronchi end in sac-like structures instead of fully developed alveoli.

New alveoli form from the edges of these sacs.

The number of pulmonary sinuses is three times lower than in adults.

The fissures (separating lung lobes) are not well-defined.

Clinical significance

Diffuse spread of pathological processes due to the absence of pleural separation between lung segments.

The segmental structure of children's lungs is similar to that of adults, with 10 segments in each lung.

In children, the lung root contains numerous blood and lymphatic vessels, as well as lymph nodes.

Tuberculous bronchoadenitis is more common in children due to increased lymphatic involvement in the lung root. The root of the right lung is positioned higher than the left.

Developmental Differences in Alveoli: In children, alveoli are single-chambered and wider, but their size is four times smaller than in adults. The total number of alveoli in newborns (24 million) is 10–12 times lower than in adults. Alveolar diameter in newborns is 0.05 mm, whereas in adults, it ranges from 0.2–0.25 mm. The elastic framework of the lungs is underdeveloped, with sparse connective tissue predominating.

Predisposition to Atelectasis and Emphysema in Early Childhood:

Atelectasis and emphysema are more common in young children, primarily due to: Low surfactant production, especially in premature infants. Lower lung aeration and increased vascularity in newborns. Underdeveloped elastic tissue, making the lungs more prone to overinflation (emphysema) or collapse (atelectasis). Limited chest excursion and narrow bronchi, further increasing the risk of atelectasis.

Gas Exchange Efficiency in Children: The amount of blood passing through the lungs per unit of time is greater in children than in adults, which provides more efficient gas exchange.

Functional characteristics of respiratory organs

1. Newborns and infants breathe frequently and superficially.

2. The younger the child, the faster their respiratory rate. This compensates for lower tidal volume (amount of air per breath) by increasing the number of breaths to maintain adequate oxygen supply.

3. Breathing depth and tidal volume are lower in children compared to adults. This is due to smaller lung mass and differences in chest structure. In infants, the anteroposterior and lateral chest dimensions are nearly equal, making the chest appear

as if it is in a constant inspiratory position. The ribs are more horizontal, forming a nearly right angle with the spine, which limits rib cage expansion and results in diaphragmatic (abdominal) breathing at this age. A full stomach and intestinal distension can further restrict chest movement. As the child grows, the chest gradually transitions to a more adult-like shape, improving lung expansion.

By 6–7 years of age, girls typically develop thoracic (chest) breathing, while boys predominantly use abdominal (diaphragmatic) breathing.

4. The number of breaths in children depends on their age:

in newborns - 40-60

At 6 months - 35-40

1 year old - 30-35

5 years old - 25

10 years old - 20

For people over 10 years old - 18-16.

5. Breathing in newborns and infants is arrhythmic.

6. Short-term apnea (temporary cessation of breathing for 5–10 seconds) is common in newborns, especially in premature infants.

This occurs due to immature development of the respiratory center and a tendency toward hypoxia (low oxygen levels).

The breathing rhythm is irregular and inconsistent in early life.

7. At birth, tidal volume (the amount of air per breath) is low:

Newborns: 15–20 ml

1-year-old: 60–80 ml

5-year-old: 150 ml

12-year-old: 200–250 ml

Adults: 500 ml (on average)

Minute ventilation (total air exchanged per minute):

Newborns: 600–700 ml

Adults: 6–9 liters

Since newborns have a low tidal volume, they compensate by breathing more frequently to meet oxygen demands.

8. Gas exchange in infants is highly efficient due to: Lungs being rich in blood vessels, allowing for rapid oxygen diffusion.

High diffusion capacity, ensuring intensive oxygen exchange to meet metabolic demands.

Clinical significance:

Rapid metabolic processes and immature enzymatic systems in children contribute to the rapid development of acidosis in respiratory diseases.

Gas exchange in the lungs occurs over a surface area of 50–90 m^2, with a lung membrane thickness of 0.4–1.5 μm.

Factors Affecting Gas Exchange:

Gas diffusion across the alveolar-capillary membrane depends on:

1. Surface area (S) – The larger the surface, the more efficient the exchange.
2. Membrane thickness (L) – Thicker membranes slow diffusion.

3. Gas pressure gradient (ΔP) – The difference in partial pressures between alveolar air and blood.

4. Diffusion coefficient (K) – Determined by the gas solubility and molecular weight.

5. Membrane condition – Any structural damage can impair diffusion.

Mechanism of Gas Exchange:

Gases move across the membrane by diffusion, driven by partial pressure gradients.

They pass through:

Alveolar epithelium

Iterstitial space

Capillary endothelium

Plasma and red blood cells (RBCs). Each gas molecule must cross 5 cellular layers and a basement membrane, dissolving in 5 aqueous solutions, including blood plasma and RBCs.

Carbon Dioxide vs. Oxygen Diffusion: CO_2 dissolves 20 times more efficiently in lipids than O_2. Despite its lower pressure gradient (CO_2 = 6 mmHg vs. O_2 = 60 mmHg), CO_2 diffuses faster across the lung membrane than O_2.

When blood passes through pulmonary capillaries:

CO_2 equilibrates within 0.2–0.25 seconds.

O_2 takes about 1 second to equilibrate.

A child's need for oxygen is greater than an adult's. In children under 1 year of age, the need for oxygen is 8 ml/min per 1 kg of body mass, in adults - 4.5 ml/min. The shallowness of breathing is compensated by the large number of breaths (in newborns - 40-60 breaths in 1 minute, in 1 year - 30-35, in 5 years - 25, in 10 years - 20, in adults - 16-18) and the participation of a large part of the lungs in breathing. Due to the large number of breaths, the minute volume of breath in children of early age is twice as high as in adults per 1 kg of body mass. The vital capacity of the lungs (VFC), that is, the volume (in milliliters) of a deep breath after a deep breath, is lower in children than in adults. HTS increases in parallel with the growth of alveoli.

Thus, the anatomical and functional characteristics of the respiratory system in children cause respiratory disorders to develop faster in children than in adults.

When examining children with respiratory pathology, the following should be determined:

1).in this patient, the respiratory organs are mainly damaged;

2). where the main pathological process is located - in the upper respiratory tract, larynx, bronchi, lungs, pleura, chest cavity;

3). Whether the nature of the process in the bronchus-lung is diffuse (spread) or local;

4). type of ventilation disorder - obstructive or restrictive;

5) whether this process is acute or repeated chronic process;

6). Is the disease related to infection? Any infection (virus, bacteria, etc.) can be the causative factor;

7).allergic factor for the development of the disease, its type;

8).or having a genetic predisposition to developing sickness;

9). the consequences of the disease for the patient's life and the possibility of permanent changes;

10). What was the effect of the previous treatment.

By answering these questions, or at least some of them, it is possible to perform a differential diagnosis of diseases based on symptoms and syndromes during the initial examination and determine the need for additional tests.

Common symptoms of respiratory diseases include:

Cyanosis

Shortness of breath (dyspnea)

Cough

Chest pain

The pale pink color of the skin and mucous membranes in a healthy child depends on the oxygen saturation of hemoglobin in arterial and capillary blood. Under normal conditions, this saturation reaches a maximum of 95-96% in the arteries. Each gram of hemoglobin can bind 1.39 ml of oxygen. Every 100 ml of plasma can transport 0.3 ml of dissolved oxygen. 100 ml of arterial blood contains 19-20 ml of oxygen, while the same volume of venous blood contains 13-15 ml of oxygen. During intense crying or screaming, arterial oxygen saturation may drop to 92%, but this is considered physiological. Any further decrease beyond this threshold is considered pathological and may indicate hypoxia.

Semiotics of damage to respiratory organs in children and methods of examination.

Getting to know a sick child begins with a patient history assessment (collecting complaints, life history, and illness history).

Children with respiratory pathologies often experience cough, which is a reflex response triggered by stimulation of the vagus nerve and lingual nerve endings. Coughs can be classified as dry or wet, each with distinct characteristics:

1) Dry Cough

When assessing a dry cough, it is important to determine:

Whether it is associated with voice changes

The time of day it worsens

Whether it is accompanied by wheezing, noisy or "whistling" breath

Its duration and periodicity

Clinical significance:

A dry, nocturnal, wheezing, and noisy "whistling" breath is characteristic of bronchial asthma.

An evening cough with hoarseness suggests acute obstructive laryngotracheitis (croup).

2) Wet (Productive) Cough

When assessing a wet cough, it is necessary to evaluate:

The color and nature of sputum:

White → Indicates mucous inflammation

Yellow-green → Suggests a purulent infection

Quantity and odor of the sputum

Recurrent nature (whether it clears freely or remains obstructed). In young children, sputum may need to be induced for evaluation by gently touching the root of the tongue with a spatula.

Clinical Indicators of Sputum Color:

Rust-colored sputum → Suggests lobar (croupous) pneumonia

Clear, foamy red sputum → Indicates pulmonary hemorrhage

Cough is characteristic in various diseases of respiratory organs:

- In the evening, repeated and reddening of the face, followed by vomiting - this is observed from whooping cough;
- wet cough or short cough - for the initial stage of pneumonia, typical for tuberculosis;
- Straining cough - in ORI;
- With strong straining expectoration of frothy sputum - in pulmonary edema;
- Constant cough due to a foreign body in the respiratory tract, ORI, laryngotracheitis;
- Dry, rough, as if "in a barrel", if it bothers for a long time - in tracheitis;
- Morning wet cough - in sinusitis, ethmoiditis;
- Periodic wet cough - in abscess, bronchiectasis;
- Superficial cough - in pleurisy;
- Bitonal, spastic cough - in tuberculosis bronchoadenitis.

The next most common complaint is wheezing. What is the cause of its occurrence, how long it lasts and changes in dynamics; It is necessary to determine whether it develops at rest or during physical exertion, what it continues with, the effect on the act of breathing.

Other complaints are increased body temperature, general weakness, lethargy, rapid fatigue, difficulty breathing through the nose, change in voice, change in skin color, lagging behind in physical development.

An objective examination of the respiratory system begins with:

I. Physical examination of the patient, in which the following are assessed:

1. Physical development (may be unsatisfactory in case of lung hypoplasia, cystic fibrosis, chronic pneumonia, fibrosing alveolitis, severe form of bronchial asthma);

2. The condition of the patient (orthopnea - in bronchial asthma, with the affected side - in exudative pleurisy);

3. The child's voice (suffocates or disappears (aphonia)) - in laryngitis, as if speaking through the nose - in sinusitis, adenoitis;

- rough, low voice - mexidema;
- the child screams (cries) - (low - was born with asphyxia, increased during sucking or pressing on the ear - in case of ear inflammation);
- wheezing - in children with bronchopulmonary pathology (pneumonia, pleuropneumonia);

4. The condition of the skin and mucous membranes (cyanosis, acrocyanosis, or total cyanosis of the nasopharyngeal triangle is typical for the pathology of the respiratory organs), its character, the time of development or the time of its symptom intensification should be determined;

- cyanosis in severe forms of pneumonia, congenital broncho-pulmonary pathologies, etc. observed;

5. Condition of nails (bruising, "hourglass" type deformation, thickening of the tip of the finger in the form of a "drum stick" - in chronic broncho-pulmonary pathology);

6. Head position (movement of the head during the act of breathing in children of breast-feeding age - a sign of respiratory failure, in newborns, the swelling of the nasal wings and the separation of foamy discharge in the corner of the mouth - in pneumonia, alveolitis, pulmonary edema);

7. Nasal area - presence or absence of discharge and its nature (clear, mucous - flu, laryngitis, allergic rhinosinusitis; mucous-purulent - sinusitis, diphtheria; mixed with blood - foreign body in the nose);

- the condition of breathing through the nose (contaminated - rhinitis, sinusitis, adenoid, foreign body);

8. Examination of the palate (performed after a complete physical examination in young children), the condition of the mucous membrane of the tonsils, its size, the presence of a wound, pus, and the condition of the back wall of the palate;

9. During the examination, it is necessary to pay attention to the shape, configuration, symmetry of the chest, equal participation of both sides in the act of breathing, and the participation of auxiliary muscles in the act of breathing;

- barrel-shaped chest in bronchial asthma, similar to "chicken" chest - in chronic diseases of the bronchus-pulmonary system;

- asymmetric - in chronic pneumonia, tuberculosis, congenital lobar emphysema;

- one side of the chest is left behind during breathing in massive inflammations of the lungs, dry pleurisy;

10. Determining the number and type of breath (superficial - in pleurisy, bronchial asthma);

tachypnea - physiological in newborns, in older children - during excitement and physical exertion, respiratory diseases, anemia, fever, heart diseases, pain syndrome;

bradypnoea - (decreased breathing rate) - in distress syndrome in newborns, coma, poisoning, etc.);

Involvement of auxiliary muscles in the act of breathing is a sign of respiratory failure;

inspiratory wheezing (habitual loud breathing, often when there is an obstruction in the upper respiratory tract, tension of the upper spine and the suprathoracic cavity when breathing during examination, intensive contraction of muscles (in laryngitis, foreign body in the respiratory tract, tumor and cysts));

high inspiratory wheezing (stridor) is a physiological condition that develops due to incomplete development of the larynx, decreases and disappears with age;

expiratory wheezing (difficult, prolonged breathing, in which the breath is noisy) - in obstructive bronchitis, bronchiolitis, bronchial asthma (based on the spasm of small bronchi and bronchioles and the muscles of the anterior abdominal wall are involved in the act of breathing);

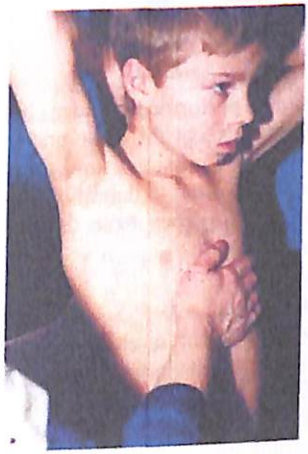
Shik's wheezing (expiratory wheezing that develops as a result of compression of the root of the lung, the lower part of the trachea and bronchi by lymph nodes in children under 2 years old);

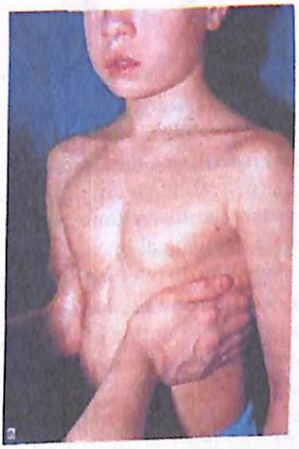
mixed type of shortness of breath (difficulty of breathing and exhalation) - in pneumonia, pleuropneumonia, bronchiolitis, extrapulmonary (ascites, flatulence, etc.) the contraction of the diaphragm to the joint and the collapse of the chest.

II. Chest palpation:

Figure 11

Chest palpation





1. identifying the painful area (superficial or deep), typical for pleural damage;

2. to determine the characteristics of the bone frame (the condition of the intercostal space);

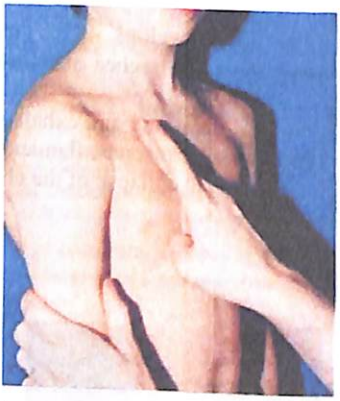
3. resistance;

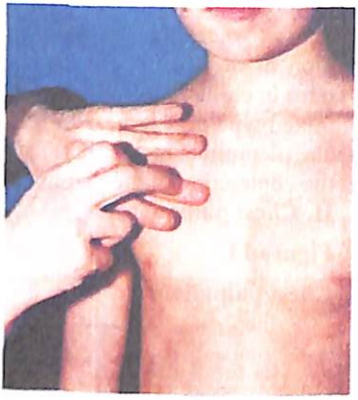
4. to determine voice vibration (increases when the lung tissue is dense or hollow, decreases when the bronchi are blocked (atelectase), when the bronchi are compressed by exudate or a tumor in the chest).

III. Percussion (comparative and topographical)

Figure 12

Chest percussion





In younger children, indirect percussion is performed in older children.

The child is placed in a vertical position, except for those under 1 month of age. The goal is to assess the characteristics of the percussion sound symmetrically in the lung area (in healthy children, a clear lung sound) and to determine the position of the lung border, the lower lung border, and the lung apex from the front and back along the main anatomical lines.

Topographic percussion of the lungs:

A) determining the lower limit of the lungs:

Stage 1: the situation of the child and the student in relation to him.

the child stands or sits. The student stands or sits in front of the child.

Stage 2: In children older than 10 years, lung percussion from the front begins over the spine to determine the height of the lung apex. The lower lung border is assessed using three main vertical topographic lines, regardless of the child's age: the midspinal line (only on the right side), the midaxillary line, and the scapular line.

Plessimeter - the finger is placed parallel to the intercostal space, starting from the 3rd-4th intercostal space.

Stage 3: percussion is performed from a clear lung sound to a dull one, the borders of the lungs are determined by the upper border of the pleximeter finger.

B) Determination of the high point of the lung apex

Stage 1: the situation of the child and the student in relation to him.

the child sits or stands. The student stands the child from the front or back.

2nd stage: in children older than 10 years, percussion begins from the front along the midline of the spine from the left and right sides. Plessimeter - finger is placed parallel to the spine, percussion is performed vertically above the spine, in which the plesimeter - finger should always be parallel to the spine.

Stage 3: percussion is performed until the lung sound changes to a dull sound. The upper limit of the peak of the lungs is determined by a clear lung sound

(from the inside of the pleximeter finger). Normally, the apex of the lung protrudes 2-4 cm above the spine.

Stage 4: percussion from the back starts from the tip of the shovel, the pleximeter-finger is placed parallel to it. Normally, the apex of the lung is located in the area of the sharp growth of the VII cervical vertebra from the back.

C) Determination of the width of the Crenig area of the lungs

Stage 1: the situation of the child and the student in relation to him

the child stands or sits. The student stands behind him.

Stage 2: The width of the Kernig area is determined in children over 10 years old. For this, the child is placed on his back, and the pleximeter-finger is placed perpendicular to the spine bone in the middle of the supraspinal cavity.

Stage 3: percussion is performed from both sides (towards the shoulder and to the opposite side - towards the roof of the neck) until the sound of the lungs changes to a dull sound. Crenig area is determined on two sides in the area of clear lung sounds (on the inner side of the pleximeter-finger). Normally, the width of the Kernig area is 3-5 cm.

Pathological lung sounds on percussion:

Contracted sound (pneumonia, lung tumor, atelectasis, pleurisy, chest tumor, abscess) occurs due to insufficient filling of lung tissue with air or the presence of another airless space, or due to fluid accumulation in the pleural cavity.

Tympanic sound appears due to increased air content in the lung tissue, as seen in pulmonary emphysema, bronchial asthma attacks, pneumothorax, the initial stages of pulmonary edema, pulmonary cavities, or when the diaphragm is positioned high.

Box-like sound is characteristic of pulmonary emphysema, bronchial asthma attacks, and obstructive syndrome.

IV. Lung auscultation

Auscultation of the lungs using a stethophonendoscope determines the type of breathing and breath sounds during normal breathing (through the nose) while the patient is in a vertical position. It is then assessed during forced (deep) breathing through the mouth. During this process, wheezing is detected, and its characteristics are evaluated before and after coughing.

To increase the depth of breathing in children during the first year of life, after standard auscultation, the baby can be gently pinched on the nose or have slight pressure applied to the ankles and heels.

The following types of breathing are distinguished: puerile, vesicular, bronchial, amphoric, harsh, and weakened.

1-pueril – heard in children from 5-6 months to 5 years, it is a higher, narrow bronchial tree, short trachea and increased breath sounds in a thin chest.

2-vesicular - continuous noises during inhalation and short noises during exhalation, which develop as a result of vibration of the wall of the alveoli and tension of the lung tissue;

3-reduced vesicular - is observed in the narrowing of the airways in the area of the larynx, trachea, bronchi, foreign body, enlarged lymph nodes, tumor, bronchopneumonia, pleurisy, obesity, dystrophies;

4-increased vesicular - sometimes heard over healthy tissue in inflamed lung tissue, and during fever, diabetic coma;

5 hard - increased exhalation (in bronchitis, bronchopneumonia, endobronchitis);

6-bronchial - in the pathological processes of the lungs with thickening of the lung tissue (pneumonia, tuberculosis, atelectasis);

7 amphoric - when there is a cavity in the lungs, it is heard during inhalation and exhalation, it is important in open pneumothorax, diaphragmatic hernia;

Wheezing occurs when there is mucus, blood, edema fluid, and fibrous viscous liquid in the air passage area of the respiratory system.

Dry wheezing is a variable, intermittent wheezing characteristic of tracheitis, laryngitis, tracheobronchitis, bronchitis and bronchospasm in bronchial asthma.

Wet wheezes–It develops in the bronchi of various calibers when a certain amount of mucus, blood, or fluid from swelling accumulates in the cavity. As air flows through the bronchi during breathing, it creates bubbles that burst, producing wet wheezes. These are classified as fine, medium, or coarse bubbling wheezes, depending on the caliber of the bronchi.

High-pitched wheezing is heard in areas of thickened lung tissue (e.g., pneumonia).

Low-pitched wheezing is typical in conditions such as bronchitis, atelectasis, and pulmonary edema.

Crepitation is a sound phenomenon that occurs when fluid and exudate (pneumonia) or transudate (pulmonary edema) are present in the alveoli, along with air. The filling and bursting of alveoli with air during breathing produce crepitant sounds, which are heard only during respiration.

Pleural friction rub occurs due to the friction between the visceral and parietal pleural layers, commonly seen in pleuritis, pleural fibrosis, tuberculosis, and pleural tumors.

Bronchophony is the transmission of sound from the bronchi to the chest wall, detected with a stethoscope. In pathological conditions, it is enhanced in cases of lung tissue consolidation (e.g., pneumonia, tuberculosis, atelectasis). A weakened bronchophony is observed in obese children or those with well-developed shoulder muscles.

Lung sounds

Patient care

1. Counting the number of breaths in young children.

Counting the number of breaths in children is carried out along with chest examination. In young children, it is best to do this when they are sleeping or when they are calm, because disturbing the child increases the number of breaths.

*The number of breaths in children under 1 month of age during sleep is counted through a stethophone endoscope, close to the nose, but without touching the tip of the nose.

*Visual counting of breaths consists of the following, the nurse observes the movement of the chest or the front wall of the abdomen without warning.

* Counting the number of breath movements by palpation with the hands placed on the chest, determining the movement of the chest when the child breathes.

It should be remembered:

1). In children, the number of breaths (respiratory movement) should be counted without informing the patient (in children older than 4 years), in order to know the effect of the mental factor;

2).to accurately count the number of breaths, it is necessary to count breath movements for 1 minute.

The obtained results are compared with the number of breaths that should normally be at this age

Semiotics of damage to respiratory organs in children and their main diseases.

Semiotics of breathlessness

Respiratory failure (RF) is a condition in which the gas composition of arterial blood is altered or excessive energy consumption is required to maintain normal levels.

There are numerous causes of shortness of breath, primarily acute dyspnea. These include:

–Diseases of the upper and lower respiratory tract
–Lung parenchymal disorders
–Airway obstruction due to vomiting, regurgitation, or foreign bodies
–Pneumothorax and pyothorax
–Chest trauma

Additionally, respiratory failure can result from:

–Central nervous system (CNS) injuries and diseases
–Nerve conduction disorders
–Muscular dystrophy
–Myasthenia

Table 9

The most common couses of RF

Factors causing RF in 1-24 months	Factors causing RF in 1-12 years old
Bacterial and viral (bronchiolitis) bronchopneumonia, aspiration	Asthmatic condition
Obstruction of the upper respiratory tract	Congenital defect of the chest and brain
Congenital heart defect	traumatic shock
Asthmatic condition	Drowning
Septicemia	Kidney failure
YOtjismaspiratsiyasi	
Foreign body aspiration Intrathoracic anomalies, developmental defects of the diaphragm, vascular neck	
Encephalitis	

The main symptoms of respiratory failure (RF) are hypoxemia, hypo- and hypercapnia. If a child is breathing atmospheric air, hypercapnia will never occur without hypoxia. Hypoxemia is often accompanied by hypocapnia.

Types of shortness of breath:

1. Obstructive – caused by airway obstruction.
2. Parenchymatous – results from lung tissue damage.
3. Ventilatory (non-pulmonary) – due to neuromuscular or central nervous system disorders affecting breathing.

Obstructive RF –can develop as a result of mechanical reasons—aspiration of a foreign body, swelling of the mucous membrane (suffocating laryngotracheitis), bronchiolospasm (bronchial asthma attack), pressure on the airways from the outside (vascular larynx or aortic bifurcation, foreign body in the esophagus, oropharyngeal inflammatory process, etc.), as well as congenital developmental defects (choanal atresia, laryngomalacia, cystic fibrosis). Often, several factors occur together (for example, inflammatory swelling of the mucous membrane accompanied by sputum discharge disorders, etc.). Damage to the large airways is manifested by inspiratory wheezing, and damage to small bronchioles is manifested by inspiratory gasping. The mechanism of development of shortness of breath in bronchial asthma is the sudden expansion of alveoli due to trapped air. This causes a disturbance in capillary blood exchange. Relieving the spasm allows the dilated alveoli to shrink, which also contributes to resolving shortness of breath.

Parenchymatous RF is characterized by impaired capillary blood circulation in the alveoli and the small pulmonary circulation. Its clinical equivalent is age-related respiratory distress syndrome (RDS). The pathophysiological basis of RDS includes an alveolar-capillary block for oxygen diffusion, lung collapse, and a decrease in physiological residual volume. Typically, this condition arises as a systemic inflammatory response of the body to endotoxemia. Inflammatory lung diseases lead to parenchymatous RF, where early hypocapnia is accompanied by hypoxemia and mixed-type dyspnea.

Ventilation RF– is based on impaired control of external respiration. This may be due to the suppression of respiratory center activity (e.g., barbiturate poisoning, CNS injuries and tumors, encephalitis), nervous system disorders (e.g., poliomyelitis), synaptic transmission dysfunctions (e.g., myasthenia, residual effects of muscle relaxants), or changes in respiratory muscles (e.g., muscular dystrophy, muscle proteolysis in hypercatabolic states).

The primary clinical symptom of this type of RF is hypoventilation. This condition can be triggered by pneumothorax, hemothorax, hydrothorax, high diaphragm positioning (e.g., due to intestinal paresis), or chest trauma. Concomitant hypoxemia and hypercapnia are characteristic of ventilatory RF. RF can also develop due to a decrease in PaO_2 in the inhaled air, leading to reduced oxygen saturation in pulmonary capillaries and subsequent tissue hypoxia (e.g., in high-altitude environments or caves). In cases of severe anemia, RF can result from impaired gas transport in the blood, as well as structural abnormalities of hemoglobin (e.g., methemoglobin or carboxyhemoglobin). Additionally, reduced blood flow in circulatory disorders can cause stagnant hypoxia in organs and tissues. Tissue

hypoxia is particularly significant, as it arises from damage to the enzymatic systems of cells that facilitate oxygen utilization from the blood (e.g., in poisoning or infections).

There are three pathogenetic stages in the development of RF

Stage I - due to compensatory breathing and acceleration of blood circulation, there is no violation of gas exchange

Stage II - the first clinical and laboratory signs of decompensation, manifested in the form of hypocapnia and hypoxia, appear

Stage III - complete decompensation, the difference between types of shortness of breath disappears.

Clinical signs of NE include:

- symptoms of the main disease,
-semiotics of changing the activity of the external respiratory system, and
- symptoms of hypoxemia and hypercapnia,
- tissue hypoxia.

Decompensation in hypoxemia manifests as neurological and circulatory disorders, leading to secondary hypoventilation and hypercapnia. Impairments in external respiration are characterized by compensatory mechanisms, increased effort of respiratory muscles, and eventual decompensation of the respiratory system. The primary compensatory symptoms include rapid breathing, prolonged inhalation or exhalation, and disruption of the normal inhalation-to-exhalation ratio. Breathing acceleration occurs due to the involvement of accessory muscles, such as the neck and deep intercostal muscles. This is observed as retraction of the chest's protruding areas during breathing (lower and upper thoracic regions, sternum, intercostal spaces) and, in young children, head bobbing with respiration. A bradyarrhythmic breathing pattern, pathological breathing types, and signs of respiratory center suppression indicate the onset of decompensation.

Clinical signs of hypercapnia and hypoxemia are early and late.

Early clinical signs primarily manifest in the cardiovascular system, including tachycardia, arterial hypertension, and skin pallor. These symptoms indicate the centralization of blood circulation to prioritize oxygen delivery to the central nervous system (CNS).

Late clinical sings indicate decompensation affecting the cardiovascular system, respiratory system, and central nervous system (CNS). These include cyanosis, cold and sticky sweat, as well as physical and mental disturbances, including lethargy or inhibition. When assessing cyanosis, its extent and changes in oxygen levels in exhaled air under different oxygen concentrations should be considered. If the response is maintained when breathing air with 45% oxygen, it suggests the absence of a ventilatory shunt and diffusion disorders. A positive response to 100% oxygen indicates active diffusion through the alveolar-capillary membrane. However, in the presence of an intrapulmonary arteriovenous shunt, this effect does not occur. Another critical group of symptoms is CNS dysfunction due to tissue hypoxia, along with signs of circulatory and respiratory decompensation and metabolic acidosis. These include life-threatening hypoxic CNS damage, coma, and seizures, requiring emergency intervention. The cardiovascular system also responds

to tissue hypoxia with arterial hypotension, bradycardia, and other rhythm disturbances. Eventually, compensatory-adaptive breathing impairment leads to respiratory arrest. Unlike chronic respiratory failure (RF), the body's compensatory mechanisms do not have time to develop in acute cases, making the relationship between arterial oxygen saturation ($RaSO_2$) and arterial oxygen pressure (RaO_2) more evident in clinical manifestations.

The first clinical signs of hypoxemia—cyanosis, tachycardia, and behavioral disturbances—appear when RaO_2 drops to 70 mmHg. Neurological disorders develop when RaO_2 falls below 45 mmHg, and death occurs at levels around 20 mmHg. Regarding $RaSO_2$, the involvement of deep neck and intercostal muscles in breathing is observed when $RaSO_2$ exceeds 60 mmHg, while signs of respiratory decompensation typically appear at $RaSO_2$ levels of 90-120 mmHg.

Table10

Clinical difference between pulmonary and gastrointestinal bleeding:

Sings	Bleeding from the lungs	Gastrointestinal bleeding
Reasons	1) respiratory diseases (pneumonia, tuberculosis); 2) infectious diseases (whooping cough, measles, flu)	Diseases of the gastrointestinal system (ulcer disease, intestinal polyposis, intussusception)
Clinical sings	Cough	Nausea
Vomiting mass is clear character	Clear - red, foamy	"Coffee grounds" (dark brown) with leftoversibilan
RNI of separation	Alkaline	Sour
Stool character	As usual, when the blood is swallowed, the color of the feces darkens	From the upper part - coal, from the lower part - pure blood mixed or with a blood clot

a) to calm the child, make him sit in a semi-sitting position;

b) putting an ice pack on the chest;

c) in order to reduce the pressure within the microcirculation, a venous tourniquet is placed in the pulmonary veins of the legs, 2.4% euphyllin is administered intravenously at the rate of 3-5 mg/kg;

g) codeine is taken in case of cough;

d) transfusion of blood and its preparations (fibrinogen, plasma);

j) hemostatic drugs are administered parenterally: vikasol, 10% calcium chloride, dicinon, 5% aminocaproic acid.

3.2.Bronchitis

Bronchitis is an inflammatory disease of the bronchi, characterized by inflammation of the bronchial mucosa. In children, it often develops as a complication of acute respiratory viral infections (ARVI).

Classification:

Bronchitis in children is classified into acute and chronic types. Acute bronchitis: Sudden onset, lasting 1 to 3 weeks, mostly caused by viral infections. Chronic bronchitis: Persistent inflammation of the bronchi, with cough and mucus production for at least 3 months per year for two consecutive years. It is less common in children than in adults.

Acute bronchitis is often a manifestation of a respiratory infection, it can develop under the influence of chemical and physical factors, as well as allergens.

Damage to the mucous membrane of the bronchi is observed in most cases of ARVI, but bronchitis does not always develop clinically. Rhino-, respiratory syncytial (RS) virus, and parainfluenza virus type 3 often cause catarrhal inflammation of the upper respiratory tract in older children and bronchitis in infants. Bronchitis caused by Mycoplasma, on the other hand, is rare in young children. Even when the bronchial epithelium is damaged in influenza A and B, toxicosis and bacterial pneumonia often obscure the symptoms of bronchitis. Bacterial bronchitis occurs in children with impaired bronchial clearance, such as those with foreign bodies, laryngeal stenosis, intubation, tracheostomy, habitual aspiration of food, or cystic fibrosis..

Prevalence and relevanceIn relapsing bronchitis, ARVI plays a key role in triggering the acute phase. However, the pronounced clinical presentation of bronchitis suggests the involvement of additional factors. These include, primarily, air pollution, a child's susceptibility to allergic reactions, and, in some cases, selective IgA deficiency. Children with recurrent bronchitis often show signs of connective tissue dysplasia. The main symptom of acute bronchitis is initially a dry cough, which progresses to sputum production and increases in volume after 1–2 days. In tracheitis, patients may experience pressure and pain behind the sternum. In the absence of clinical signs of obstruction, wheezing may occasionally be heard during exhalation, especially during sleep. Sputum is typically mucous in nature, and by the second week, it may take on a greener color due to fibrin admixture, which is not indicative of microbial inflammation. Cough usually lasts up to two weeks, but in older children, it can persist longer in cases of RS-virus, mycoplasma, or adenovirus infections. Following tracheitis, a cough may persist for 4–6 weeks without other symptoms. In bronchitis, diffuse dry and coarse or medium bubbling rales can be heard, with fine bubbling rales occurring less frequently. These sounds often change with coughing. No percussive abnormalities are typically present. Hematological changes in bronchitis are inconsistent; in mycoplasma infections, leukocyte counts are usually normal, while erythrocyte sedimentation rate (ESR) may be elevated despite an overall reduction in inflammatory markers.

Symptoms of acute bronchitis in children

Symptoms of bronchitis in children differ from those of other respiratory diseases. Cough is the primary sign of bronchitis in children. However, since cough is also common in other respiratory tract infections, what distinguishes the cough associated with bronchitis? The initial symptoms of bronchitis in children begin with a dry, non-productive cough. The transition to sputum production and the onset of a wet cough indicate the recovery process. Sputum may be colorless, yellow, or green. Another symptom of acute bronchitis in children is an increase in body temperature. However, in bronchitis, fever is usually not very high, often remaining at a subfebrile level, though in some cases, it can rise to 39°C. This is relatively lower compared to the fever associated with lung tissue inflammation. In catarrhal (ordinary) bronchitis, body temperature does not exceed 38°C. Additional symptoms of bronchitis include general intoxication, such as headache, weakness, nausea, sleep disturbances, and loss of appetite in nursing infants. During auscultation, dry wheezes can be heard in the chest area. Bronchitis caused by Mycoplasma is associated with high fever but typically lacks significant general intoxication symptoms. As mentioned earlier, bronchitis often develops as a complication of upper respiratory tract infections. Therefore, symptoms of pharyngitis, laryngitis, and rhinitis—such as nasal congestion, sore throat, runny nose, and mucosal hyperemia—may accompany bronchitis.

In bronchitis accompanied by tracheitis, there is also a feeling of pain and heaviness in the chest area.

Symptoms of bronchiolitis and obstructive bronchitis in children

The symptoms of bronchiolitis and obstructive bronchitis in children differ from those of simple (catarrhal) bronchitis. Bronchiolitis is also characterized by cough and fever. However, unlike catarrhal bronchitis, bronchiolitis and obstructive bronchitis are accompanied by symptoms of respiratory failure. These include an increased respiratory rate, cyanosis around the mouth and lips, noisy breathing, and the involvement of additional muscles in respiration. Children with obstructive bronchitis exhibit wheezing in the chest, which is typically moist and soft. In some cases, these wheezing sounds can be heard from a distance without a stethoscope. Exhalation is prolonged. A key indicator of wheezing in obstructive bronchitis among infants is an increased respiratory rate:

Up to 60 breaths per minute in nursing infants

Up to 50 breaths per minute in children under 2 years

Up to 40 breaths per minute in children older than 2 years

In bronchiolitis, panting respiration can reach 80–90 breaths per minute, often accompanied by tachycardia. In such cases, cardiac involvement may lead to muffled heart tones.

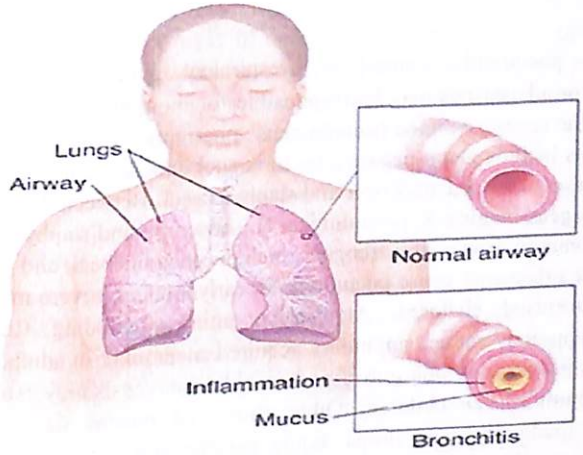
Diagnosis of bronchitis.

When diagnosing bronchitis, the doctor must first determine its type (obstructive or simple) and its etiology (viral, bacterial, or allergic). It is also crucial to differentiate bronchiolitis from simple bronchitis. Additionally, obstructive bronchitis should be distinguished from bronchial asthma. Diagnosis involves a general physical examination of the patient and auscultation of the chest. If hospital admission is required, a chest X-ray is performed to clearly assess the condition of

the bronchi and lungs. To identify the causative agent of the disease, bacteriological culture of sputum samples and viral detection via PCR are conducted. In a complete blood count (CBC), particular attention is given to ESR (erythrocyte sedimentation rate) and the leukocyte formula:

An increase in leukocytes (*leukocytosis*) suggests a bacterial infection. A decrease in leukocytes (leukopenia) along with an increase in lymphocytes (lymphocytosis) suggests a viral infection. However, during an exacerbation of chronic bronchitis, blood test changes may not always be observed. Additionally, further diagnostic tests such as bronchography, bronchoscopy, and computed tomography (CT) may be prescribed.. (Fig. 13).

Figure 13



Consequences and complications

If bronchitis in children is treated promptly and correctly, the outcome is generally positive. However, bronchitis is a prolonged illness, and it may take several weeks for a child to fully recover. The most important goal is to prevent simple bronchitis from progressing into more severe forms, such as obstructive bronchitis or bronchiolitis, and to avoid complications like pneumonia. It is crucial to remember that obstructive bronchitis in children can be life-threatening, especially for young children. This is because bronchial spasms or mucus accumulation in the airways can lead to severe breathing difficulties.

Possible complications of bronchitis include:

Bronchial asthma

Recurrent bronchitis

Chronic bronchitis

Additionally, if the infection spreads throughout the body, serious complications such as endocarditis and kidney inflammation (nephritis) may develop.

Prevention of bronchitis includes avoiding colds, strengthening the immune system, maintaining a proper diet, and ensuring that children are not exposed to smoke. If there are smokers in the family, smoking should not take place near children. Additionally, timely treatment of acute respiratory infections is essential to prevent the development of bronchitis.

3.3. Pneumonia

Pneumonia may be classified anatomically as lobar or lobular pneumonia, bronchopneumonia and interstitial pneumonia. Pathologically, there is a consolidation of alveoli or infiltration of the interstitial tissue with inflammatory cells or both.

Etiology

Viral pneumonia caused by respiratory syncytial virus, influenza, parainfluenza or adenovirus may be responsible for about 40% of the cases. In over two-thirds of the cases, common bacteria cause pneumonia. In the first 2 months, the common agents include gram-negative bacteria such as Klebsiella, E. coli and gram-positive organisms like pneumococci and staphylococci. Between 3 months and 3 yr common pathogens include S. pneumoniae, H. influenzae and staphylococci. After 3 yr of age, common bacterial pathogens include pneumococci and staphylococci. Gram-negative organisms cause pneumonia in early infancy, severe malnutrition and immunocomprornised children. Atypical organisms including Chlamydia and Mycaplasma spp. may cause community acquired pneumonia in adults and children. Pneurnocystis jiroveci, histoplasmosis and coccidioidomycosis may cause pneumonia in immunocomprornised children. Other causes of pneumonia include ascaris, aspiration of food, oily nose drops, liquid paraffin and kerosene poisoning. The etiology remains unknown in one-third of cases of pneumonia.

Clinical Features

Risk factors for pneumonia include low birth weight, malnutrition, vitamin A deficiency, lack of breastfeeding, passive smoking, large family size, family history of bronchitis, advanced birth order, crowding, young age and air pollution. Indoor air pollution is one of the major risk factor for acute lower respiratory tract infection in children in developing countries. Onset of pneumonia may be insidious starting with upper respiratory tract infection or may be acute with high fever, dyspnea and grunting respiration. Respiratory rate is always increased. Rarely, pneumonia may present with symptoms of acute abdominal emergency. This is attributed to referred pain from the pleura. Apical pneumonia may be associated with meningismus and convulsions. In these patients the cerebrospinal fluid is always clear. On examination, there is flaring of alae nasi, retraction of the lower chest and intercostal spaces. Signs of consolidation are present in lobar pneumonia.

Pneumococcal Pneumonia

Respiratory infections due to S. pneumoniae are transmitted by droplets and are more common in the winter months. Overcrowding and diminished host resistance predisposes the children to infection with pneumococci. Bacteria multiply in the alveoli and an inflammatory exudate is formed. Scattered areas of consolidation occur, which coalesce around the bronchi and later become lobular or lobar in distribution. There is no tissue necrosis. Pathological process passes from the stage of congestion to red and gray hepatization before the final stage of resolution. Clinical features. Incubation period is 1 to 3 days. The onset is abrupt with headache, chills, cough and high fever. Cough is initially dry but may be associated with thick rusty sputum. Child may develop pleuritic chest pain. Respiration is rapid. In severe cases there may be grunting, chest indrawing, difficulty in feeding and cyanosis. Percussion note is impaired, air entry is diminished, crepitations and bronchial breathing may be heard over areas of consolidation. Bronchophony and whispering pectoriloquy may be observed. Meningismus may be present in apical pneumonia.

Diagnosis. The diagnosis is based on history, physical examination, X-ray findings of lobar consolidation and leukocytosis. Bacteriological confirmation is difficult; sputum is examined by Gram staining and culture. Blood culture may be positive in 5-10% of cases. Demonstration of polysaccharide antigen in urine and blood do not have sufficient specificity for confirming pneumococcal pneumonia as it may be also be positive in children with colonization in throat.

Treatment. Antibiotic therapy may be empiric while awaiting confirmation of etiology. While the treatment of choice for pneumococcal pneumonia is penicillin (penicillin V 250 mg q 8-12 hr orally, penicillin G 0.5 MU/ kg/ day IV or procaine penicillin 0.6 MU IM daily, for 7 days), amoxycillin (30-40 mg/kg/ day for 7 days) with or without clavulanic acid is a useful alternative. The need for oxygen administration should be guided by signs of respiratory distress (rapid breathing, chest retractions, nasal flare), presence of cyanosis or hypoxernia on pulse oximetry. Patients may be dehydrated, and require IV fluids. Fever should be managed with paracetamol.

Staphylococcal Pneumonia

Staphylococcal pneumonia occurs in infancy and childhood. The pulmonary lesion may be primary infection of the parenchyma; or may be secondary to generalized staphylococcal septicemia. It may be a complication of measles or influenza; other risk factors include cystic fibrosis, malnutrition and diabetes. In infants, the pneumonic process is diffuse initially, but soon the lesions suppurate, resulting in bronchoalveolar destruction. The illness is characterized by the formation of multiple pneumatoceles. The pneumatoceles fluctuate in size and finally resolve and disappear within a period of few weeks to months. Staphylococcal abscesses may erode into the pericardium causing purulent pericarditis. Empyema in a child below two yr of age is nearly always secondary to staphylococcal infections.

Clinical manifestations. The illness usually follows upper respiratory tract infection, pyoderma or a purulent disease. The patient is toxic and sick looking.

Cyanosis may be present. Progression of the symptoms and signs is rapid. Pulmonary infection may occasionally be complicated by disseminated disease, with metastatic abscesses in joints, bone, muscles, pericardium, liver, mastoid or brain. Diagnosis. The diagnosis of staphylococcal pneumonia is suspected in a newborn or an infant with respiratory infection who has evidence of staphylococcal infection elsewhere in the body. The characteristic complications of pyopneumothorax and pericarditis are highly suggestive. Pneumatoceles are present in X-ray films, characteristically in pneumonia due to staphylococci or Klebsiella. These pneumatoceles persist as thin walled asymptomatic cysts for several weeks. Staphylococci can be cultured from the blood. Treatment. The child should be hospitalized and isolated to prevent the spread of resistant staphylococci to the other patients. Fever is controlled with antipyretics; intravenous fluids may be required. Oxygen is administered to relieve dyspnea and cyanosis.

Empyema is aspirated and the pus is sent for culture and sensitivity. Prompt antibiotic therapy should be initiated with coamoxiclav, or a combination of cloxacillin and a thirdgeneration cephalosporin, e.g. ceftriaxone. If the patient does not show improvement in symptoms within 48 hr, therapy with vancomycin, teicoplanin or linezolid may be necessary. Therapy should continue till all evidence of the disease disappears both clinically and radiologically, which usually takes 2 weeks in uncomplicated cases. Therapy is continued for 4--6 weeks in patients with empyema or pneumothorax. Following initial IV therapy, the remaining course may be completed with oral antibiotics.

Complications. Pneumatoceles do not require specific measures. Empyema and pyopneumothorax are treated by intercostal drainage under water seal or low pressure aspiration. Metastatic abscesses require surgical drainage. Significant pleural thickening that prevents complete expansion of the underlying lung may require decortication. Early thoracoscopic drainage of empyema helps prevent pleural thickening. Installation of streptokinase or urokinase in pleural cavity or loculated pleural effusion may also be useful.

Haemophilus Pneumonia

Haemophilus influenzae infections occur usually between the age of three months and three years and are nearly always associated with bacteremia. Infection usually begins in the nasopharynx and spreads locally or through the bloodstream. Most nasopharyngeal infections are mild and confer immunity from subsequent serious illness after the early months of life. As the infants have transplacentally transferred antibodies during the first 3 to 4 months of life, infections are relatively less frequent during this period.

Clinical features. The onset of the illness is gradual with nasopharyngeal infection. Certain viral infections such as those due to influenza virus act synergistically with H. influenzae. The child has moderate fever, dyspnea, grunting respiration and retraction of the lower intercostal spaces. Complications include bacteremia, pericarditis, empyema, meningitis and polyarthritis.

Treatment. Haemophilus infection is treated with ampicillin at a dose of 100 mg/kg/day or coamoxiclav. Cefotaxime (100 mg/kg/ day) or ceftriaxone (50-75 mg/kg/ day) are recommended in seriously ill patients.

Streptococcal Pneumonia

Infection of the lungs by group A beta hemolytic streptococci is secondary to measles, chickenpox, influenza or whooping cough. Group B streptococcal pneumonia is an important cause of respiratory distress in newborns. Pathologically it causes interstitial pneumonia, which may be hemorrhagic. Tracheobronchial mucosa may be ulcerated and lymph nodes enlarged. Serosanguineous or thinly purulent pleural effusion is frequently associated.

Clinical feature. The onset is abrupt with fever, chills, dyspnea, rapid respiration, blood streaked sputum, cough and extreme prostration. Signs of bronchopneumonia are generally less pronounced, as the pathology is usually interstitial. X-ray film shows interstitial pneumonia, segmental involvement, diffuse peribronchial densities or an effusion.

Complications. Thin serosanguineous or purulent empyema is a usual complication. Pulmonary suppuration is less frequent. Ten percent of the patients have bacteremia. When pneumatoceles are present, the condition mimics staphylococcal pneumonia.

Treatment. Therapy for streptococcal pneumonia is carried out as outlined for pneumococcal pneumonia. The response is gradual but recovery is generally complete. Empyema is treated by closed drainage with indwelling intercostal tube.

Primary Atypical Pneumonia The etiological agent of primary atypical pneumonia is Mycoplasma pneumoniae. The disease is transmitted by droplet infection, chiefly in the winter months. The illness is uncommon in children below the age of four yr, although subclinical and mild infections are reported in infants.

Primary atypical pneumonia involves the interstitial tissue with round cell infiltration. The alveolar septae are edematous and mucosa of the bronchioles is inflamed and ulcerates. Obstruction of the terminal bronchioles causes emphysema and atelectasis. Pleura may show patchy fibrinous exudates.

Clinical features. Following an incubation period of 12-14 days, patients have malaise, headache, fever, sore throat, myalgia and cough. Cough is dry at first but later associated with mucoid expectoration, which may be blood streaked. Dyspnea is unusual. There are very few physical signs, except mild pharyngeal congestion, cervical lymphadenopathy and few crepitations. Hemolytic anemia may be seen. X-ray findings are more extensive than suggested by the physical findings. Poorly defined hazy or fluffy exudates radiate from the hilar regions. Enlargement of the hilar lymph nodes and pleural effusion are reported. Infiltrates involve one lobe, usually the lower.

Diagnosis. It is difficult to distinguish Mycoplasma pneumonia from viral or rickettsial pneumonia. The leucocyte count is usually normal. Cold agglutinins are elevated in many patients. M. pneumoniae may be cultured from the pharynx and

sputum. The diagnosis is made rapidly by demonstration of IgM antibody by ELISA during the acute stage. IgG antibodies are seen on a complement fixation test after one week of illness.

Treatment. Patients are treated with macrolide antibiotics (erythromycin, azithromycin or clarithromycin) or tetracycline (for older children) for 7 to 10 days

Chlamydia Pneumoniae

It may cause pneumonia in young infants. Clinical features include spasmodic cough. A history of purulent conjunctivitis during early neonatal period may be present.

Pneumonia Due to Gram-negative Organisms

The etiological agents are E. coli, Klebsiella and Pseudomonas. These organisms affect small children (<1 yr of age) or children with malnutrition and deficient immunity. Pseudomonas may colonize airways of patients with cystic fibrosis and causes recurrent pulmonary exacerbations. The clinical features are similar, but patients can be very sick. Signs of consolidation are minimal, particularly in infants. Constitutional symptoms are more prominent than respiratory distress. X-ray shows unilateral or bilateral consolidation. Infection with E. coli or Klebsiella pneumoniae may be associated with pneumatoceles.

Treatment. Intravenous use of third generation cephalosporins (cefotaxime or ceftriaxone, 75-100 mg/kg/ day) with or without an aminoglycoside is recommended for 10 to 14 days. Ceftazidime or piperacillin-tazobactam are effective in patients with Pseudomonas infection.

Viral Pneumonias

Respiratory syncytial virus is the most important cause in infants under 6 months of age. At other ages, influenza, parainfluenza and adenoviruses are common. The bronchial tree or alveoli are involved resulting in extensive interstitial pneumonia. Features of consolidation are usually not present. Radiological signs consist of perihilar and peribronchial infiltrates.

Ingestion of Aliphatic Hydrocarbons

Kerosene exerts its toxic effects on the lungs and the central nervous system. It is poorly absorbed from the gastrointestinal tract. Milk and alcohol promote its absorption. It has low viscosity and less surface tension, and therefore, diffuses quickly from the pharynx into the lungs. Administration of oil apparently decreases its absorption from the gastrointestinal tract but is not recommended. Clinical features of hydrocarbon pneumonia include cough, dyspnea, high fever, vomiting, drowsiness and coma. Physical signs in lungs are minimal. X-ray film of the chest shows ill defined homogeneous or patchy opacities; occasionally features resemble rniliary mottling. Vomiting is not induced. Gastric lavage is usually avoided to prevent inadvertent aspiration. The patient is kept on oxygen. The routine use of antibiotics and/ or corticosteroids is not recommended.

Loeffler Syndrome

Larvae of many nematodes, during their life cycle, enter the portal circulation, liver and then through the hepatic vein and inferior vena cava into the heart and lungs. In the lungs, the larvae penetrate the capillaries, enter the alveoli, plug the bronchi with mucus and eosinophilic material due to allergic reaction. There are fleeting patchy pulmonary infiltrations. Some cases may be due to drug reaction to aspirin, penicillin, sulfonamide or irnipramine. Clinical features include cough, low fever, feeling unwell and scattered crepitations. There is eosinophilia and X-ray lungs shows pulmonary infiltrates of varying size, which superficially resemble miliary tuberculosis. Treatment is symptomatic.

3.4.Diseases of blood and blood-forming organs

Anemia

Anemia is a condition characterized by a decrease in the number of erythrocytes in the blood, a reduction in the amount of hemoglobin per unit volume of blood, and a decrease in the average hemoglobin content in a single erythrocyte.

Classification of Anemias

In clinical practice, the following classification of anemias is most commonly used:

1. Anemia due to acute blood loss
2. Anemia caused by impaired erythrocyte production

Aplastic

Iron deficiency

Megaloblastic

Sideroblastic

Anemia of chronic diseases

3. Anemia due to excessive breakdown of red blood cells

Hemolytic

Severity Levels of Anemia

Depending on the degree of hemoglobin reduction, anemia is classified into three severity levels:

Mild – hemoglobin level above 90 g/L

Moderate – hemoglobin level between 70 and 90 g/L

Severe – hemoglobin level below 70 g/L

Etiology. Anemia in older children can be caused by bleeding from various areas or by helminthiasis. Additionally, anemia may appear as a symptom of diseases affecting other systems and organs, such as leukemia, nephritis, diffuse liver damage, infections, intoxications, and hereditary disorders. In young infants (mostly between 6 and 18 months old), 90% of all anemias are infectious-alimentary in nature. This is because the infant's blood-forming system is functionally immature and highly sensitive. Infectious-alimentary anemias in young babies are often caused by iron deficiency and are therefore classified as iron-deficiency anemias.

In addition to iron deficiency anemia, anemia can also be classified based on its cause:

Vitamin- or protein-deficiency anemia
Posthemorrhagic anemia (due to significant blood loss)
Hemolytic anemia (caused by excessive breakdown of red blood cells)
Postinfectious anemia (occurring after infectious diseases)
Hypoplastic and aplastic anemia (due to reduced or completely halted blood production)

Posthemorrhagic, hemolytic, postinfectious, and hypoplastic types of anemia are more commonly seen in older children.

Iron deficiency anemia

Iron Deficiency Anemia (IDA) is a manifestation of iron deficiency, characterized by a decrease in hemoglobin concentration per unit of blood volume, a reduction in erythrocytes, microcytosis, anisocytosis, poikilocytosis, a low color index, decreased iron and ferritin levels in the blood serum, low transferrin saturation with iron, increased iron-binding capacity, and elevated erythrocyte protoporphyrin levels.

IDA is one of the most common forms of anemia in childhood. It is frequently observed in the second year of life, during adolescence, and in young children. The latent iron deficiency period occurs 1.5 to 2 times more frequently than clinically apparent iron deficiency anemia.

Causes of Iron Deficiency Anemia:
1. Iron deficiency at birth.
Risk group:
Premature babies
Infants born to mothers with anemia during pregnancy
Orphaned or neglected children
Infants with fetal growth retardation
Infants who experienced significant blood loss during the perinatal period
2. Dietary factors (leading cause of iron deficiency anemia).
Risk group:
Infants fed with unadapted formula
Delayed introduction of complementary foods
Children fed only plant-based foods at any age
High milk consumption in the diet (more than 0.5 L per day)
3. Excessive Iron Loss or High Iron Requirement
Risk groups:
Acute and chronic infectious diseases, primarily of the gastrointestinal tract
Chronic non-infectious inflammatory diseases of the gastrointestinal tract (e.g., malabsorption syndrome, which leads to excessive iron loss or insufficient iron absorption)

In iron deficiency, the first changes occur in the tissues—the body's iron stores decrease, leading to a reduction in serum ferritin levels. This is followed by decreased transferrin saturation with iron, an increase in total iron-binding capacity (TIBC) in the serum, and a rise in free erythrocyte protoporphyrins, which are precursors of heme. These changes affect the child's blood parameters, leading to a

progressive decline in iron levels, hemoglobin concentration, and erythrocyte size, ultimately resulting in anemia.

Depending on the level of hemoglobin decrease, mild (hemoglobin 90-110 g/l), moderate to severe (60-80 g/l) and severe (hemoglobin less than 60 g/l) types of anemia are distinguished.

Clinically, the following syndromes are observed:

1. Asthenoneurotic Syndrome:

- Fatigue, irritability, nervousness, emotional instability
- Excessive sweating
- Delayed physical and psychomotor development
- Lethargy, weakness, apathy
- Poor appetite, reduced attention span
- Fainting, headaches (in older children), dizziness, tinnitus (ringing in the ears), blurred vision
- Chest pain, altered appetite and sense of smell, dysuric disorders (urinary dysfunction)

2. Epithelial Syndrome:

- Skin and mucosal manifestations, particularly on the palms, nails, auricles, and mucous membranes
- Dry, flaky skin
- Dystrophic changes in the skin, nails, hair, and oral mucosa
- Tongue abnormalities: cracks at the corners of the mouth (angular stomatitis), flattening of the tongue papillae, a glossy ("varnished") tongue, redness, and atrophic glossitis
- Difficulty swallowing solid food
- Gastrointestinal issues: gastritis, duodenitis, malabsorption and maldigestion enteropathy, loose stools, nausea

Rare cases: alabaster-green skin discoloration (chlorosis)

3. Cardiovascular Syndrome:

- Tachycardia (increased heart rate)
- Tendency to arterial hypotension (low blood pressure)
- Weakening of heart tones
- Expansion of the relative cardiac border
- Functional systolic murmur at the apex of the heart

In some cases, a murmur over large vessels

4. Muscle Syndrome:

- Muscle hypotonia (reduced muscle tone)
- Rapid fatigue
- Urinary incontinence

5. Secondary Immunodeficiency Syndrome:

- Increased susceptibility to frequent acute respiratory viral infections (ARVI)
- Recurrent pneumonia

- Intestinal infections

The diagnosis of iron deficiency anemia is based on detecting changes in hematological indicators, including a decrease in hemoglobin levels (less than 110 g/L in children under 5 years old and less than 120 g/L in older individuals), a color index below 0.8, and a mean hemoglobin content per erythrocyte below 27 pg/erythrocyte. Other signs include a reduction in the average erythrocyte size and iron metabolism disturbances, such as:

- Serum ferritin levels below 30 ng/mL
- Transferrin saturation below 25%
- Serum iron levels below 11.6 μmol/L
- Increased total iron-binding capacity (TIBC) above 50 μmol/L

Laboratory findings also include microcytosis, anisocytosis, and poikilocytosis.

In the early stages of iron deficiency, the color index remains within the normal range, meaning that a normochromic color index does not rule out iron deficiency anemia. A decrease in erythrocyte count is typically seen only in severe anemia.

Bone marrow examination often shows signs of increased erythropoiesis, confirmed by reticulocytosis in the blood.

Differential Diagnosis:

Iron deficiency anemia should be distinguished from other rare microcytic hypochromic anemias, including:

- Thalassemia
- Heavy metal poisoning (silver, mercury)
- Sideroblastic anemia

Prevention of iron deficiency anemia begins with preventing iron deficiency in women, particularly during pregnancy.

In premature infants, a preventive dose of 2 mg/kg of iron per day is recommended starting from 1 month of age. In children's diets, it is advised to include iron-fortified porridges and supplements to ensure adequate iron intake.

Megaloblastic anemias

Megaloblastic anemia is a type of anemia caused by impaired DNA and RNA synthesis in erythroid cells due to a deficiency of vitamin B12 and folic acid.

Anamnesis: The disease typically develops gradually, with general weakness being a key symptom.

Clinical Examination: The Characteristic Triad of Syndromes

1. Anemia – Pale skin and mucous membranes, thinning of the skin and sclera.

2. Gastrointestinal Damage –

Early stage: Bright red, painful tongue.

Later stage: Smooth, shiny tongue; atrophic gastritis.

3. Neurological Syndrome – Funicular myelosis (degeneration of the spinal cord due to B12 deficiency).

Laboratory Findings

Hyperchromic anemia (color index > 1.0).

Leukopenia (low white blood cell count).

Thrombocytopenia (low platelet count).

Peripheral blood smear:

Macrocytosis (large RBCs)

Ovalocytosis (oval-shaped RBCs)

Anisocytosis (variation in RBC size)

Basophilic stippling in RBCs

Cabot rings and Howell-Jolly bodies in RBCs

Hypersegmented neutrophils

Types of Macrocytic Anemia

Megaloblastic anemia – Caused by vitamin B12 or folic acid deficiency, characterized by specific changes in peripheral blood and bone marrow.

Non-megaloblastic macrocytic anemia – Occurs in liver diseases and myelodysplastic syndromes.

Macrocytosis in reticulocyte crisis – Seen when reticulocytes exceed 10%.

Diagnosis: Peripheral blood and bone marrow examination

Serum levels of vitamin B12 and folic acid

Consultation. A hematologist consultation is usually required for definitive diagnosis and treatment planning.

Diagnosis of vitamin B12 deficiency anemia

To confirm B12 deficiency anemia, the following tests are required:

1. Serum Vitamin B12 Level – Measures the concentration of vitamin B12 in the blood.

2. Bone Marrow Aspiration and Biopsy

Performed if serum B12 testing is unavailable or if there is no response to treatment within 5–8 days.

Helps assess megaloblastic changes in bone marrow cells.

These anemias occur due to insufficient intake or impaired utilization of vitamin B12 and folic acid, both of which have hematopoietic (blood-forming) properties.

Role of Vitamin B12 and Folic Acid

Essential for red blood cell (RBC) formation.

Their deficiency prevents the proper maturation of RBCs, leading to anemia.

B12-folate deficiency anemia belongs to the megaloblastic anemia group. These anemias have been known for a long time, but their cause was discovered in the 1940s. Due to clinical and laboratory similarities, distinguishing between B12 and folic acid deficiency anemia is challenging. Vitamin B12 (cyanocobalamin) was first synthesized in 1948, leading to the identification of its role in anemia. Previously, it was believed that anemia resulted from the lack of an intrinsic factor, known as Castle's factor—a gastromucoprotein produced by the parietal cells of the gastric mucosa.

Later, it was established that vitamin B12 is the extrinsic antianemic factor associated with Castle's factor.

Types of Vitamin Deficiency Anemia

Exogenous – Due to inadequate dietary intake.

Endogenous – Due to impaired absorption or metabolism.

Vitamin B12 and folic acid are widely available in nature and are found in foods such as meat, eggs, milk, cheese, animal kidneys, spinach and yeast. The amount of vitamin B12 in the body of adults is 2-5 mg, folic acid is less. The main storage of vitamin B12 and folic acid is the liver. Their daily losses are negligible. If B12 does not enter the body, anemia can appear only after 5-6 years. Vitamin B12 is involved in the synthesis of DNA and RNA, especially in red blood cells. Therefore, with this deficiency, the structure of red blood cells is disturbed. The process of maturation and differentiation in bone marrow cells slows down. The process of hemoglobin formation is not disturbed (B12 and folic acid do not participate in this process). Vitamin B12, upon entering the gastrointestinal tract, is released in the stomach and binds to intrinsic factor, a glycoprotein produced by parietal cells of the gastric mucosa. This complex is essential for B12 absorption in the small intestine. After entering the villi in the intestine, the complex breaks down and the already pure B12 is absorbed through the intestinal wall and enters the bloodstream. The factor is needed for transport and assimilation. In the blood, B12 is transported by transcobalamin proteins, which are distinguished by several types (1, 2, 3, 4). The main transport function is carried out by transcobalamins 1 and 2, which deliver vitamin B12 to the depot - the liver, whose reserves are very large. If necessary, B12 is delivered to the bone marrow with the help of cyanocobalamin, where it participates in the construction of red blood cells. Vitamin B12 deficiency anemia, also known as Addison-Biermer disease, is common worldwide. It primarily affects women over 40 years old. The disease develops gradually and often follows a chronic, recurrent course if left untreated.

Causes of B12 and folic acid deficiency anemia.

I. Violation of vitamin B12 (folic acid) absorption.

1. Atrophy of gastric fundal glands (Addison-Birmer disease).

2. Damage to the stomach (polyposis, cancer).

3. Intestinal disease (terminal ileitis, diverticulosis, intestinal fistulas, tumors).

4. Surgery of the stomach and intestine (subtotal resection of the stomach, gastrectomy, intestinal resection).

II. Excessive consumption of vitamin B12 (folic acid) and impaired utilization in the bone marrow.

1. Intestinal parasites (difilobothriasis).

2. Intestinal dysbacteriosis.

3. Pregnancy, childbirth.

4. Liver diseases (chronic hepatitis, cirrhosis).

5. Hemoblastoses (acute leukemia, erythromyelosis, osteomyelofibrosis).

6. Taking certain drugs (anticonvulsants, sulfonamides, folic acid antagonists).

III. B12 (folate acid) alimentary deficiency.

1. Due to feeding goat's milk and milk powder in children.

2. In adults, among some socio-ethnic groups.

Folic acid (fteroylglutamic acid) is present in small amounts in the human body and found in foods such as spinach, meat, milk, eggs. If vitamin B12 loses 10-15% activity during heat treatment of the product, folic acid - 50%. Folic acid is absorbed in the small intestine. But unlike vitamin B12, when it enters the bloodstream, it can be in a free and bound state (with blood proteins). In a free state, it can be in feces, urine, sweat. Folic acid reserves are small, deficiency is 3-6 weeks, folic acid reserve - liver. When necessary, it enters the bone marrow from the liver.

Clinical presentation of B12 deficiency anemia.

The disease follows a chronic, relapsing course, with periods of remission alternating with relapses. It is characterized by a combination of symptoms affecting the circulatory, digestive, and nervous systems. Due to its slow progression, the body gradually adapts to the anemia. As a result, despite significant reductions in hemoglobin levels, patients may remain functional for a long time before experiencing severe clinical and hematological decompensation.

General group of symptoms: weakness, rapid physical fatigue, dizziness, blurred vision, palpitations, shortness of breath. Acute pallor of lemon-yellow skin. Dry skin, brittle nails. Most patients have a fever of up to 38°C. Gunter's symptom is the main symptom of anemia, in which a blood point appears on the tip of the tongue, a feeling of pain, burning, itching in the tongue. If hot food falls on the tongue, an unpleasant sensation appears. The tongue is "lacquered" (smooth), such a surface may be on the mucous membrane of the mouth and esophagus. The mucous membrane of the stomach is definitely affected, atrophic gastritis with constant pain is noted. Epigastric pain radiating to the intestinal mucosa, nausea, vomiting, abdominal pain and diarrhea are characteristic.

Changes in the central nervous system are noted: the lateral and posterior columns of the spinal cord are affected. The lateral columns are responsible for the autonomic centers (the work of internal organs), there is a sensitive impulse from the back columns to the center. In such patients, heart failure (tachycardia, arrhythmia), bladder and bowel disorders, paresis and paralysis are observed. Megaloblastic anemia develops. The type of hematopoiesis changes (normoblastic type of hematopoiesis in a healthy person). With the megaloblastic type of hematopoiesis, the structure of red and white blood cells changes. The picture of peripheral blood is characterized by hyperchromic macrocytic anemia with degenerative changes in red blood cells. In bone marrow cells, the process of maturation of the nucleus and cytoplasm is disturbed. Cytoplasm develops before the maturation process of the nucleus. Therefore, the nucleus is young, and the cytoplasm is old. At the peak of the disease, the number of red blood cells per unit volume of blood can decrease sharply by 1 g/l. The process of hemoglobin formation is not disturbed, the amount of hemoglobin is within normal limits, the color index is 1.3-1-1.5. If the average amount of hemoglobin in erythrocytes (MCH) exceeds 31 pg, anemia is of the hyperchromic type. Hyperchromic anemia is usually macrocytic (MCV > 95 fl). The value of MCHC does not exceed the norm, and the decrease in hemoglobin is usually explained by a sharp decrease in the number of red blood cells in which large cells (macrocytes) increase. This type of anemia includes B12 deficiency, folate

deficiency, and autoimmune hemolytic anemia. One of the characteristic signs in the acute period of the disease is the decrease or loss of reticulocytes in the peripheral blood due to the violation of the maturation process. If B12 folic acid deficiency anemia is suspected, reticulocytes must be determined. Degenerative types of red blood cells appear during stress - poikilocytes, schizocytes, erythrocytes with basophilic granules. Poikilocytosis is a change in the shape of red blood cells, macrocytes and megalocytes. Schizocytes are destroyed, torn red blood cells.

Along with changes in red blood cells, the recurrence of anemia is characterized by leukopenia up to 1.5 g/l with the presence of giant polysegmented neutrophils. Neutrophilia is noted with a shift to the left, myelocytes. In a small number of patients, leukocytosis is noted, eosinophils, monocytes decrease. Thrombocytopenia reaches 50 g/l, it can be more pronounced during the peak period, but there is never bleeding due to thrombocytopenia. ESR is almost always accelerated. Due to the increase of red cells in the bone marrow, the ratio of white and red cells changes. A large number of basophilic megaloblasts are noted. Indirect bilirubinemia is noted in the blood serum - 18-36 μmol/l, an increase in the amount of stercobelin in the feces, and the presence of urobilin in the urine.

Diagnostic criteria of B12 deficiency anemia:

• high value of MCH (> 31 pg);

Macrocytosis (MCV value > 95 fl), megalocytosis;

• red blood cells with nuclear remnants (Jolly body, Cabot ring);

• reticulocytopenia;

Hypersegmentation of neutrophils;

• leukopenia (neutropenia);

• thrombocytopenia;

Megaloblastic hematopoiesis in the bone marrow.

Folate deficiency anemia

Folate deficiency anemia (FDA) belongs to the megablastic anemia group. Megablastic anemia (MA) is an anemia resulting from ineffective erythropoiesis, characterized by changes in the formation and morphology of erythrocytes.

FDA is a rare disease, observed in children of breast-feeding age, mainly in premature babies.

Etiology and pathogenesis. The demand for folic acid is satisfactory in full-term babies with a rational natural diet.

Causes: congenital disorders of absorption and folate metabolism (in rare cases), acquired malabsorption (celiac disease, exudative enteropathy), high demand for folic acid in premature babies, hemolytic anemias, treatment with certain drugs (methotrexate, sulfonamides, anti-tuberculosis drugs), and long-lasting infections. Folic acid deficiency anemia is observed in children fed with goat's milk. Megaloblastic changes in the bone marrow and peripheral blood appear after 3–3.5 months. It is classified according to the level of severity.

Clinic. Folate deficiency anemia develops gradually and is often mild to moderate in severity. The main clinical manifestations include:

- General symptoms: Fatigue, weakness, dizziness, pale skin, and reduced exercise tolerance.

- Hematologic symptoms: Macrocytic anemia, megaloblastic changes in bone marrow, neutropenia, thrombocytopenia (without a tendency to bleeding)
- Gastrointestinal symptoms: Glossitis (swollen, red, and painful tongue), stomatitis, diarrhea, anorexia, and weight loss.
- Neurological symptoms: Unlike vitamin B12 deficiency anemia, folate deficiency anemia does not typically cause neurological disorders.

In severe cases, patients may experience complications such as increased susceptibility to infections due to neutropenia.

Diagnosis. In peripheral blood, megalocytes predominate—these are enlarged erythrocytes with a diameter of 10 to 12 µm, typically round or oval in shape. The average erythrocyte volume ranges from 100 to 146 fl. A peripheral blood smear reveals anisocytosis (variation in cell size), poikilocytosis (abnormal cell shapes), and hypersegmented neutrophils (neutrophils with more than five nuclear lobes). In the bone marrow, erythroid hyperplasia is observed, along with an increase in the size of all hematopoietic cells, reflecting ineffective erythropoiesis characteristic of megaloblastic anemia.

Differential Diagnosis. Folate deficiency anemia must be distinguished from B12 deficiency anemia. A key differentiating factor is urinary methylmalonic acid excretion—it is elevated in B12 deficiency anemia but remains normal in folate deficiency anemia. This biochemical marker helps differentiate the two conditions, as their clinical and hematological features can be very similar.

IV CHAPTER MEDICAL GENETICS

4.1.Genetics and development of medical genetics

It first outlines the foundations of medical genetics that lay in more general genetics in the first half of the 20th century, before examining the key later scientific discoveries, including the human gene map and the Human Genome Project (HGP), the clinical advances that have increasingly followed from these advances, and the growth of medical genetics as a specialty in both clinical and laboratory medicine. Medical genetics is the science of human biologic variation as it relates to health and disease. Clinical genetics is that part of medical genetics concerned with the health of individual humans and their families. Alternatively, clinical genetics can be defined as the science and practice of diagnosis, prevention, and management of genetic disorders. Within recent years, medical genetics has become established as a clinical specialty, as the culmination of developments that began in 1956 with the description of the correct chromosome number of the human. With the discovery of specific microscopically visible chromosomal changes associated with clinical disorders, beginning with Down syndrome in January 1959, medical genetics acquired an anatomic base. Medical geneticists now had their specific organ—the genome—just as cardiologists had the heart and neurologists had the nervous system. The anatomic base of medical genetics was greatly extended with the mapping of genes to chromosomes and specific chromosomal regions, at an ever-accelerating pace, since the late 1980s. Gene mapping has not only enlarged the base for medical genetics but, indeed, as pointed out to me by Charles Scriver (personal communication, 1980), has also provided a neo-Vesalian basis for all of medicine. Medical historians tell us that the anatomy of Vesalius published in 1543 was of pivotal importance in the development of modern medicine. It was the basis of the physiology of William Harvey. Similarly, human gene mapping constitutes an approach to the study of abnormal gene function in all diseases; the gene mapping approach has been adopted by researchers in almost all branches of medicine in the study of their most puzzling disorders. Through mapping, they have sought the basic defect in these disorders, and their clinical colleagues have used mapping information for diagnosis and carrier detection. The ultimate anatomic basis for medical genetics, the DNA sequence, was provided by the HGP. In this brief history of medical genetics, I trace the foundations of the field that were laid between 1865, when Mendel published his work, and 1956, when the correct chromosome number was reported. I then discuss the events since the late 1960s that have seen the main evolution of the discipline. Most specialties started as crafts (or grew out of a technological advance such as radiography) and only subsequently acquired basic science foundations. The basic science that developed before 1956 and served as the foundation for the developments since the late 1960s included Mendelism, cytogenetics, biochemical genetics, immunogenetics, and statistical, formal, and population genetics. Mendelism. The demonstration of the particulate nature of inheritance was the contribution of Gregor Mendel (1822–84), a monk and later abbot in an Augustinian monastery in Brünn (now Brno), Moravia

(now the Czech Republic). The terms dominant and recessive were his. The delay in recognition of his work has been attributed to various factors, but the most likely is poor timing; in 1865, when Mendel reported his findings and conclusions, the chromosomes had not yet been discovered. Because its physical basis, meiosis had not yet been described, Mendelism had no plausible basis to qualify it over other possible mechanisms of inheritance, such as blending inheritance, which was favored by Francis Galton (1822–1911), one of Mendel's contemporaries.

Molecular basis of heredity.

CELLS are often called the microscopic building blocks of the body. They are active and dynamic, they continually grow and specialize, function, die, and replenish themselves, by the millions every second. The whole body contains about 37.2 trillion (37,200,000,000,000 cells. Cells provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. They also contain the body's hereditary material in the form of DNA and make copies of themselves. The cell is the basic functional unit of the human body. Cells are considered as the basic unit of Life !! Cells are extremely small, typically only about 0.01 millimeter (.0004 or 4 ten-thousandths of an inch) across – even our largest cells are no bigger than the width of a human hair.

The Parts of the Cell .(Fig1)• Each living cell carries out the tasks of taking food, transforming food into energy, getting rid of wastes, and reproducing. • Most of our body cells have three main parts: • Cell outer Membrane • Cytoskeleton structure inside to keep its shape • The nucleus. The cell membrane is a double layer of lipids and proteins that surrounds a cell and separates the cytoplasm (the liquid contents of the cell) from its surrounding environment. It is selectively permeable, which means that it only lets certain molecules enter and exit and it controls the amount of some substances that go into or out of the cell.

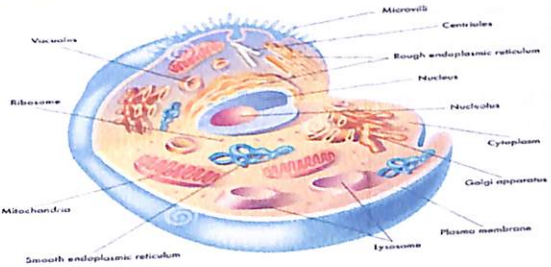


Fig1

The cell membrane also contains many different proteins which make up about half of its surface. Many of these proteins are embedded in the membrane but stick out on both sides. There are thousands of proteins and ion channels on each of the 37.2 Trillion cells in the body !! Some of these proteins are receptors which bind to signal molecules, while others are ion channels which are the only means of allowing ions into or out of the cell.

Nucleus • Structure: • The nucleus is a sphere that contains another sphere called a nucleolus • It's function: - the storage center of the cell's DNA • Manages cell functions.

As mentioned, there are 226 types of Body cells - some can form sheets like those in your skin or lining your mouth, while others can store or generate energy, such as fat and muscle cells. All cells have an outer membrane, a control center called a nucleus that contains our DNA, and tiny powerhouses called mitochondria

CELL DIVERSITY- INTERNAL ORGANIZATION • The Nucleus of each cell contains DNA (deoxyribonucleic acid) which directs the activity of the cell. • Eukaryotes are cells in animals and plants that contain a nucleus and membrane-bound organelles (small internal parts), which includes all of our body cells. • As a group, the Eukaryotes and the sex cells in our bodies are called Somatic cells. • Prokaryotes are cells that lack nuclei and membrane-bound inside parts, such as those in bacteria.

STRUCTURE AND FUNCTION OF ORGANELLES • An organelle is a tiny cellular structure that performs specific functions within a cell. • Organelles are embedded within the cytoplasm (liquid) of our cells and are held in there by an outside membrane. – Cell Membrane – Nucleus – Cell Wall – Cytoplasm – Cytoskeleton – Ribosomes – Endoplasmic Reticulum – Golgi Apparatus – Mitochondria – Lysosomes – Peroxisomes – Cilia and Flagella – Basal Bodies – Centrioles – Vacuoles – Plastids.

MITOSIS Out of the 37.2 Trillion cells in your body, 96 million of them die every minute but luckily, 96 million new cells are created each minute. To do this, there has to be an efficient process in place to do that. This is called Mitosis, when one cell divides to produce two genetically identical cells, with the same DNA in them. The longer name for the final part of the process is Cytokinesis. It takes 2 hours for each cell to divide into 2 cells !! There is another type of cell division called Meiosis which is a process where a single cell divides twice to produce four cells, with each containing half the original amount of genetic information. These cells are our sex cells – sperm in males, eggs in females.

Medical genetics methods

There are various methods of studying hereditary diseases, the main ones being clinical and genealogical, twin, population, cytogenetic, biochemical and molecular genetic.

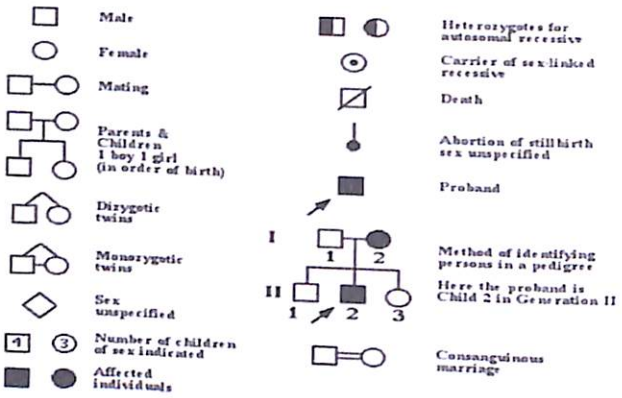
4.2. Clinical and genealogical method

Includes a clinical examination of the family members of the patient seeking counseling, drawing up a family tree and conducting a genealogical analysis.Genealogical analysis is the most common, the simplest and at the same time highly informative method available to everyone who is interested in his or her ancestry and family history. It does not require any material costs and apparatus. We are convinced that in time every medical history will include the patient's genealogy as an obligatory part of the life history.

One of the founders of clinical genetics and medical and genetic counseling in Russia S.N. Davidenkov (1960) wrote: "In clinical diagnosis, that is, in the direct practical work of the doctor genealogical research is extremely important, and often decisive moments of recognition:the habit of using the method of genealogy and personal examination of relatives for diagnosis is such a strong help in daily work that anyone who has at least a little experience in this, it seems strange how one could be content to consider only the bare phenotypes, completely ignoring the hereditary features that were characteristic of these people (family) long before the disease".

The pedigree reveals the medical and pathological background of the family, it can be used to judge with certain accuracy the type of inheritance of pathology, the family members who need examination and observation by a doctor.When compiling a family tree, a much warmer and more trusting contact with the patient and his or her relatives occurs than simply talking about the illnesses of loved ones. A well-compiled pedigree helps to predict the health status of the patient's relatives, their children and future offspring.The founder of the genealogical method of studying heredity is considered to be the German historian O. Lorenz, who published in 1898 a textbook of genealogy, which examines the patterns of origin of various family diseases.

In this textbook genealogy is considered not as a branch of historical knowledge, but as an independent science, delivering abundant material for biology, psychology, psychiatry, etc., and having its own tasks to establish patterns in the succession of generations.In 1912, the American Eugenic Institute issued sample straight-line pedigree tables, which are still in use today with little change.Symbols used in drawing up a pedigree are reflected in Fig. 1, the principle of drawing up a pedigree is presented in Fig. 2. The person from whom the study of pedigree begins is called proband, and not in all cases it is a patient, especially in pediatric practice.It is best to draw a family tree on a large sheet of paper with horizontal lines. All relatives belonging to the same generation should be placed on one line.Generations are designated by Roman numerals and individual members of each generation by Arabic numerals. In this case, each family member will have an individual number of one Roman and one Arabic numeral.The ages of all members of the pedigree should be given, since different diseases appear at different ages of life, and those personally examined should be marked with "!". More detailed explanations of the pedigree are called legends and are usually written on separate cards.



Pedigree symbols

Fig 2.

A well-compiled pedigree can answer many questions. In particular, it shows which diseases are most common in a family and which of its members should be tested for genetic predisposition to a certain pathology.The pedigree can be used to determine the type of inheritance of the disease and to find out which family members have a high risk of getting or giving birth to a similar patient. This data determines the choice of diagnosis method, preventive measures and timely medical care.

The use of the clinical and genealogical method implies a thorough clinical examination of the maximum number of members of the pedigree in order to detect sterile and atypical signs of the disease.Anamnestic data are collected according to a specific scheme. Information about the proband, information about the proband's siblings and parents, information about maternal and paternal relatives is recorded in the medical genetic card. The obstetric history of women is very important, including the course and background of pregnancy, details of spontaneous abortions, stillbirths, infertile marriages and early infant mortality. The presence and nature of occupational hazards, factors affecting fetal pathology (medications, maternal illness, etc.) should also be taken into account.Family genealogy can be a good help for its young members in solving social and professional issues. "The creation and accumulation of "life histories" and "family chronicles" is not only a humanitarian-scientific task, but also a general cultural one," says St. Petersburg sociologist A.N. Alekseev.Moreover, the scholar adds, "Any 'life story', for whatever purpose it is created, should include genealogical information - as detailed as the author of the story can provide. Family chronicles are based on a clear definition of the degrees of kinship, it is desirable to build a genealogical tree, which requires minimal training".

Vladimir Nabokov in his autobiographical novel "Other Shores" writes: "Eighteen years of leaving St. Petersburg, I was too young in Russia to show any curiosity about my ancestry; now I regret it - for technical reasons: with a distinct personal memory, the vagueness of family memory affects the balance of words".

4.3. The twin method

The twin method is based on clinical examination and comparison of mono- and dizygotic twins reared in the same or different environmental conditions.Monozygotic twins develop from a single fertilized egg and have the same hereditary constitution. Thus, the differences detected between them are not related to hereditary factors. Dizygotic twins develop from different eggs fertilized by different sperm.Their degree of genetic similarity is the same as that of normal sibs, but due to their simultaneous birth and co-parenting they share more environmental factors. Monozygotic twins separated in infancy or early childhood and reared in different environments are of particular value in the study of hereditary factors affecting behavioral, psychological, or intellectual traits.Using the twin method, it has been possible to prove the importance of genetic predisposition to many widespread diseases.

The result of comparing two groups of twins is a calculation of the percentage of identity or concordance of various traits or diseases exhibited by each twin pair.

The greater the heritable component of a trait or disease, the higher the concordance values, but most importantly, the greater the level of discordance between mono- and dizygotic twins.A quantitative estimate of the proportion of heritability of a trait is the coefficient of heritability (H), calculated according to the following formula proposed by Holzinger:

Disease Twins(%)		
	Monozygotic	**Dizygotic**
Type 1 diabetes	60-70	10-15
Type 2 diabetes	65-90	20-30
Grave's disease	30-35	2-5
Hashimoto's thyroiditis	50-55	0-2
Congenital hypothyroidism	1-20	0-2
Autoimmune throid disease	80-85	30-40
Thyroid nodules	50-60	20-40
Obesity	70-80	20-40
Osteoporotic fracture	9-10	2-7
Growth hormone deficiency	40-80	10-20
Congenital adrenal hyperplasia	70-90	10-25

H=(CMT– CDT)/(100-CDT),

where CMT and CDT are the percent concordance of the trait for mono- and dizygotic twins, respectively. If H>70%, the decisive role in the manifestation of the trait belongs to hereditary factors.At H<30%.- environmental factors are the main factors in the formation of the trait. At intermediate values of H, approximately equal participation of both genetic and environmental factors in trait control is assumed.

For example, when one of the partners of a twin pair contracts measles or pertussis, the probability of the other partner contracting the disease (pair concordance) is almost the same in the mono- and dizygotic twin groups: 98% and 94% and 97% and 93%, respectively.

The predominant role of the infectious factor in this case is obvious. In tuberculosis, the probability of the second twin in a monozygotic pair is almost 3 times higher than in a dizygotic pair - 67% and 23%. That is, with identical genotype, a similar reaction to tuberculosis infection occurs more often than with different genotypes. (Fig 3).

This fact shows the significant role of hereditary predisposition of the child to tuberculosis, which is now very important to keep in mind in connection with the data on the increasing prevalence of tuberculosis.

4.4.Population-basedmethod

The population method is aimed at studying the frequencies of alleles and genotypes in different populations, as well as the factors influencing their dynamics. This method is especially important in epidemiologic studies. Genetic study of human populations is impossible without taking into account geographical and climatic conditions.But especially important are demographic characteristics of the population, such as size, fertility, mortality, age and social structure, national composition, religious affiliation, lifestyle, nutrition, presence of bad habits, etc. The demographic characteristics of the population, such as size, fertility, mortality, age and social structure, national composition, religious affiliation, lifestyle, nutrition, presence of bad habits, etc., are also important. Hereditary diseases occur with different frequencies in different populations, ethnic groups and races, and this is due to differences in mutation frequencies and spectra.

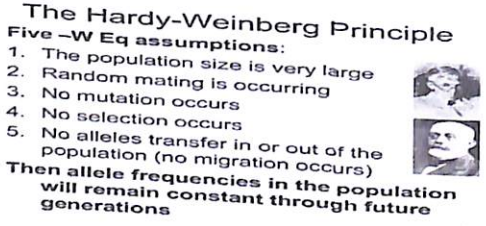


Fig 4.

The analysis of the conformity of allele and genotype frequency distribution in different populations to the Hardy-Weinberg law allows us to judge whether a population is panmictic (Fig 5), i.e. whether the principle of random interbreeding is

observed in it regardless of the genotypes of individuals. Important practical tasks are the analysis of spectra and frequencies of distribution in separate populations of mutant alleles associated with certain hereditary diseases and the identification of major mutations among them. (Fig 4)

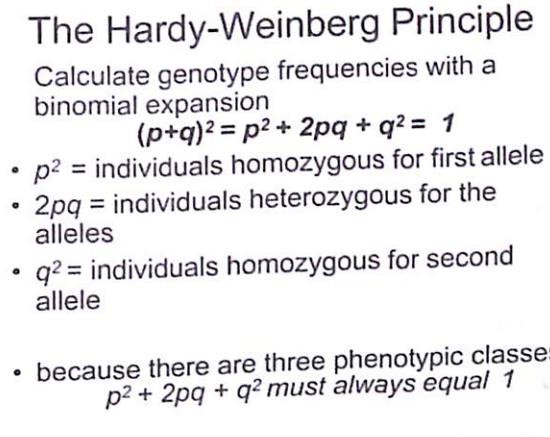


Fig 5.

4.5.Cytogenetic method

The cytogenetic method is used to analyze the karyotype and its abnormalities in individuals. It is sufficient to obtain a 1-2 ml sample of the patient's peripheral blood for the study. Karyotype analysis is performed in three stages: cultivation of blood lymphocytes, staining of the preparation and its microscopic analysis.Culturing is performed in order to stimulate lymphocyte division, since the success of cytogenetic study depends on the number of cells at the metaphase stage, when chromosomes are in the most compact form. The duration of cultivation is usually 72 hours. To increase the number of metaphase cells, colchicine is injected into the medium at the end of cultivation, which halts division at the metaphase stage, destroys the division spindle, and increases chromosome condensation. Next, the cells are placed in a hypotonic solution, which leads to the rupture of the nuclear envelope and free movement of chromosomes in the cytoplasm. At the next stage, the cells are fixed with a mixture of ethanol and acetic acid in the ratio of 3:1, their suspension is scraped onto slides and dried. Depending on the purposes of karyotyping, different methods of differential staining of chromosomes (G-, R-, C-, Q-methods) are used. The staining procedure takes a few minutes and results in a cross-linking pattern specific to each chromosome. Light microscopy of stained preparations is the most time-consuming step of the whole study, requiring high qualification. To detect chromosomal anomalies, at least 30 metaphase plates should be analyzed. Computerized chromosome analysis methods are very effective.

The introduction of molecular technologies combined with the use of fluorescent staining dramatically increases the resolution of cytogenetic analysis. In this case, individual segments of chromosomes can be stained in different colors, and karyotypes as a whole look like fantastic amazingly colorful pictures. Methods have also been developed for staining chromosomes in quiescent cells, when chromosomes are maximally stretched. With their help, chromosome segments of about 50 kilobases in size can be identified.

4.6.Biochemical, immunological and microbiological methods.

Biochemical and immunological methods are based on the analysis of various classes of organic and inorganic compounds defective in different hereditary diseases, primarily hereditary metabolic diseases.Biochemical disorders, as a rule, precede the appearance of clinical symptoms of the disease and are more constant in comparison with them. The subject of biochemical diagnosis can be proteins, amino acids, carbohydrates, lipids, metal ions, etc., as well as their metabolitesDifferent tissues and body secretions (blood, urine, saliva, sweat, liquor, amniotic fluid, biopsies of muscle, skin, liver and other specialized tissues) can be examined. Biochemical methods play a primary role in the diagnosis of inherited metabolic disorders. In some cases, they allow the detection of heterozygous mutation carriers. The role of biochemical methods of analysis is very important in the mass screening of pregnant women or newborns for earlier detection of hereditary diseases.

The key role in the pathogenesis of any monogenic disease belongs to the primary biochemical defect - the protein encoded by the mutant gene. Identification and analysis of the primary biochemical defect, determination of the primary pathological metabolic chain - these are the main goals of biochemical genetics, the solution of which is the basis for the development of pathogenetic methods of prevention and therapy of hereditary diseases. The role of biochemical methods in the diagnosis of secondary disorders is equally important. For example, the primary biochemical defect in Duchenne/Becker muscular dystrophy is a deficiency of dystrophin, a protein that connects the cytoskeleton of the muscle cell to the extracellular matrix. As a result of this disorder, the level of one of the muscle enzymes creatine phosphokinase increases in the blood of patients, both at the beginning of the disease and in its advanced stage. Moreover, the content of this enzyme is elevated in 30% of heterozygous carriers of the mutation. Although this disorder is secondary, the prostate testing of creatine phosphokinase and the persistence of its elevation in patients make it a convenient diagnostic marker of the disease.

The variety of biochemical methods is enormous and they are constantly being improved. They are subdivided into qualitative, quantitative and semi-quantitative. Qualitative reactions allow the detection of excessive amounts of intermediate metabolites that accumulate in hereditary metabolic diseases as a result of enzymatic reaction block. They are simple, inexpensive and quite sensitive.

Urine is often used as a substrate for qualitative reactions. Semi-quantitative and quantitative tests are performed with both urine and blood. The simplest of these

are the measurement of pyruvate, lactate, ammonium ions, and the measurement of acid-base balance. The leading role in the diagnosis of hereditary metabolic diseases belongs to highly accurate quantitative tests using fluorimetry, spectrophotometry, chromotography, electrophoresis, and mass spectrometry. Some methods allow simultaneous quantification of several thousand metabolic markers. However, these methods require the use of rather expensive equipment and consumables. In some cases, immunological methods of protein analysis are more effective than biochemical methods. Among them we should mention the immunohistochemical method, which makes it possible to analyze proteins and determine their localization in specialized cells and tissues of the organism. Immunologic methods are used in the examination of patients with immunodeficiency states (agammaglobulinemia, ataxia-teleangiectasia-Louis-Bar syndrome, etc.), in suspected antigenic incompatibility of the blood of the mother and fetus, in the establishment of paternity.

Microbiological methods are used to analyze the presence in a biological sample of certain substances - amino acids, sugars, etc., necessary for the growth of certain strains of microorganisms. This method is the basis of the well-known Guthrie test used in the diagnosis of phenylketonuria, histidinemia, galactosemia and leucinosis.

4.7.Molecular genetic method

The molecular genetic method is based on the analysis of nucleic acids, primarily DNA molecules. The main purpose of these methods is to diagnose mutations, study their association with inherited diseases, and identify heterozygous and homozygous carriers of the mutation.

In essence, molecular diagnosis is the most objective method of verification of hereditary diseases. It is important to emphasize that finding mutations in homozygous or heterozygous states in recessive or dominant diseases, respectively, is an indisputable confirmation of the diagnosis. However, in cases where mutations cannot be detected, the clinician retains the decisive conclusion in making the diagnosis, since the molecular diagnostic methods used in practice most often do not allow the identification of all possible mutations in the gene under investigation. The introduction of molecular genetic methodology into clinical practice was facilitated by the development of polymerase chain reaction (PCR) or specific DNA amplification, which occurred more than 20 years ago. The pioneer of this method, Kerry Moulis, was awarded the Nobel Prize for his invention in 1993. The PCR method allows the testing of gene states in individuals. Its essence consists in selective in vitro copying of a small fragment of a gene in which a mutation is suspected to be localized, using the subject's genomic DNA as a matrix. The small size of the gene fragment to be copied (or amplified), combined with their huge number, makes it possible to further use very simple methods to analyze this DNA fragment, to identify its features in the patient under study. The main of these methods are electrophoresis of amplified DNA, its staining, cutting with specific enzymes - restriction enzymes, and determination of the nucleotide sequence of this fragment - sequencing.

PCR is the basis for DNA diagnosis of any hereditary disease. This approach is also widely used to analyze genetic risk factors predisposing to the development of widespread multifactorial diseases. In the case of molecular diagnostics of infections, a DNA fragment specific for a certain pathogen is amplified, and then the presence of this fragment, and thus of the pathogen itself, in the biological sample that was taken for analysis is tested using electrophoresis and DNA staining. The use of PCR in forensic medicine is based on the amplification of highly variable regions of the genome, which allows for personal identification - the method of genomic fingerprinting.

The advantage of DNA diagnostics compared to biochemical or immunological diagnostics is the use of a unified set of methods, virtually independent of the goals of the study. These are methods of DNA isolation, PCR, electrophoresis, DNA restriction, hybridization with specific *DNA probes* and sequencing.

Thus, it is possible to perform DNA diagnostics of a wide range of diseases within one laboratory. Let us elaborate on the key methods of molecular diagnostics.

*DNA isolation.*First of all, it should be remembered that the bulk of DNA is located in nuclei as part of chromosomes in a supercoiled state due to interaction with certain proteins. Thus, DNA can be isolated from any type of tissue or cell that contains nuclei.There are many modifications of DNA isolation methods. We will only discuss the basic fundamentals of one of these methods. In humans, DNA is most often isolated from blood leukocytes, for which 1 to 5 ml of blood is taken from the vein. Blood should be collected in the presence of anticoagulants. After sedimentation of the blood, a leukocyte-rich layer is taken and detergents are added to disrupt the cell membrane. Nuclei are precipitated to the bottom of the tube by gentle centrifugation. The supernatant is drained, and detergents to destroy the membranes and proteolytic enzymes to destroy the proteins are added to the nuclei suspension. Most often proteinase K is used. Thus DNA is released into solution. The next step is to separate the high molecular weight DNA fraction from low molecular weight compounds such as protein fragments, lipids, carbohydrates, etc. One method of such separation is phenol extraction. When phenol is added and thoroughly stirred, low molecular weight compounds will pass into phenol, which will turn brown due to the presence of hemoglobin fragments, while DNA molecules will remain on the surface of phenol, as they will not be able to enter this dense solution. The light solution over phenol containing DNA is withdrawn and several rounds of repeated purifications with phenol are carried out with the addition of chloroform in the last stages. The DNA can then be precipitated from the solution by adding ethanol. At 700 alcohol, the DNA precipitates as an amorphous formation. In this state it can be stored at low temperatures for long periods of time.

Polymerase chain reaction (PCR) or specific DNA amplification is the selective in vitro synthesis of a large number of copies (on the order of a million) of a small DNA fragment, usually hundreds of nucleotides in size, from a matrix DNA molecule.PCR requires the artificial synthesis of small single-stranded DNA molecules of 15 to 30 nucleotides, complementary to the ends of the DNA fragment to be amplified. These molecules are called *primers.*They serve as a primer for DNA

synthesis and therefore determine its specificity. PCR is performed in special disposable tubes in a very small volume, usually not exceeding 50 µl. To this volume of defined buffer is added matrix DNA (DNA of the subject), two types of commercially synthesized primers, the enzyme of complementary DNA synthesis - thermophilic DNA polymerase, isolated from thermophilic bacteria and therefore able to withstand high temperatures, and 4 types of deoxytriphosphates (dNTP), which serve as a building material for DNA synthesis.

In the first step, matrix DNA is converted to single-stranded form by heating the solution above 950 for several minutes. Then three short-term procedures lasting a few tens of seconds are cycled: (1) annealing or primer seeding - this occurs when the solution is cooled to a temperature optimal for the formation of a double-stranded structure of matrix DNA with primers; (2) DNA synthesis starting from the primer - this occurs when the solution temperature is raised to values optimal for the operation of thermophilic DNA polymerase; and (3) denaturation of synthesized DNA - achieved by raising the solution temperature above 900 to convert the DNA to the single-stranded form. Then everything is repeated starting from procedure (1). In this way, at each cycle of temperature change, the DNA strand located between the primers is doubled, with the length of this strand exactly corresponding to the distance between the outer ends of the primers. After 25-30 such cycles, the number of newly synthesized DNA fragments reaches or even exceeds one million copies. The choice of the temperature change program and the duration of each cycle procedure, along with the choice of primers and buffer, depend on the length and specificity of the DNA fragment to be amplified. These parameters determine the art of PCR and are very often chosen empirically. The cyclic temperature change is done automatically in a device called a DNA amplifier or thermocycler. Thus, PCR is an easy to perform, low cost, highly accurate and modern method of molecular diagnostics.

DNA electrophoresis is not fundamentally different from protein electrophoresis. Amplified DNA is applied to a polyacrylamide or agarose gel and the current is turned on. This starts the progression of DNA in the gel from minus to plus, and the speed of this progression depends on the length of the molecule and its configuration.After a certain amount of time, DNA molecules of equal length will concentrate in narrow zones. The number of copies of DNA synthesized during the PCR process is usually sufficient to visualize the DNA using the routine ethidium bromide staining method. When this dye is added to the gel, the DNA bands appear red when the gel is viewed under an ultraviolet lamp.

There are many modifications of PCR convenient for specific studies. For example, not one but several DNA fragments can be amplified at one time - *multiplex or multiple PCR. Asymmetric PCR* allows for preferential synthesis of one DNA strand. By introducing specific dyes into primers it is possible to estimate the number of copies of amplified DNA fragments on an automatic scanner - quantitative PCRThe real-time PCR method is very powerful. On the basis of PCR, molecular cytogenetics methods are being developed - *PRINS*, quantitative fluorescent PCR. The latter method, based on multiplex amplification of repetitive chromosome-specific polymorphic DNA sequences, allows estimating the number of copies of

specific chromosomes or their fragments, and it is very convenient for prenatal diagnosis of fetal aneuploidies, such as Down syndrome, Edwards syndrome, Patau, and others.

4.8.Molecular mutation diagnosis or DNA diagnosis.

Clinical methods of molecular diagnostics depend on the nature of gene damage, i.e. the type of mutation. Structural intragenic mutations, such as deletions and insertions, are the easiest to diagnose, as they change the length, and thus the electrophoretic mobility, of the amplified DNA fragment. To diagnose such mutations, it is sufficient to perform PCR using specific primers and electrophoresis, and then compare the length of the amplified DNA fragment in normal and in the patient. In homozygotes for the deletion, the size of the amplified fragment will be shorter by the size of the deletion, which means that this fragment will move faster during electrophoresis and will be located below the normal fragment. Heterozygotes will have two fragments on the electrophoregram, one of normal size and the other shorter. Similarly, insertions are diagnosed, but the length of the amplified fragment in mutant homozygotes will be longer, and the fragment itself will be located higher than normal on the electrophoregram. Heterozygotes will also have two fragments on the electrophoregram - a normal fragment and a long fragment, i.e. located above the normal fragment. the results of the diagnosis of a major mutation in the cystic fibrosis gene - delF508 - a deletion of 3 nucleotides in the 10th exon of the CFTR gene are presented.

The multiplex PCR method followed by electrophoretic separation of mapped DNA fragments is convenient for diagnosing more extended intragenic deletions. Fig. 34 the results of the diagnosis of deletions in the Duchenne myodystrophy gene by multiplex PCR are presented.

Molecular diagnosis of missense- or nonsense-type point mutations is more difficult because the length of the amplified fragment does not change.The most common method for diagnosing such mutations is *restriction analysis*.This method can be used only when mutations randomly alter sequences specific for recognition by restrictionases - endonucleases that catalyze the cutting of DNA sequences at the localization sites of these specific sites.To diagnose such mutations, it is sufficient to perform PCR, restriction of the amplified DNA fragment using a specific endonuclease, and electrophoresis. In the presence of a normal restriction site, the amplified fragment will be cut and the electrophoregram will show two bands corresponding to DNA fragments whose total length is equal to the value of the original amplified fragment.Disappearance of the restriction site as a result of the mutation will result in the mutant homozygotes having no cutting of the amplified fragment and a single band on the electrophoregram, with a pattern similar to that seen after electrophoresis before restriction.

Heterozygotes will show all three bands, one of which corresponds to the uncut amplified fragment and two of which correspond to restriction products.Currently, more than 500 different restriction enzymes have been identified, and for each of these enzymes there is a different recognition site. Therefore, as soon as a new mutation is described, the surrounding nucleotide sequence is immediately analyzed for restriction sites using certain computer technology.If this search is successful, clinical diagnosis of such a mutation is made by restriction analysis using a site-specific endonuclease.Since the method of restriction analysis is very simple and easy to perform, there are many modifications of this method aimed at artificial introduction of restriction sites, etc. However, we will not dwell on them. Fig. 35 shows the results of diagnosis of the R408W mutation in the phenylketonuria gene by restriction analysis.

A universal method for diagnosing point mutations is the allele-specific oligonucleotide (ASO) method. This method is based on hybridization of amplified DNA with specific oligonucleotide DNA probes. It is more labor-intensive, as it requires synthesis and specific labeling of DNA probes. However, this method is amenable to automation, and on its basis, technologies are being developed that allow simultaneous testing of tens or even hundreds of mutations. Microarray technology is used, i.e. labeled oligonucleotides are applied in micro quantities to solid carriers (chips) and then hybridized with the DNA samples under study.

A similar technology - "microarray" - is used to analyze the expression profile of genes, i.e. a set of genes selectively expressed in specific tissues or cells, in patients with certain pathological conditions, differing in age, ethnicity and other parameters. The microarray technique allows simultaneous analysis of the expression of tens of thousands of genes.

DNA sequencing is the most objective method of mutation registration which accurately identifies the molecular nature of the lesion.

However, this method is rarely used in clinical practice due to its labor-intensive and high cost.

Autosomal syndromes are divided into three groups: complete trisomies, partial aneuploidies and microcytogenetic anomalies. Numerical abnormalities of sex chromosomes, including polyploidies and monosomies, are quite common. Autosomal polyploidies and monosomies are always lethal, and they are found only in abortus material.

Trisomies

Trisomies among live births have been described only for chromosomes 8, 9, 13, 18, 21, and 22; the remaining chromosomes are lethal. Of these, Down syndrome is the most frequent and clinically significant. Edwards (trisomy 18) and Patau (trisomy 13) syndromes are less common, and the life expectancy of these patients is usually less than a year. The remaining autosomal trisomies are even rarer, and their carriers die in early neonatal age.

The most common cause of trisomy is chromosome divergence during gametogenesis of the parents. Chromosome divergence in meiosis increases sharply with the age of the mother, while the age of the father is almost irrelevant. This is due to the peculiarities of meiosis in women. Female germ cells, the precursors of the oocyte (oocytes), are formed in the third month of embryogenesis, when the first division of meiosis takes place. Meiosis is then blocked and is completed only after fertilization. With age, there is a decline in ovulatory reproductive function, which contributes to follicle over-ripening. One consequence of this over-ripening is a disturbance in the even distribution of chromosomes during division. In males, both phases of spermatogenesis occur every 70 to 72 days.

5.1. Down syndrome

The best known numerical chromosome abnormalities include Down syndrome, a form of mental retardation caused by the presence of an extra 21 chromosomes - trisomy on chromosome 21. This disease was first described in 1866 by John Down, a physician at the Earlsweed Psychiatric Hospital (Surrey, England). The frequency of pathology on average is equal to 1:700 newborns, in the population - 1: 4000. Among patients with oligophrenia, Down syndrome is the most common form and accounts for about 10%.

The critical segment for clinical manifestations of Down syndrome is the distal part of the long arm of chromosome 21 - 21q22, (Fig 6) where the gene for the key enzyme of antioxidant defense, superoxide dismutase, is localized. Trisomy results in hyperexpression of this enzyme with subsequent dysregulation of reactive oxygen species. Hyperproduction of free radicals leads to neurodegenerative processes in the CNS, premature aging and other clinical manifestations of Down syndrome.

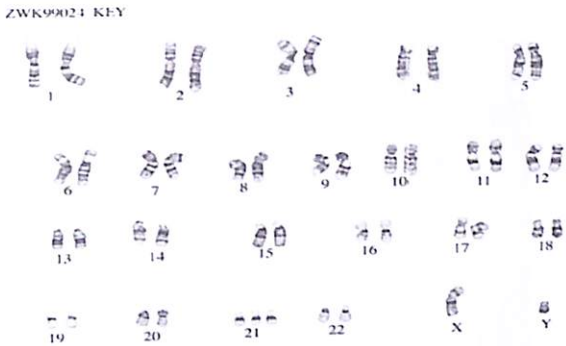


Fig 6

The diagnosis of Down syndrome should be assumed by a neonatologist immediately after the birth of a sick child, and this assumption should then be confirmed by karyotype analysis.

Down syndrome patients are characterized by peculiar phenotypic features, primarily facial anomalies, well known to any medical worker: slanting eyes, often epicanthus (a vertical skin fold covering the medial corner of the eye slit) (Fig 7) short nose with a wide bridge of the nose, small deformed ears, often a half-open mouth with a protruding (Fig 7) lower jaw, cracked dry lips, problems with sucking due to hyperglossia, "carp mouth", general hypotonia and adynamia. The patient's figure is relaxed, gait and movements are awkward, voice is rough, speech is one-syllable, eloquent. In addition, in 60% of cases, patients have one large transverse furrow on the palm, often on two palms. (Fig 8)

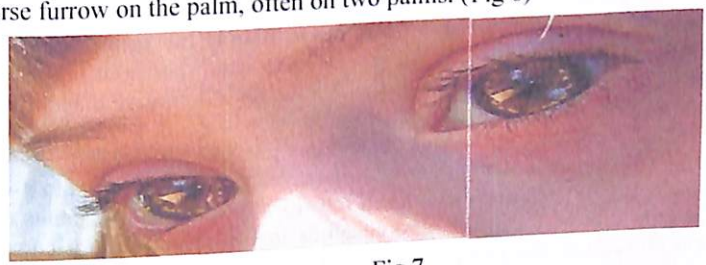


Fig 7

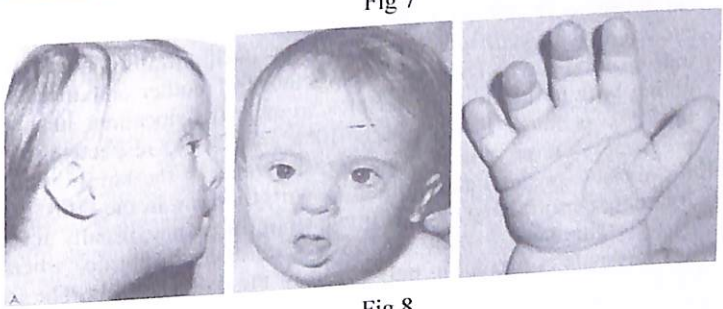
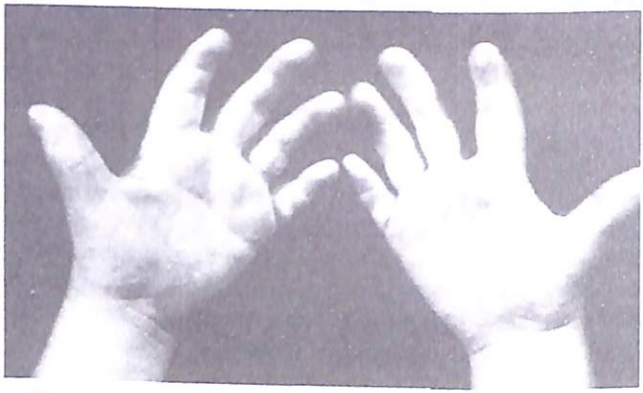


Fig 8

It should be noted that in 3% of cases such a furrow is also present in healthy people, and sometimes it is inherited by autosomal dominant type.



Therefore, on the basis of this sign alone, one should not assume Down syndrome in a newborn, much less report his or her assumption to the mother without obtaining karyotype data. Unfortunately, we have seen such cases in the practice of novice inexperienced doctors, which ended with the cessation of lactation in the mother. Often patients with Down syndrome have congenital heart defects, biliary system, leukemia. All patients have congenital dementia. In infancy, Down syndrome patients are apathetic and abnormally calm, never cry, and have sharply reduced muscle tone. A well-known expert on chromosomal diseases I.I. Shtilbans (1965) wrote: "Children with Down syndrome are affectionate, obedient, but sometimes stubborn, they are fearful and like to imitate those around them, so they can be taught to help others in the household, dress, but they are not capable of systematic labor. Simple life skills are usually learned by many of them". However, we repeat once again that even in the presence of the most striking manifestations of the disease for a definitive diagnosis it is necessary to study the karyotype of the patient. In 96% of cases, the karyotype in a boy with Down syndrome is 47, XY (+21) and in a girl - 47,XX (+21).

Translocation variant of Down syndrome is registered in 3-4% of cases. In this case, one of the parents has a translocation between segments of chromosome 21 and one of the other chromosomes in the presence of a complete set of 46 chromosomes. Most often, translocation of the 3rd segment of chromosome 21 to chromosome 13 or 15 is observed - translocation variants 21/13 or 21/15. Segment exchange can occur on chromosome 21 itself - translocation variant 21/21. In translocation 21/21, regardless of whether the mother or father has it, the risk of giving birth to a sick child is 100%, in other translocations in a woman or a man this risk is much lower and is 10% and 2-3%, respectively. In the case of pregnancy, the presence of such translocations in the family is a strict indication for invasive prenatal diagnosis of Down syndrome in the fetus. Such diagnosis is routinely performed in the first trimester of pregnancy, usually at 9-10 weeks.

The third variant of Down syndrome is mosaic, when the added 21 chromosome is present in only a part of the patient's cells. The frequency of this

variant is 1-2% . "Mosaics" have more erased manifestations of the syndrome, often their intelligence is preserved, but the external manifestations of the disease remain. To diagnose mosaicism, it is sometimes necessary to karyotype not only blood cells, but also other tissues of the patient (cultured fibroblasts, biopsies of various organs).

5.2. Patau syndrome

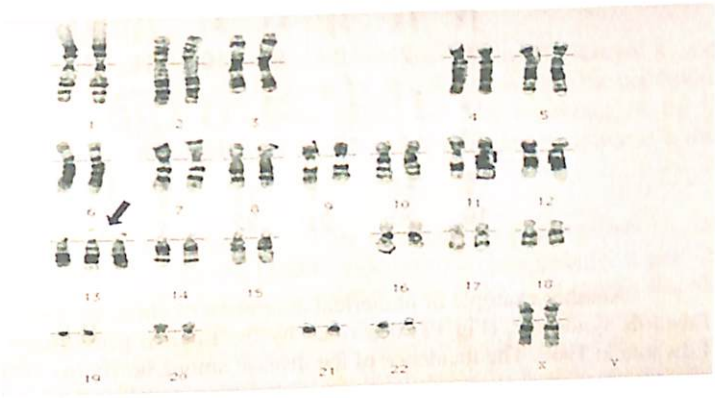


Fig 9

Trisomy on chromosome 13 (Fig 9) or Patau syndrome was described in 1960 in children with multiple congenital malformations. The frequency of the disease is 1:5000 - 1:7000 newborns. The clinical manifestations of the syndrome are quite specific and allow diagnosis already in the newborn period. These include craniofacial anomalies such as microcephaly, trigonocephaly, cleft lip and palate, microphthalmia, (Fig 10) narrow eye slits, sunken nose bridge, etc., often accompanied by severe brain development defects and combined with poly- and syndactyly of the hands and/or feet.

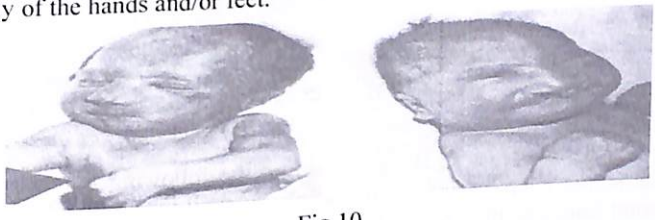


Fig 10

Patients have dermatoglyphic features in the form of loops and arcs in finger patterns, distal palm triradius. Often patients have malformations of other organs - heart, kidneys, genitalia, intestines. Deafness, muscle hypotonia, seizures, mental retardation are observed. All this leads to early death, and life expectancy of such children rarely exceeds 1 year.

5.3.Edwards syndrome

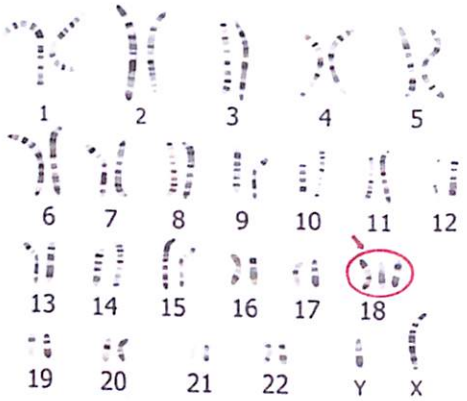


Fig 11

Another example of numerical aberration of chromosomes is trisomy 18 or Edwards syndrome, (Fig 11) described by the English pediatrician and geneticist Edwards in 1960. The incidence of the disease among newborns averages 1:7000.

Fig 12

This disease is characterized by the following symptoms: severe mental retardation, microcephaly, dolichocephalic skull with a step-like depression of the frontal bones in the area of the fontanelle, the auricles are low, the lower jaw is reduced in size (microgenia), the external opening of the mouth is small (microstomia), cleft upper lip and palate,(Fig 12) eye slits are narrow and short, spinal hernia, cryptorchidism and hypospadias in boys and clitoral hypertrophy in girls, congenital heart defect. Life expectancy is not more than a year. In mosaic forms, patients aged 19 years and older have been described.

In the prenatal period, the disease can be detected during biochemical screening of pregnant women by a sharp decrease in serum levels of chorionic

gonadotropin, which is an indirect sign of the presence of Edwards syndrome in the fetus. In this case, the pregnant woman should be referred for a level 2 ultrasound scan, because in Edwards syndrome, ultrasound markers of chromosomal diseases are detected in almost 100% of cases. Prenatal fetal karyotyping is indicated to confirm the diagnosis and further medical and genetic prognosis of future offspring of the parents.

5.4.Cri du Chat Syndrome

Cri du chat syndrome is a rare chromosomal disorder caused by a deletion of genetic material on part of chromosome 5. Other names for the condition are cat cry syndrome and 5p- syndrome. Symptoms can vary depending on the size and area of the deletion of chromosome 5. The most common symptom is a shrill, cat-like cry that newborns make.

Overview

Cri du chat syndrome, or cat cry syndrome, is a rare genetic disorder that happens because of a missing piece (deletion) of a chromosome. It gets its name from the distinct cry that infants with the disease make — it sounds like the high-pitched mewing of a cat. "Cri du chat" means "cry of the cat" in French.

5p- (pronounced "5p minus") syndrome is another name for the condition. 5p- describes the genetic deletion on the small arm (the p arm) of chromosome 5. 5p- syndrome is a spectrum disorder. The size and location of the deletion can vary, so symptoms can range from mild to severe. If your child has a larger deletion, they may have more serious symptoms.

Symptoms and Causes

Symptoms of cri du chat syndrome can vary widely. The most common symptom of the disorder is a distinct high-pitched, shrill cry. It sounds like a cat cry and may be present during the first few weeks of your baby's life. The cry becomes less noticeable as your baby grows older.

Your baby may also have distinct facial features that include:

Unusually small head (microcephaly).

Abnormally round face.

Wide nose.

Widely set eyes (hypertelorism).

Crossed eyes (strabismus).

Downward slanting eyelid folds (palpebral fissures).

Extra fold of skin over the inner corner of your child's eyes (monolid eyes).

Low-set ears.

Abnormally small jaw (micrognathia).

Unusually short distance from your child's upper lip to their nose (short philtrum).

As your baby grows, their face may lose its plumpness and become abnormally long and narrow.

Other symptoms of cri du-chat may include:

Low birth weight.

Delayed growth.

Feeding difficulties, such as poor sucking, difficulty swallowing (dysphagia).

Weak muscle tone (hypotonia).

Curvature of the spine (scoliosis).

Heart defects.

Developmental delays, such as head control, sitting up and walking.

Speech and language delays.

Moderate to severe intellectual disability.

Cri du chat syndrome is a chromosomal disorder. A deletion of part of the short arm (the p arm) of chromosome 5 causes the condition. This deletion most often occurs randomly during the formation of reproductive cells (eggs or sperm) in early fetal development. The parents of a child with a random deletion usually have normal chromosomes.

About 10% of people with the disorder inherit the chromosome abnormality from an unaffected parent. When this happens, the parent carries a chromosomal rearrangement called a balanced translocation. The parent doesn't lose or gain any genetic material, and they don't usually have any medical problems. But balanced translocations can become unbalanced when a parent passes them on to their child.

Diagnosis

Your child's healthcare provider will usually be able to diagnose cri du chat syndrome at birth. They'll see and hear the usual symptoms — including the cat-like cry — associated with the disease. They'll perform a complete physical exam and evaluate your child's symptoms. More than likely, your child's provider will recommend chromosomal testing to confirm the diagnosis.

There are three genetic tests your child's healthcare provider may use to diagnose cri du chat:

Karyotype: A karyotype chromosomal analysis maps out your child's chromosomes and lets you know if something is missing or added.

FISH testing: FISH stands for fluorescence in situ hybridization. FISH testing looks for specific gene changes or parts of genes in your child's cells.

Chromosome microarray analysis: Microarray analysis is a type of genetic testing that compares your child's DNA to a control group. It can identify deletions and duplications of whole chromosomes, parts of chromosomes and specific locations of chromosomes.

Management and Treatment

There's no cure for cri du chat. But, with prompt diagnosis and early intervention, your child may be capable of reaching their fullest potential and leading a meaningful life.

Treatment for cri du chat syndrome varies depending on your child's specific symptoms. Treatment will most likely require ongoing care from a team of healthcare providers. The most common form of treatment is rehabilitation through physical therapy, occupational therapy and speech therapy.

Physical therapy

If your baby has feeding difficulties, they should start physical therapy right away to address problems with sucking and swallowing. Physical therapy can also help your child's physical development by teaching them to sit, stand and improve their fine motor skills.

Occupational therapy

Occupational therapy may benefit your child by providing interventions that can help them develop skills to interact with the world around them. These may include fine motor, visual, self-care and sensory skills.

Speech therapy

Speech therapy can assist your child with communication issues. Speech therapists teach your child different methods of communicating, such as sign language and technology-assisted communication. Speech therapists also help with feeding issues from an early age.

In addition to supportive therapies, your child's healthcare provider may recommend surgery to treat a variety of symptoms. Surgery may correct congenital heart defects, strabismus and scoliosis.

Prevention

You can't prevent cri du chat syndrome since it's a genetic condition. If you plan on becoming pregnant, talk to your healthcare provider about genetic counseling. Genetic counseling can help you understand your risk of having a child with a genetic condition.

Outlook / Prognosis

What is the life expectancy for cri du chat?

The outlook for most children with cri du chat syndrome is variable. The size and location of the deletion of chromosome 5 is a major factor in your child's prognosis. Your child will have noteworthy limitations in their physical and mental development. But most children with cri du chat have a normal life expectancy.

Some children, however, are born with life-threatening health issues. Of these children, about 75% will die during their first month of life. About 90% of deaths occur during the first year of life. Rates of death decrease after the first few years of life.

One of the most important factors in the prognosis of your child's disease is a prompt diagnosis. This allows for early intervention and therapeutic methods that can help your child succeed.

5.5. Sex chromosome abnormalities

Quite often numerical anomalies affect sex chromosomes. Thus, the presence of an extra X chromosome in males leads to Klinefelter syndrome, and the absence of one of the X chromosomes in females leads to Sherechevsky-Turner syndrome. Both of these diseases are characterized by infertility and various deviations from normal development.

Kleinfelter's syndrome

Klinefelter's syndrome was described by the American physician H.F. Klinefelter in 1942. Infertility, testicular atrophy, oligospermia (small ejaculate volume) and azoospermia (absence of spermatozoa in semen), gynecomastia and

often mental retardation are characteristic symptoms of this disease. The clinical symptomatology of the disease is most pronounced in prepubertal and pubertal age. More often such patients are identified by the medical commission at the military enlistment office during the examination of conscripts. Young men with Kleinfelter syndrome are distinguished from their peers by their tall stature and the discrepancy between height and arm span, which sometimes exceeds height by at least 10 cm, eunuchoid physique (long legs, high waist, relatively wide pelvis) with a tendency to obesity. The penis is of normal size and the testicles are descended into the scrotum, but soft to the touch and very small. The diameter of the testicles rarely exceeds 1.5 cm, while in a healthy young man this value is equal to 5 cm. The frequency of the syndrome among newborn boys is 1:850, in the population is equal to 1:18,000 healthy men, among boys with mental retardation - 1:100 and with the same frequency among men suffering from infertility.

Male sex hormones (testosterone propionate and its analogs) are used in the treatment of patients with Kleinfelter syndrome. In case of gynecomastia - surgical intervention. Psychostimulants and neurometabolic drugs may be recommended when indicated, as is generally accepted in other forms of oligophrenia. When creating a family, the use of assisted reproductive technologies using donor sperm is indicated.

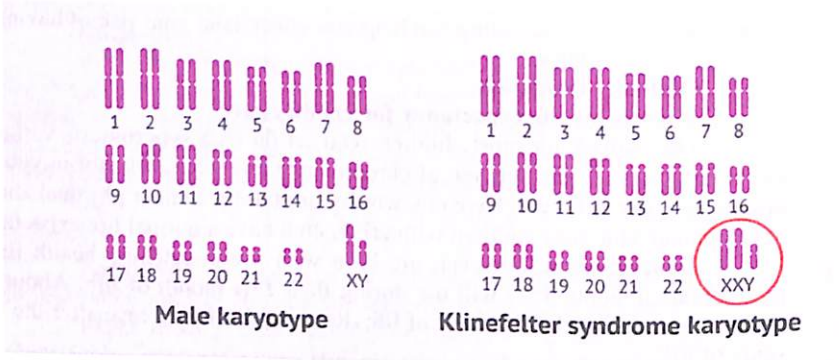


Fig 13

In 1958, in the work of P. E. Polanyi et al. for the first time in the cytogenetic study of patients with Klinefelter syndrome were identified two X-chromosomes along with a Y-chromosome. Later it turned out that the most common variant of karyotype in Klinefelter syndrome is 47, XXY, (Fig 13) but there are patients in whom the number of X-chromosomes reaches 4 or more. Thus, the above symptoms are a reason to investigate the karyotype of the patient.

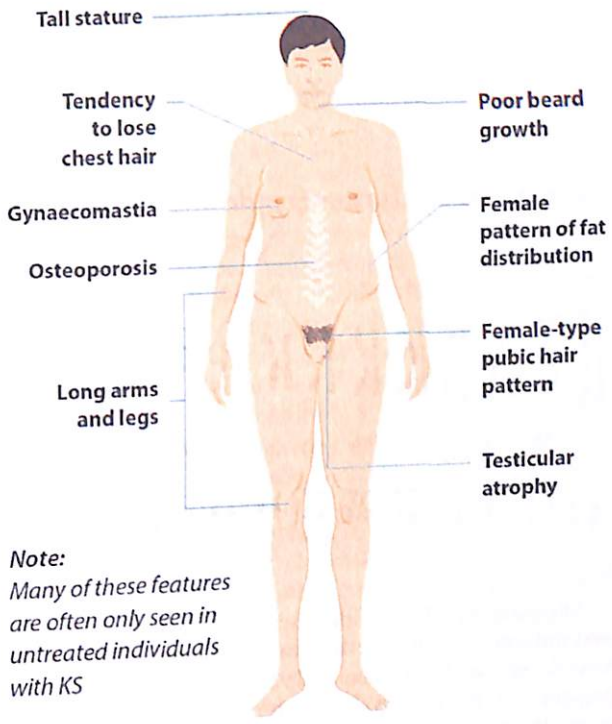


Fig 14

It is interesting to note that polysomy on the X chromosome in women (trisomy - 47,XXX, tetrasomy - 47,XXXX and pentosomy - 47,XXXXX) most often does not lead to any pathological processes, as the additional chromosomes are inactivated, and at karyotyping of such women look like additional Barr's corpuscles. Most carriers of such anomalies retain a normal phenotype. However, in some cases, complete inactivation of the extra X chromosomes does not occur. This can lead to menstrual irregularities, pregnancy failure, and early menopause.In some women, abnormalities are expressed in reduced intelligence, aggressive behavior, sometimes infertility, and signs of dysmorphogenesis. (Fig 14) The frequency of triplo-X (47,XXX) and quadri-X (48,XXX) is 1:800.

5.6.Y-chromosome polysomia in males

The appearance of an extra Y chromosome in the male karyotype (47,XYYY), as a rule, does not lead to any sexual anomalies. Such men are fertile, and the probability of having a child with chromosomal abnormalities is no higher than normal. However, such men have tall stature, mandibular prognathia, increased aggressiveness and are prone to antisocial behavior. The syndrome was

first described in a survey of inmates in US prisons. It is assumed that such patients may have criminogenic tendencies.

5.7.Shereshevsky-Turner disease.

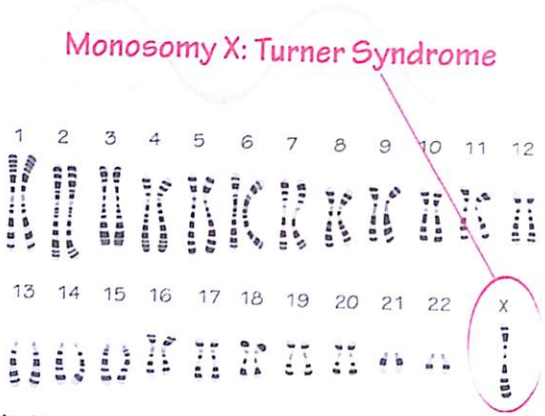


Fig 15

Shereshevsky-Turner disease or monosomy on the X chromosome is observed only in women. The first to describe this disease was our compatriot N. A. Shereshevsky in 1925, then in 1938 the American endocrinologist H. Turner. The presence of monosomy-X can be suspected in newborn girls with a body weight of 2500 g or less, wing-shaped skin folds on the back of the neck, and lymphoedema of the hands and feet. Similar clinical manifestations are observed in half of newborns with Sherechevsky-Turner syndrome. The origin of lymphoedema is attributed to cardiovascular insufficiency due to congenital heart disease, often observed in these patients. About a quarter of patients are diagnosed with malformations of internal organs, most often the heart and kidneys. (Fig 16)

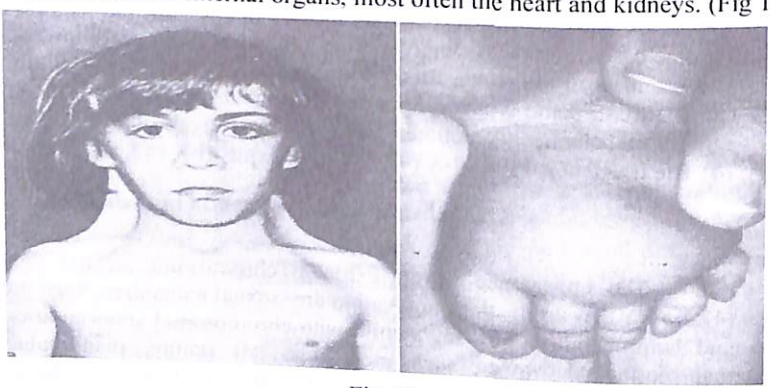


Fig 16

Until 9-10 years of age, sick girls develop without peculiarities. Then they have growth retardation and a mild degree of mental retardation. Minor signs of dysembryogenesis in this disease are epicanthus, less commonly ptosis (drooping of the upper eyelid), strabismus, and clouding of the lens and/or cornea of the eye. The leading symptom of Shereshevsky-Turner disease is sexual infantilism associated with dysgenesis of the gonads, which is fully revealed at puberty and beyond. The genitalia have a female structure with a significant degree of underdevelopment. Sexual infantilism, primary amenorrhea and infertility are the result of changes in the gonads caused by the absence of one X chromosome. (Fig 15) Patients do not have normal primordial follicle formation. Germinal and follicular cells degenerate and produce almost no estrogen. This results in primary amenorrhea, underdevelopment of mammary glands, and scanty pubic and axillary hair. Patients have a hormone-dependent decrease in height. At the age of 16-23 years, the average height of patients is 135 cm (in healthy peers 158 cm). Short stature of a girl in combination with primary amenorrhea is a mandatory indication for her karyotyping, in which the absence of one X chromosome - 45,XO - is observed. The incidence of the disease is 1:2000 - 1:5000 newborns, and at the height of adult women 130 - 145 cm this frequency increases to 1:14. The course of the disease depends largely on which X chromosome is lost - maternal or paternal. The loss of the maternal X chromosome can lead to the termination of embryo development and its spontaneous elimination already at the stage of embryogenesis. If this does not happen, the fetus develops severe disorders of the cardiovascular system. In the case of paternal X chromosome loss, congenital malformations are usually absent and the mental development of the affected girls is more preserved than in the first case. It should be noted that special studies make it possible to determine the X chromosome identity. This is important in the medical and genetic prognosis of the future child and the decision of parents to prolong pregnancy with a fetus in whom prenatal karyotyping has revealed Sherechevski-Turner disease.

In some girls who are clinically diagnosed with this chromosomal disease, a mosaic variant of the disease may be observed. In this case, along with cells with a normal karyotype, patients have cells with a pathological karyotype, i.e. without one X chromosome. The karyotype in these cases looks like this: 46,XX/45,XO. Moreover, the ratio between the number of cells with normal and pathologic karyotype is indicated. The ratio of cells with normal and pathologic karyotype correlates with the patient's condition.

Some women with the mosaic variant of Sherechevski-Turner disease have normal development of secondary sex characteristics, including genitalia, normal development of secondary sexual characteristics, including genitalia. Furthermore, these women are able in some cases to have traditional pregnancies. Some of them in vitro fertilisation techniques. Of course, these pregnant women need to undergo prenatal karyotyping.

Autosomal recessive diseases

Autosomal recessive diseases are manifested only when the mutant alleles are carried homozygously. In this case, there is partial or complete inactivation of the function of the mutant gene. One of the mutations of the sick child inherits from the mother, the other - from the father. In general, the parents of the patient, being healthy themselves, are heterozygous carriers of the mutation. According to Mendel's law, the probability of a sick child being born in such a family is 25%. Girls and boys are sick with the same frequency, and the birth of a sick child does not depend on the age of the parents, the order of pregnancy and childbirth. Often several sick sibs can be observed in one family.

In many forms of autosomal recessive diseases, patients do not leave offspring due to the severity of their condition. Most often, sick children are born to healthy parents, each of whom carries the mutation in a heterozygous state. Thus, when analysing the pedigree, the "horizontal" nature of hereditary transmission of the disease can be traced. Two thirds of healthy children in the marriage of heterozygous parents also turn out to be heterozygous carriers of the mutation. In the marriage of a heterozygous carrier of a recessive mutation with a spouse who does not have the mutant allele, all children will be healthy, but half of them will be heterozygous carriers of the mutation. Analysis of pedigrees of patients with autosomal recessive diseases shows that often (about 60%) parents of such patients are relatives or their ancestors come from the same village or district, which is also an indirect sign of inbreeding.

6.1. Phenylketonuria

Phenylketonuria (PKU) is an inborn error of metabolismthat results in decreased metabolism of the amino acidphenylalanine

Itisduetothedefetctofenzymephenylalanine

hydroxylasethatbreaksdownphenylalanine.

GThisenzymenormallyconvertsphenylalaninetoanotheraminoacidtyros ine

History

Before the causes of PKU were understood, PKU caused severe disability in most people who inherited the relevant mutations. Nobel and Pulitzer Prize winning author Pearl S. Buck had a daughter named Carol who lived with PKU before treatment was available, and wrote an account of its effects in a book called *The Child Who Never Grew*.Many untreated PKU patients born before widespread newborn screening are still alive, largely in dependent living homes/institutions.

Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Følling in 1934 when he noticed hyperphenylalaninemia (HPA) was associated with intellectual disability. In Norway, this disorder is known as Følling's disease,

named after its discoverer. Følling was one of the first physicians to apply detailed chemical analysis to the study of disease.

In 1934 at Rikshospitalet, Følling saw a young woman named Borgny Egeland. She had two children, Liv and Dag, who had been normal at birth but subsequently developed intellectual disability. When Dag was about a year old, the mother noticed a strong smell to his urine. Følling obtained urine samples from the children and, after many tests, he found that the substance causing the odor in the urine was phenylpyruvic acid. The children, he concluded, had excess phenylpyruvic acid in the urine, the condition which came to be called phenylketonuria (PKU).

His careful analysis of the urine of the two affected siblings led him to request many physicians near Oslo to test the urine of other affected patients. This led to the discovery of the same substance he had found in eight other patients. He conducted tests and found reactions that gave rise to benzaldehyde and benzoic acid, which led him to conclude that the compound contained a benzene ring. Further testing showed the melting point to be the same as phenylpyruvic acid, which indicated that the substance was in the urine.

In 1954, Horst Bickel, Evelyn Hickmans and John Gerrard published a paper that described how they created a diet that was low in phenylalanine and the patient recovered. Bickel, Gerrard and Hickmans were awarded the John Scott Medal in 1962 for their discovery.

PKU was the first disorder to be routinely diagnosed through widespread newborn screening. Robert Guthrie introduced the newborn screening test for PKU in the early 1960s. With the knowledge that PKU could be detected before symptoms were evident, and treatment initiated, screening was quickly adopted around the world. Ireland was the first country to introduce a national screening programme in February 1966,Austria also started screening in 1966 and England in 1968.

In 2017 the European Guidelines were published.They were called for by the patient organizations such as the European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria.They have received some critical reception.

WhenPAHactivityisreduced,phenylalanineaccumulatesandis converted into phenylpyruvate (phenylketone), which canbedetectedintheurine.

PKUiscaused byamutatedgeneforPAHenzymeduetodefectInthebiosynthesisofcofactortetrahydrobioptrin(BH4).

eThePAHgeneislocatedonchromosome12.

e PAHdeficiencycausesawidespectrumofdisorders includingPKUandhyperphenylalaninemia

Phenaylalanine

-Itisessentialaminoacid

-Normallydegradedbywayofthetyrosinepathway

-Phenylalanineandtyrosinearepreursoraminoacidsforimportant compoundsLike: Thyroid hormone,Neurotransmitters,Melaninetc.,

Hyperphenylalaninemia'strictly means elevatedbloodphenylalanine.itisusuallyusedtodescribea groupof disordersotherthanclassicPKU

-Normalbloodphenylalaninelevelisabout1mg/dl.

-InclassicPKU,levelsmayrangefrom6to80mg/dl.

- Classic PKU and the other causesofhyperphenylalaninemia affectabout 1 of every10,000to20,000

-

PKUisinheritedinfamiliesinanautosomalrecessivepattern.Autosomalrecessivein heritancemeansthataperson has two copies of the gene that is altered. Usually,each parent of an individual who has PKU carries one copyofthealteredgene.Sinceeachparentalsohasagene,theydonotshowsignsorsympt omsofPKU.

Signs and symptoms

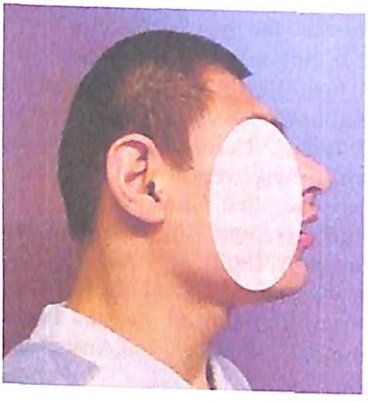


Fig 17

Abnormally small head (microcephaly) (Fig 17), untreated PKU can lead to intellectual disability, seizures, behavioral problems, and mental disorders. It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.

Because the mother's body is able to break down phenylalanine during pregnancy, infants with PKU are normal at birth. The disease is not detectable by physical examination at that time, because no damage has yet been done. Newborn screening is performed to detect the disease and initiate treatment before any damage is done. The blood sample is usually taken by a heel prick, typically performed 2–7 days after birth. This test can reveal elevated phenylalanine levels after one or two days of normal infant feeding.

If a child is not diagnosed during the routine newborn screening test and a phenylalanine-restricted diet is not introduced, then phenylalanine levels in the blood will increase over time. Toxic levels of phenylalanine (and insufficient levels of tyrosine) can interfere with infant development in ways that have permanent effects. The disease may present clinically with seizures, hypopigmentation (excessively fair hair and skin), and a "musty

odor" to the baby's sweat and urine (due to phenylacetate, a carboxylic acid produced by the oxidation of phenylacetone). In most cases, a repeat test should be done at approximately two weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed.

Untreated children often fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, EEG abnormalities, and seizures, and severe learning disabilities are major clinical problems later in life. A characteristic "musty or mousy" odor on the skin, as well as a predisposition for eczema, persist throughout life in the absence of treatment.

The damage done to the brain if PKU is untreated during the first months of life is not reversible. It is critical to control the diet of infants with PKU very carefully so that the brain has an opportunity to develop normally. Affected children who are detected at birth and treated are much less likely to develop neurological problems or have seizures and intellectual disability (though such clinical disorders are still possible including asthma, eczema, anemia, weight gain, renal insufficiency, osteoporosis, gastritis, esophagus, and kidney deficiencies, kidney stones, and hypertension). Additionally, major depressive disorders occur 230% higher than controls; dizziness and giddiness occur 180% higher; chronic ischemic heart disease, asthma, diabetes, and gastroenteritis occur 170% higher; and stress and adjustment disorders occur 160% higher. In general, however, outcomes for people treated for PKU are good. Treated people may have no detectable physical, neurological, or developmental problems at all.

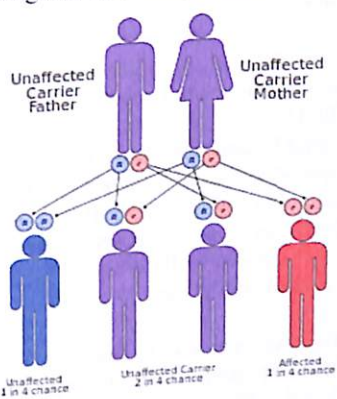


Fig 18

Phenylketonuria is inherited in an autosomal recessive fashion (Fig 18) PKU is an autosomal recessive metabolic genetic disorder. As an autosomal recessive disorder, two PKU alleles are required for an individual to experience symptoms of the disease. For a child to inherit PKU, both parents must have and pass on the defective gene. If both parents are carriers for PKU, there is a 25% chance any child they have will be born with the disorder, a 50% chance the

child will be a carrier and a 25% chance the child will neither develop nor be a carrier for the disease.

PKU is characterized by homozygous or compound heterozygous mutations in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH), rendering it nonfunctional. This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine (Tyr). When PAH activity is reduced, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which can be detected in the urine.

Carriers of a single PKU allele do not exhibit symptoms of the disease but appear to be protected to some extent against the fungal toxin ochratoxin A. Louis Woolf suggested that this accounted for the persistence of the allele in certain populations,in that it confers a selective advantage—in other words, being a heterozygote is advantageous.

The PAH gene is located on chromosome 12 in the bands 12q22-q24.2.As of 2000, around 400 disease-causing mutations had been found in the PAH gene. This is an example of allelic genetic heterogeneity.

Pathophysiology

When phenylalanine (Phe) cannot be metabolized by the body, a typical diet that would be healthy for people without PKU causes abnormally high levels of Phe to accumulate in the blood, which is toxic to the brain. If left untreated (and often even in treatment), complications of PKU include severe intellectual disability, brain function abnormalities, microcephaly, mood disorders, irregular motor functioning, and behavioral problems such as attention deficit hyperactivity disorder, as well as physical symptoms such as a "musty" odor, eczema, and unusually light skin and hair coloration.[23]

Classical PKU

Classical PKU, and its less severe forms "mild PKU" and "mild hyperphenylalaninemia" are caused by a mutated gene for the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine ("Phe") to other essential compounds in the body, in particular tyrosine. Tyrosine is a conditionally essential amino acid for PKU patients because without PAH it cannot be produced in the body through the breakdown of phenylalanine.

PAH deficiency causes a spectrum of disorders, including classic phenylketonuria (PKU) and mild hyperphenylalaninemia (also known as "hyperphe" or "mild HPA"),a less severe accumulation of phenylalanine. Compared to classic PKU patients, patients with "hyperphe" have greater PAH enzyme activity and are able to tolerate larger amounts of phenylalanine in their diets. Without dietary intervention, mild HPA patients have blood Phe levels higher than those with normal PAH activity. There is currently no international consensus on the definition of mild HPA, however, it is most frequently diagnosed at blood Phe levels between 2–6 mg/dL.

Phenylalanine is a large, neutral amino acid (LNAA). LNAAs compete for transport across the blood–brain barrier (BBB) via the large neutral amino acid transporter (LNAAT). If phenylalanine is in excess in the blood, it will saturate the

transporter. Excessive levels of phenylalanine tend to decrease the levels of other LNAAs in the brain. As these amino acids are necessary for protein and neurotransmitter synthesis, Phe buildup hinders the development of the brain, causing intellectual disability.

Recent research suggests that neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology are slightly suboptimal even for patients who are treated and maintain their Phe levels in the target range, if their diet is not supplemented with other amino acids.

Classic PKU affects myelination and white matter tracts in untreated infants; this may be one major cause of neurological problems associated with phenylketonuria. Differences in white matter development are observable with magnetic resonance imaging. Abnormalities in gray matter can also be detected, particularly in the motor and pre-motor cortex, thalamus and the hippocampus.

It was recently suggested that PKU may resemble amyloid diseases, such as Alzheimer's disease and Parkinson's disease, due to the formation of toxic amyloid-like assemblies of phenylalanine.

Tetrahydrobiopterin-deficient hyperphenylalaninemia

A rarer form of hyperphenylalaninemia is tetrahydrobiopterin deficiency, which occurs when the PAH enzyme is normal, and a defect is found in the biosynthesis or recycling of the cofactor tetrahydrobiopterin (BH_4). BH_4 is necessary for proper activity of the enzyme PAH, and this coenzyme can be supplemented as treatment. Those with this form of hyperphenylalaninemia may have a deficiency of tyrosine (which is created from phenylalanine by PAH), in which case treatment is supplementation of tyrosine to account for this deficiency.

Levels of dopamine can be used to distinguish between these two types. Tetrahydrobiopterin is required to convert Phe to Tyr and is required to convert Tyr to L-DOPA via the enzyme tyrosine hydroxylase. L-DOPA, in turn, is converted to dopamine. Low levels of dopamine lead to high levels of prolactin. By contrast, in classical PKU (without dihydrobiopterin involvement), prolactin levels would be relatively normal.[32][*citation needed*]

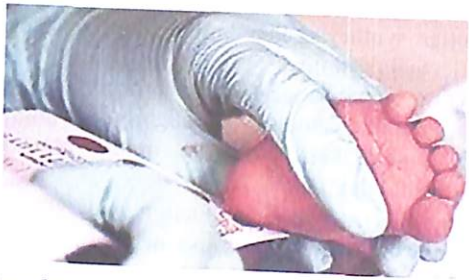
As of 2020, tetrahydrobiopterin deficiency was known to result from defects in five genes.

Metabolic pathways

Pathophysiology of phenylketonuria, which is due to the absence of functional phenylalanine hydroxylase (classical subtype) or functional enzymes for the recycling of tetrahydrobiopterin (new variant subtype) utilized in the first step of the metabolic pathway.

The enzyme phenylalanine hydroxylase normally converts the amino acid phenylalanine into the amino acid tyrosine. If this reaction does not take place, phenylalanine accumulates and tyrosine is deficient. Excessive phenylalanine can be metabolized into phenylketones through the minor route, a transaminase pathway with glutamate. Metabolites include phenylacetate, phenylpyruvate and phenethylamine. Elevated levels of phenylalanine in the blood and detection of phenylketones in the urine is diagnostic, however most patients are diagnosed via newborn screening.

Screening



Blood is taken from a two-week-old baby to test for phenylketonuria

PKU is commonly included in the newborn screening panel of many countries, with varied detection techniques. Most babies born in Europe, North America, and Australia are screened for PKU soon after birth.Screening for PKU is done with bacterial inhibition assay (Guthrie test), immunoassays using fluorometric or photometric detection, or amino acid measurement using tandem mass spectrometry (MS/MS). Measurements done using MS/MS determine the concentration of Phe and the ratio of Phe to tyrosine, the ratio will be elevated in PKU.

Treatment

PKU is not curable. However, if PKU is diagnosed early enough, an affected newborn can grow up with normal brain development by managing and controlling phenylalanine ("Phe") levels through diet, or a combination of diet and medication. If dietary treatment is not initiated within 2 weeks after birth, the child is likely to develop permanent intellectual disability, even if dietary interventions begin shortly thereafter.

Diet

People who follow the prescribed dietary treatment from birth may (but not always) have no symptoms. Their PKU would be detectable only by a blood test. People must adhere to a special diet low in Phe for optimal brain development. Since Phe is necessary for the synthesis of many proteins, it is required for appropriate growth, but levels must be strictly controlled.

Warning for people with phenylketonuria on a label for an aspartame-containing drink

Optimal health ranges (or "target ranges") are between 120 and 360 µmol/L or equivalently 2 to 6 mg/dL. This is optimally to be achieved during at least the first 10 years, to allow the brain to develop normally.

The diet requires restricting or eliminating foods high in Phe, such as soybeans, egg whites, shrimp, chicken breast, spirulina, watercress, fish, nuts, crayfish, lobster, tuna, turkey, legumes, and lowfat cottage cheese.[40] Starchy foods, such as potatoes and corn are generally acceptable in controlled amounts, but the quantity of Phe consumed from these foods must be monitored. A corn-free diet may be prescribed in some cases. A food diary is usually kept to record the amount of Phe consumed with each meal, snack, or drink. An "exchange" system can be used to calculate the amount of Phe

in a portion of food from the protein content identified on a nutritional information label. Lower-protein "medical food" substitutes are often used in place of normal bread, pasta, and other grain-based foods, which contain a significant amount of Phe. Many fruits and vegetables are lower in Phe and can be eaten in larger quantities. Infants may still be breastfed to provide all of the benefits of breastmilk, but the quantity must also be monitored and supplementation for missing nutrients will be required. The sweetener aspartame, present in many diet foods and soft drinks, must also be avoided, as aspartame contains phenylalanine.

The amino acid tyrosine becomes essential in people with phenylalanine hydroxylase deficiency. Thus, in addition to the careful *reduction* of Phe in the diet, Tyr must be *supplemented* to ensure that nutritional needs are met.

Different people can tolerate different amounts of Phe in their diet. Regular blood tests are used to determine the effects of dietary Phe intake on blood Phe level.

Nutritional supplements

Supplementary "protein substitute" formulas are typically prescribed for people PKU (starting in infancy) to provide the amino acids and other necessary nutrients that would otherwise be lacking in a low-phenylalanine diet. Tyrosine, which is normally derived from phenylalanine and which is necessary for normal brain function, is usually supplemented. Consumption of the protein substitute formulas can actually reduce phenylalanine levels, probably because it stops the process of protein catabolism from releasing Phe stored in the muscles and other tissues into the blood. Many PKU patients have their highest Phe levels after a period of fasting (such as overnight) because fasting triggers catabolism. A diet that is low in phenylalanine but does not include protein substitutes may also fail to lower blood Phe levels, since a nutritionally insufficient diet may also trigger catabolism. For all these reasons, the prescription formula is an important part of the treatment for patients with classic PKU.

Evidence supports dietary supplementation with large neutral amino acids (LNAAs).The LNAAs (e.g. leu, tyr, trp, met, his, ile, val, thr) may compete with phe for specific carrier proteins that transport LNAAs across the intestinal mucosa into the blood and across the blood–brain barrier into the brain. Its use is limited in the US due to the cost but is available in most countries as part of a low protein / PHE diet to replace missing nutrients.

Another interesting treatment strategy is casein glycomacropeptide (CGMP), which is a milk peptide naturally free of Phe in its pure formCGMP can substitute for the main part of the free amino acids in the PKU diet and provides several beneficial nutritional effects compared to free amino acids. The fact that CGMP is a peptide ensures that the absorption rate of its amino acids is prolonged compared to free amino acids and thereby results in improved protein retention and increased satietycompared to free amino acids. Another important benefit of CGMP is that the taste is significantly improvedwhen CGMP substitutes part of the free amino acids and this may help ensure improved compliance to the PKU diet.

Furthermore, CGMP contains a high amount of the Phe-lowering LNAAs, which constitutes about 41 g per 100 g protein[44] and will therefore help maintain plasma phe levels in the target range.

Enzyme substitutes

In 2018, the FDA approved an enzyme substitute called pegvaliase which metabolizes phenylalanine.[4] It is for adults who are poorly managed on other treatments.[4]

Tetrahydrobiopterin (BH4) (a cofactor for the oxidation of phenylalanine) when taken by mouth can reduce blood levels of this amino acid in some people.

Mothers

For women with PKU, it is important for the health of their children to maintain low Phe levels before and during pregnancy. Though the developing fetus may only be a carrier of the PKU gene, the intrauterine environment can have very high levels of phenylalanine, which can cross the placenta. The child may develop congenital heart disease, growth retardation, microcephaly and intellectual disability as a result. PKU-affected women themselves are not at risk of additional complications during pregnancy.

In most countries, women with PKU who wish to have children are advised to lower their blood Phe levels (typically to between 2 and 6 mg/dL) before they become pregnant, and carefully control their levels throughout the pregnancy. This is achieved by performing regular blood tests and adhering very strictly to a diet, in general monitored on a day-to-day basis by a specialist metabolic dietitian. In many cases, as the fetus' liver begins to develop and produce PAH normally, the mother's blood Phe levels will drop, requiring an increased intake to remain within the safe range of 2–6 mg/dL. The mother's daily Phe intake may double or even triple by the end of the pregnancy, as a result. When maternal blood Phe levels fall below 2 mg/dL, anecdotal reports indicate that the mothers may experience adverse effects, including headaches, nausea, hair loss, and general malaise. When low phenylalanine levels are maintained for the duration of pregnancy, there are no elevated levels of risk of birth defects compared with a baby born to a non-PKU mother.

6.2.Tyrosinemia type 1

Disease definition

A rare inborn error of tyrosine catabolism characterized by progressive liver disease, renal tubular dysfunction, porphyria-like crises and a dramatic improvement in prognosis following treatment with nitisinone.

Synonym(s):

FAH deficiency
Fumarylacetoacetase deficiency
Fumarylacetoacetate hydrolase deficiency
Hepatorenal tyrosinemia
Tyrosinemia type I

Prevalence: Unknown

Inheritance: Autosomal recessive

Summary

Epidemiology

Birth incidence is 1/100.000 in most areas but is higher in some regions, notably in Québec, Canada.

Clinical description

The disease is clinically heterogenous. Symptoms may start during the first few months (acute type), in second half of the first year (subacute type) or in the following years up to adulthood (chronic type). In the acute type, manifestations of hepatic failure predominate (bleeding diathesis, hypoglycemia, ascites etc) with frequent sepsis and rapid deterioration. Mild proximal tubular disease is usually present. Subacute type manifests a similar but less severe clinical picture presenting usually with hepatomegaly or hypophosphatemic rickets (due to tubular dysfunction). Intercurrent illness may precipitate hepatic crisis. Chronic type presents with hepatomegaly secondary to cirrhosis and often tubulopathy, leading to rickets and renal failure. Neurological crises are infrequent presenting symptoms (in Europe but not in Canada); however, they can complicate any type of the disease when untreated. The crises resemble those of acute intermittent porphyria, manifesting with painful parasthesias (causing patients to assume ophisthotonic position, self mutilation), autonomic signs (hypertension, tachycardia, ileus) and respiratory decompensation. All patients stand a high risk of developing hepatocellular carcinoma (HCC).

Etiology

The deficiency of fumarylacetoacetate hydrolase, FAH(15q23-q25) results in accumulation of fumaryl-,maleyl-acetoacetate and their derivates, succinyl-acetone (SA) and succinyl-acetoacetate (SAA), that cause hepatorenal damage. SA leads to accumulation of delta-aminolevulinate (δ-ALA) resulting in inhibition of porphobilinogen synthesis and porphyria-like crises.

Diagnostic methods

Liver synthetic functions are usually severely affected with coagulopathy and hypoalbuminemia. Elevated levels of SA in dried blood spots, plasma or urine are pathognomonic. Other abnormalities include elevated α -fetoprotein, increased plasma levels of tyrosine, phenylalanine and methionine, increased urinary δ-ALA excretion and features of Fanconi tubulopathy. Confirmation of diagnosis is usually by mutation analysis. Newborn screening programs include testing for tyrosinemia type 1 (SA is the recommended marker).

Differential diagnosis

Differential metabolic diagnoses include classic galactosemia, hereditary fructose intolerance, and fructose 1,6 diphosphatase deficiency, Wilson's disease and some mitochondrial disorders.

Antenatal diagnosis

Antenatal diagnosis is possible with chorionic villus sampling and amniocentesis when a mutation has been identified in the family.

Genetic counseling

Tyrosinemia type 1 is an autosomal recessive disorder. Genetic counseling should be offered to at-risk couples (both individuals are carriers of a disease-causing mutation) informing them there is a 25% chance of having an affected child at each pregnancy.

Management and treatment

As soon as the diagnosis is confirmed (or even highly suspected) start nitisinone (NTBC) orally in a dose of 1-2 mg/kg a day along with the emergency treatment for acute liver failure if necessary. A protein-restricted diet must also be started in parallel. Patients should be referred to a specialist center for long term management. Liver transplantation should be considered in acutely ill infants (if liver function fails to respond to nitisinone within a week), suspected or diagnosed HCC, and non-compliance or unavailability of medical treatment.

Prognosis

Nitisinone treatment, combined with a low-protein diet allows most the patients to survive in good health. The prognosis is dominated by the risk of HCC, which increases the later the treatment is started.

6.3.Alkaptonuria

Alkaptonuria is a rare autosomal recessive genetic disorder. Basically, problems arise in the metabolism of tyrosine and phenylalanine in the body. Tyrosine and phenylalanine metabolism plays a role in the production of sufficient amounts of the enzyme called homogentisic dioxygenase (HGD) in the body. Enzymes are proteins that allow chemical reactions to take place and the HGD enzyme's job is to break down a toxic substance called homogentisic acid.

When homogentisic acid cannot be broken down, it accumulates in the body and discoloration and fragility of bones and cartilages are observed. It leads to osteoarthritis, especially in the spine and large joints. When homogentisic acid comes into contact with air, it causes urine to turn black, the earliest symptom being blackness in diapers.(Fig 19)

Fig 19

Diagnostic Criteria for Alkaptonuria

Physical examination, patient history and various tests should be performed to diagnose alkaptonuria. Urinalysis is the most commonly used method. When alkaptonuria is suspected, the patient is asked to collect urine for 24 hours. The diagnosis is made by examining the amount of homogentisic acid in the urine.

Since alkaptonuria is a genetic disorder, genetic testing is performed to identify the presence of a recessive mutation in the HGD gene. Genetic testing is

important to make a definitive diagnosis. X-rays or other imaging methods are used to examine bone and joint findings. Various scoring systems are also used to evaluate clinical findings.

Symptoms of Alkaptonuria

The most important symptom of alkaptonuria in infancy is dark urine. Homogentisic acid causes urine to turn black when exposed to air for several hours and can be seen in diapers. If this symptom is missed, alkaptonuria may not be recognized until adulthood.

Until the patient reaches his or her 30s, there are usually no other noticeable symptoms, but as the patient gets older, the following symptoms appear:

Inflammation and pain in the joints
Darkening of the ears or other areas of the skin
Black or dark colored earwax
Dark spots on the white part of the eye
Appearance of a blue or brownish color on the nails
Shortness of breath due to hardening of the bones around the lungs
Dark urine
Back pain
Low back pain and lumbar stiffness
Heart diseases due to accumulation of homogentisic acid around the heart valves

Symptoms such as kidney, bladder or prostate stones are seen in alkaptonuria.

Alkaptonuria Treatment Methods

Although there is no definitive treatment method for alkaptonuria, treatment is usually aimed at reducing the patient's symptoms. Medications and changes in the patient's lifestyle aim to reduce the symptoms of the disease.

In alkaptonuria, drugs with the active substance nitisinone are preferred medically. There are ongoing studies showing that nitisinone reduces the level of homogentisic acid in the body.

For people with involvement of the joints and spine, relief is provided with painkillers. In advanced cases, joint replacement can be performed with surgical operations.

Physiotherapy support to strengthen muscles and joints improves the patient's quality of life.

Regular light exercise helps to reduce the pain of the disease. Activities that reduce stress levels such as yoga, pilates, cycling and walking can be preferred.

Surgery may be necessary in patients with involvement of heart valves or heart vessels.

The use of vitamin C slows down calcification in some patients and reduces the dark color of urine.

Reduce consumption of foods rich in tyrosine and phenylalanine, such as milk, meat and eggs.

Alkaptonuria Diet

People with alkaptonuria should avoid foods containing excess tyrosine and phenylalanine. Patients should pay attention to their diet as there are problems in tyrosine and phenylalanine metabolism. Meat, milk and dairy products, eggs, nuts, legumes, bakery products, packaged foods are foods rich in phenylalanine. Patients should avoid these foods or consume as little as possible.

Fish, chicken, soy products, sunflower seeds, pumpkin seeds, nuts are also rich in tyrosine. The treatment process will be difficult in patients who consume these foods uncontrolled and without restrictions. Eating according to the recommended diet helps to reduce the patient's symptoms.

6.4.Galactosemia

Galactosemia is a disorder that affects how the body processes a simple sugar called galactose. A small amount of galactose is present in many foods. It is primarily part of a larger sugar called lactose, which is found in all dairy products and many baby formulas. The signs and symptoms of galactosemia result from an inability to use galactose to produce energy.

Researchers have identified several types of galactosemia. These conditions are each caused by mutations in a particular gene and affect different enzymes involved in breaking down galactose.

Classic galactosemia, also known as type I, is the most common and most severe form of the condition. If infants with classic galactosemia are not treated promptly with a low-galactose diet, life-threatening complications appear within a few days after birth. Affected infants typically develop feeding difficulties, a lack of energy (lethargy), a failure to gain weight and grow as expected (failure to thrive), yellowing of the skin and whites of the eyes (jaundice), liver damage, and abnormal bleeding. Other serious complications of this condition can include overwhelming bacterial infections (sepsis) and shock. Affected children are also at increased risk of delayed development, clouding of the lens of the eye (cataract), speech difficulties, and intellectual disability. Females with classic galactosemia may develop reproductive problems caused by an early loss of function of the ovaries (premature ovarian insufficiency).

Galactosemia type II (also called galactokinase deficiency) and type III (also called galactose epimerase deficiency) cause different patterns of signs and symptoms. Galactosemia type II causes fewer medical problems than the classic type. Affected infants develop cataracts but otherwise experience few long-term complications. The signs and symptoms of galactosemia type III vary from mild to severe and can include cataracts, delayed growth and development, intellectual disability, liver disease, and kidney problems.

Frequency

Collapse Section

Classic galactosemia occurs in 1 in 30,000 to 60,000 newborns. Galactosemia type II and type III are less common; type II probably affects fewer than 1 in 100,000 newborns and type III appears to be very rare.

Causes

Collapse Section

Mutations in the *GALT*, *GALK1*, and *GALE* genes cause galactosemia. These genes provide instructions for making enzymes that are essential for processing galactose obtained from the diet. These enzymes break down galactose into another simple sugar, glucose, and other molecules that the body can store or use for energy.

Mutations in the *GALT* gene cause classic galactosemia (type I). Most of these genetic changes almost completely eliminate the activity of the enzyme produced from the *GALT* gene, preventing the normal processing of galactose and resulting in the life-threatening signs and symptoms of this disorder. Another *GALT* gene mutation, known as the Duarte variant, reduces but does not eliminate the activity of the enzyme. People with the Duarte variant tend to have much milder features of galactosemia.

Galactosemia type II results from mutations in the *GALK1* gene, while mutations in the *GALE* gene underlie galactosemia type III. Like the enzyme produced from the *GALT* gene, the enzymes made from the *GALK1* and *GALE* genes play important roles in processing galactose. A shortage of any of these critical enzymes allows galactose and related compounds to build up to toxic levels in the body. The accumulation of these substances damages tissues and organs, leading to the characteristic features of galactosemia.

Inheritance

Collapse Section

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Marfan's syndrome

Marfan syndrome was first described in 1896 by the French paediatrician A. B. Marfan. Therefore, we will focus on it in more detail. Marfansyndromeisahereditaryconnectivetissuedysplasia. Three systems are affected simultaneously: the musculoskeletal, cardiovascular and visual systems. Characteristic clinical manifestations of Marfan syndrome include tall stature, arachnodactyly (long, thin, "spider-like" fingers), (Fig 20), joint hypermobility, lens subluxation and myopia, damage to large vessels (aortic aneurysm), and heart defects (mitral valve prolapse). Each of these symptoms may vary in severity and combination with each other in individual family members.

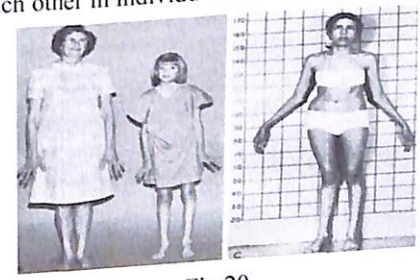


Fig 20

Marfan disease is characterised by marked pleiotropism, variable expressivity and high penetrance. The diagnosis of Marfan syndrome is made in the presence of at least five symptoms - aortic aneurysm, lens dislocation, arachnodactyly, sternal deformity, kyphoscoliosis. (Fig 21)

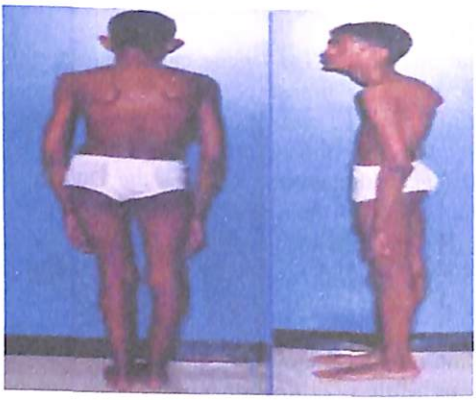


Fig 21

There is an increase (twofold and more) in urinary excretion of glucosoaminoglycans and their fractions. Renal excretion of chondroitin-4-6-sulfates increases especially sharply and to a lesser extent - hyaluronic acid and heparan-sulfate. In the urine of patients is also determined increased content (two or more times) of the amino acid oxyproline. The population frequency is 1:25000. The disease is caused by heterozygous mutations in the fibrillin 1 gene, an extracellular matrix protein that performs architectural functions in most connective tissues. The fibrillin gene is mapped in the 15q21.1 region, and more than 550 mutations have now been identified in the gene. These mutations have a wide range of clinical manifestations from isolated lens ectopia with mild skeletal manifestations of the Marfanoid type to severe neonatal forms of Marfan syndrome, ending in death within the first two years of life. The vast majority of mutations in the fibrillin 1 gene are diagnosed in patients with the classical variant of Marfan syndrome. Molecular genetic diagnosis of Marfan disease both prenatally and postnatally, although fundamentally possible, is complicated by the fact that the vast majority of mutations in the fibrillin gene are unique, that is, described only in one patient or in one family

CHAPTER VII.NEURODEGENERATIVE DISEASES

Neurodegenerative diseases (NDD) are diverse conditions characterized by selective dysfunction and ongoing loss of neurons, glial cells and the neural networks in the brain and spinal cord. Accordingly they causes diverse problems examples being with movement (called ataxias), mental functioning (called dementias) and a person's ability to move, speak and breathe. NDD are incurable and debilitating conditions, and are becoming increasingly prevalent in part due to global population ageing

7.1.Alzheimer's disease

Alzheimer's disease is the most common cause of dementia.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes significant deterioration in mental performance. This leads to impairment in normal social and occupational function. Unfortunately, AD is an incurable condition that has a variable clinical course. It is the most common cause of dementia.

Dementia

Dementia describes a clinical syndrome that is characterised by a significant deterioration in mental function that leads impairment of normal function.

In healthcare, we measure 'normal function' by activities of daily living (ADLs). These are a series of routine activities that people should be able to do without assistance. They can be broadly divided into personal tasks and domestic tasks.

Personal: washing, dressing, toileting, continence, transferring (e.g. bed to chair)

Domestic: cooking, cleaning, shopping, managing finances, taking medication

Types of dementia

Dementia can be caused by several conditions, which all manifest with poor mental performance and impaired normal functioning. The clinical manifestations of dementia can reflect the underlying aetiology.

Alzheimer's disease (AD): 50-75%

Vascular dementia (VD): 20%

Dementia with Lewy body (DLB): 15-20%

Frontotemporal dementia (FTD): 2%

Rare causes: Parkinson's disease dementia (PDD), Huntington's disease (HD), Prion disease, others.

For a comprehensive overview of dementia, see our Dementia note.

Epidemiology

Dementia is primarily a disease of older adults.

The World Health Organisation (WHO) estimates that almost 50 million people have a diagnosis of dementia worldwide. In the UK, it is estimated that > 500,000 people have a diagnosis of AD.

The prevalence of dementia increases with age. The estimated prevalence at 60-64 years is 0.9% compared to 41.1% in those aged 95 years and over.

A significant proportion of patients with dementia remain undiagnosed and up to 54% of patients with dementia require care home placement.

Etiology

The exact cause of AD remains unknown.

The overarching theory involves environmental and genetic risk factors that increase the chance of developing pathological processes, which lead to dementia.

Commonly recognised risk factors

Age: older age is a major risk for AD

Genetics*: most cases of AD are sporadic. Small number of inherited causes exist (<5%, autosomal dominant inheritance). Inherited causes suggested by early-onset disease. Mutations in the amyloid precursor protein (*APP*) and presenilin genes (*PSEN1, PSEN2*) have been identified.

Cardiovascular disease: smoking and diabetes increase risk. Exercise decreases risk.

Depression

Low educational attainment

Low social engagement and support

Others: head trauma, learning difficulties.

*NOTE: *alleles of the cholesterol-carrying apolipoprotein E (APOE) have also been identified as a biological risk factor for AD.*

Pathophysiology

The neurodegeneration in AD is hypothesised secondary to altered amyloid and tau protein metabolism.

The brain is composed of billions of neurons. The normal functioning of theses neurons is dependent on surrounding supportive structures such as microtubules and the protein tau, which stabilise these microtubules.

Pathological changes that occur in AD leads to interruption of key neuronal process including communication, metabolism and repair. This ultimately leads to neuronal cell death.

The two key pathological changes in AD are senile plaques and neurofibrillary tangles:

Senile plaques (SP): deposits of beta-amyloid (aggregation of protein with a beta-sheet secondary structure). Dense, insoluble. Occur outside of neurons (i.e. extracellular).

Neurofibrillary tangles (NFT): aggregations of hyperphosphorylated tau proteins. Typically occur in areas of the brain involved in memory. Promote neuronal cell death. Form inside neurons (i.e. intracellular)

Both SP and NFT are characteristic of AD but no pathognomonic. They can be seen in other neurodegenerative conditions. SP is also seen in normal ageing. Therefore, it is the amount of these pathological changes and the

topographic location within the brain (e.g. hippocampus and medial temporal lobes) which is characteristic of AD.

The amyloid deposition hypothesis is supported by identification of genetic mutations in the amyloid precursor gene *APP* leading to early-onset AD, and evidence of neuronal apoptosis on treatment of cells with beta-amyloid. However, some patients with severe AD do not have evidence of amyloid deposition on autopsy, and other patients who had no evidence of dementia have amyloid deposition. Therefore, it is not the complete story.

Several additional mechanisms are part of the pathological processes in AD. Alongside SP and NFT, these result in neuronal cell death that leads to memory failure, personality changes and problems with activities of daily living (hallmarks of dementia).

Clinical features

Dementia can be difficult to identify due to the insidious and non-specific symptoms.

Many clinical features are attributable to dementia. Some are characteristic of all dementias whereas others are typical of a particular type, like AD. There is usually a slow onset of symptoms and a lack of insight with accommodation to cognitive or functional changes.

The clinical features of dementia can be considered in the following domains:

Cognitive impairment: poor memory, disorientation, language problems

Behavioural and psychological symptoms of dementia (BPSD): agitation, depression, sleep cycle disturbance, motor disturbance

Disease-specific features: AD is characterised by early impairment of memory. This manifests as short-term memory loss and difficulty learning new information

Activities of daily living: an increasing reliance on others for assistance, problems with high-level functioning (e.g. work, finance), problems with basic personal care

Cognitive assessment

A formal mental status examination should be completed using a recognised cognitive assessment tool.

There are multiple cognitive assessment tools, which are designed to test different areas of higher cortical functioning. Cognitive domains assessed include:

Attention and concentration

Recent and remote memory

Language

Praxis: planned motor movement (e.g. perform a task)

Executive function

Visuospatial function

There are a variety of different cognitive assessment tools that range from basic screening tools, to in-depth assessments of each cognitive domain.

A comprehensive summary of cognitive assessment tools can be found in our Dementianote.

Diagnosis

It is essential to exclude all alternative causes before making a diagnosis of dementia.

Patients with suspected dementia are usually referred to a memory clinic.

At memory clinic, patients undergo a formal history and examination (including medication review), full complement of baseline investigations including bloods and neuroimaging to exclude an underlying cause, and formal cognitive assessment.

During these investigations, the specific type of dementia may become apparent. In AD, this may be reflected by the lack of other neurological symptoms, absence of major cardiovascular risk factors and predominant impairment in memory, thinking and behaviour.

Diagnostic criteria

There is a diagnostic criteria for dementia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

We have simplified this into three key components:

Functional ability: inability to carry out normal functions. Represents a decline from previous functional level

Cognitive domains: impairment involving ≥2 cognitive domains (see chapter on cognitive assessment)

Differentials excluded: clinical features cannot be explained by another cause (esp. psychiatric disorders and delirium)

Mild cognitive impairment

This describes cognitive deficits in one or more of the major cognitive domains, but the deficit is insufficient to interfere with independence in daily activities.

Mild cognitive impairment is an increasingly important term because it helps identify patients at risk of progression to dementia. Patients should have regular follow-up and be advised to undertake healthy brain activities (e.g. exercise, socialising).

Differential diagnosis

Dementia is a clinical syndrome that reflects deterioration from an underlying cause, the most common being AD. The main differentials to exclude in a patient with features of dementia are the three 'D's':

Depression (and other psychiatric disorders): psychosis can be a feature of dementia.

Drugs: consider drugs with anti-cholinergic effects (e.g. anti-histamines, anti-psychotics, anti-epileptics)

Delirium: acute confusional state. May be prolonged recovery following episode.

Investigations

Baseline investigations are essential to exclude an alternative diagnosis.

Typical baseline investigations involve a routine set of blood tests and neuroimaging.

Bloods

Full blood count

Erythrocyte sedimentation rate (ESR)

Urea and electrolytes
Bone profile
HbA1c
Liver function tests
Thyroid function tests
Serum B12 and folate levels

Other

ECG
Virology (e.g. HIV)
Syphilis testing
CXR

Neuroimaging

Typically magnetic resonance imaging (MRI) but CT may be used if MRI not available or unsuitable. Important to exclude an alternative diagnosis (e.g. brain tumour) and can be used to help characterise the type of dementia (e.g. small vessel disease in VD).

Future areas

The use of biomarkers and more advanced imaging (e.g. functional MRI) are being increasingly used in a research capacity to predict the likelihood of developing AD.

Management

Pharmacological therapy can be used in patients with AD, but it is only a small part of overall management.

The management of AD, and dementia as a whole, should involve a full assessment of the biological, psychological and social needs of the patient. With significant deterioration in normal activities of daily living, patients will become dependent on others. This means help from families, organisation of carers, and with more advancing symptoms, need for care home placement.

There are multiple facets to management, which we summarise.

Assess capacity and advanced care planning: ideally completed when patients still retain capacity. Consideration of advance statements/decisions and appointment of lasting power of attorney.

Physical and mental health: consider co-existing anxiety and depression. Manage physical health needs as normal. Consider delirium if any acute deterioration.

Driving: must inform the DVLA. Check website for guidance.

Pharmacological: (see below)

Non-pharmacological: programmes to improve/maintain cognitive function (e.g. structured group cognitive stimulation programmes). Also exercise, aromatherapy, therapeutic use of music/dancing, massage.

Managing BPSD: non-pharmacological interventions. Consider referral to old-age psychiatry if difficult to control. Pharmacological therapy should be used on specialist advice.

Care plans: people with dementia require a care manager and care plan. This includes details on diagnosis, treatment, environmental modifications and review plans.

End-of-life care: focus on physical, psychological, social and spiritual needs. Oral nutrition encouraged as long as possible. Long-term feeding (i.e. NG feeding, gastrostomy tube) inappropriate in severe dementia. No evidence for increased survival or reduced complications. Resuscitation discussions.

Pharmacological therapy

Medical therapy for the treatment of dementia should be initiated by a specialist in treating patients with dementia. The two main drugs are acetylcholinesterase inhibitors and N-methyl-D-aspartic acid receptor antagonists.

Pharmacological agents are primarily indicated in patients with AD. They should not be used in patients with mild cognitive impairment.

Choice of therapy depends on severity:

Mild-to-moderate AD: acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine).

Moderate-to-severe AD: N-methyl-D-aspartic acid receptor antagonist (e.g. memantine). May be used in combination with acetylcholinesterase inhibitors.

Acetylcholinesterase inhibitors are associated with small improvements in cognition, neuropsychiatric symptoms, and ADLs in patients with mild-to-moderate AD. However, there is conflicting evidence on there impact on long-term outcomes (e.g. need for care home, effect on critical ADLs).

Memantine has modest effects in patients with moderate-to-severe AD in terms of reducing functional decline.

7.2. Parkinson's disease (shaking palsy) is a degenerative neurological pathology.

The nature of the disease is associated with several factors:

Malfunctions within nerve cells: for example, due to injury or complications after infectious diseases of the brain.

Disorders of the body due to interaction with harmful chemicals.

Mutations in genes.

presynaptic proteins in nerve cells - alpha-synucleins .

Alpha-synuclein proteins are produced by the nervous system itself. When they accumulate in large quantities, they become toxic and poison the brain. Human nerve cells begin to die, and the production of such an extremely important hormone for humans as dopamine significantly deteriorates. But it is dopamine that determines how capable a person is of learning, whether he is able to easily remember information and even simply hold a pen or pencil. The quality of sleep, the ability to concentrate, and coordination of movements depend on the same hormone. If there is little dopamine in the body, then processes associated with thinking and motor activity slow down significantly.

Parkinson's disease is diagnosed more often these days than it was 50 years ago. But this is not due to the fact that the disease progresses, but to the fact that people more often suffer from it after 50-60, and even more often 70-80 years old. Since life expectancy has increased over the past half century, the number of

people diagnosed with this disease has also increased. Currently, Parkinson's disease affects about 1% of the world's population.

But the pathology cannot be called a purely elderly disease. People under 50 may also have Parkinson's disease. As a percentage, the number of cases is several times smaller, but people aged 20-40 can also suffer from this disease.

It also cannot be said that Parkinson's disease is an occupational disease of people in certain professions. But at the same time, practice shows: there are areas in which you can more often meet people with Parkinson's disease. This includes mining in mines and working with pesticides and agrochemicals .

Symptoms

Parkinson's disease can begin with a wide variety of symptoms. In this case, symptoms can be associated both with disorders of motor and mental activity, and with functions that, at first glance, are not related to the nervous system, but relate to the functioning of the digestive tract and even the nose. What symptoms most often bother those suffering from Parkinson's disease?

Tremor at rest (in a calm state - sitting, lying down, a person begins to tremble, a person begins to walk - the trembling goes away). Especially often the problem begins with hand tremors and head tremors.

Stiffness in the legs. A person cannot walk quickly - but not because he has shortness of breath (as happens with diseases of the cardiovascular and respiratory systems), but it is difficult for him to control the work of his muscles. In this case, you can often hear "Your legs won't listen."

Problems maintaining balance.

Circulatory disorders.

Chronic constipation.

Disturbances of the so-called REM sleep phase: at the moment of falling asleep, a person behaves not just restlessly, but actively - to the point of causing injury to himself. However, after waking up, a person cannot remember this.

Loss of smell.

But despite the general symptoms, the development of the disease in young and old, men and women has some differences. Moreover, the differences relate to both the progression of the disease and the very first symptoms. Let's take a closer look at these differences.

In young people

If Parkinson's disease began to develop at the age of 20-40 years, then its progression (in the absence of treatment) is very rapid.

The disease begins in young people, usually with muscle problems . The first signs of pathology in young people are most often involuntary muscle contractions in the shoulders and feet. Moreover, at first they can be described simply as unpleasant, and then as very painful sensations.

Moreover, sometimes the patient does not understand that it is the muscles that are contracting: it seems to him that the joints hurt. He starts using ointments for arthritis, but not only is there no result, it is the opposite of what he wanted: the pain intensifies. That is why, if such signs exist, it is important to consult a doctor immediately.

In the elderly

In older people, the disease progresses more slowly at the beginning of the disease. If the disease develops after 60 years, sometimes 10 years pass from the appearance of the first symptoms to diagnosis. And this is a great danger. After all, the sooner the disease is identified and treatment is started, the higher the chances that it will be possible to take measures that will not allow the person to lose legal capacity.

Most often, the disease in old age begins with changes in gait. The person begins to speed up and at the same time shorten his steps. This gait is often called mincing.

Important! You cannot independently diagnose yourself based on one of the symptoms. For example, a shuffling gait is a characteristic symptom not only of Parkinson's disease. Very often this symptom is observed in patients with diseases of the hip joint. And only a doctor can recognize what is really causing the change in gait.

Another feature of Parkinson's disease in older people is the "disguise" of the disease as other diseases: for example, pathologies of the cardiovascular system. But there are differences. For example, if we are talking about problems with blood pressure, then in those suffering from Parkinson's disease it falls more often only when the person is standing or walking, and at rest the pressure stabilizes.

Among women

Women are more likely than men to develop the following symptoms at the initial stage of the disease:

Neck muscle tension, which at first is difficult (without a special examination) to distinguish from signs of osteochondrosis and periarthritis.

Decrease in intelligence.

Severe emotional depression.Suicidal thoughts (especially during menopause).

Expressive painful manifestations begin in the area of the shoulders and neck.

Difficulty putting on clothes (fastening buttons, turning sleeves inside out, threading your head through the neck of a blouse or dress becomes problematic).

Note! In addition to difficulties in putting on clothes, other everyday problems may arise, but since putting on clothes is one of the most common actions, neurologists most often include it in a mandatory test to identify signs of the disease in women. This problem can also appear in men, but at the initial stage of the disease it happens much less often than in women.

In men

For many men, Parkinson's disease is accompanied by problems with potency from the very beginning. This is due to the fact that erection is under the direct control of the autonomic system, one of the parts of the nervous system.

Another characteristic feature is the difficulty of controlling the hands when walking. If a healthy person, when walking, instinctively bends his arms at the elbows and often swings his arms (which is important for efficient movement

and conservation of energy), then with Parkinson's disease, great effort must be made to perform these actions.

Like women, men with Parkinson's disease experience deteriorating emotional health. But instead of depression, men develop excessive aggression and embitterment.

Causes

The most common cause of pathology is heredity. Cell death is associated with the activation of apotosis , a mechanism that is genetically programmed. 20% of patients with Parkinson's disease have or have had relatives familiar with this disease. At risk are individuals with changes in one of the genes (PARK2 gene).

A significant problem is that the transmission of the disease through genes is autosomal recessive, which means that, as a rule, it does not manifest itself directly from parents to children, but after a generation or even several generations. And many are unaware of the danger. But if there was a person in the family who suffered from this disease, there should be regular examinations of the body in a neurological "section": especially after 50 years.

But besides the hereditary factor, there are other provocateurs for the development of the disease:

Taking a number of medications. As practice shows, the disease can be caused by antipsychotic antidepressants (metoclopramide), reserpine, calcium antagonists (diltiazem), and lithium preparations. That is why these drugs are prescription drugs and their use requires strict medical supervision. At the same time, if the drugs were truly dangerous, naturally, no one would prescribe them. Everything is very individual.

All kinds of injuries (concussions are especially dangerous).

Encephalitis - regardless of what nature they are - viral or bacterial. In both cases, there is a high risk of damage to the structure of the autonomic ganglia - clusters of multipolar nerve cells

Other diseases. Provocateurs can be malignant formations, endocrine pathologies, and atherosclerosis.

Several methods are used to diagnose Parkinson's disease:

Visual inspection.

Functional diagnostics: method of clinical - accelerometric differential diagnosis of tremor (shaking), transcranial ultrasound sonography (TCS), tomography.

Laboratory tests (blood, urine).

A number of these diagnostic methods are basic, primary, and a number are auxiliary, clarifying ones.

First of all, a patient with suspected Parkinson's disease is shown a visual examination by a neurologist, laboratory tests, clinical and accelerometric differential diagnosis of tremor and transcranial ultrasound sonography .

Visual inspection

During a visual examination, the nature of finger trembling must be studied. If this is really Parkinson's disease, then most often the "pill rolling" rule works: it seems to the patient that the fingers are not just trembling, but that some object similar to a pill is rolling between them. In addition, the tremor is

asymmetrical. On one of the hands it is more pronounced, on the other - less pronounced. Very often, during the initial illness, one can determine by the nature of the tremor: it is necessary to continue diagnosing Parkinson's disease, or whether the patient has Wilson-Konovalov disease, accompanied by metabolic disorders.

A detailed gait analysis is also performed. The doctor asks the patient to walk around the office and observes the speed. At risk are patients who experience obvious acceleration when moving forward. Thus, patients unwittingly try to compensate for difficulties in maintaining balance.

Functional diagnostics

The most effective - transcranial ultrasound sonography and clinical - accelerometric differential diagnosis. They help not only to confirm or refute the presence of the disease, but also to choose the right treatment, including dosage.

Ultrasound transcranial Sonography helps to determine what area of nerve cells in the brain is affected and even predisposition to Parkinson's disease, and accelerometric differential diagnosis is informative for analyzing the dynamics of tremor.

Tomography is auxiliary in diagnosis. It is indicated not to identify the nature of Parkinson's disease, but to distinguish it from other pathologies and (or) identify neoplasms and degenerative pathologies in the patient.

According to indications, electroencephalography, Dopplerography , and ultrasound of the brachycephalic arteries may also be prescribed. The data obtained through these surveys is also clarifying.

Stages

To determine the severity of the condition, Parkinson's disease is usually divided into several periods - stages. Understanding the stage is important for choosing the right treatment method.

Stage 1 .Impaired motor activity of one of the hands, insomnia, problems with charm. Later, tremor appears, handwriting deteriorates significantly, stiffness is felt in the upper back, and sometimes in the neck area.

Stage 2 . Impaired motor function is noticeable on both sides. The lower jaw and tongue begin to tremble, speech may slow down, and facial expressions may become distorted. Many people have problems with sweating (a characteristic sign is wet or, on the contrary, excessively dry palms).

Stage 3 .The gait changes. When walking, a person begins to involuntarily place his feet parallel to each other. The steps themselves become mincing and small. The so-called "supplicant pose" begins to form: half-bent legs + bent head + stooped posture. A person is still able to serve himself, but many things in everyday life become very difficult for him to do.

Stage 4 . Complete loss of balance. A person can even fall forward when getting out of bed. Speech becomes slurred, blurred, voice becomes quiet. Mood – excessively depressed. To carry out basic tasks (for example, brushing your teeth) you need the help of loved ones.

Stage 5 . The patient cannot walk or sit up independently. The process of urination becomes uncontrollable. Serious swallowing problems occur. The speech is similar to the babble of a child.

Treatment

Nowadays, doctors have been able to develop effective drug methods for symptomatic treatment. Unfortunately, drug therapy does not help overcome the cause of the pathology, but it significantly alleviates the manifestation of the disease, reduces complications, and increases the life expectancy of patients.

If the disease develops at the age of 40-65 years, then patients live about 20 more years. If caught at an earlier age, then the predicted life expectancy is about 40 more years.

The main thing is that it is important to carry out a comprehensive diagnosis in a timely manner and begin treatment under the supervision of an experienced neurologist or neurosurgeon. Some patients suffering from even the 3rd stage of the disease, having started treatment in a timely manner, return to work that requires motor and intellectual activity.

The best way to bring the disease under control is by using neurosurgical techniques or combining drug treatment with physiotherapy - especially hypobaric therapy oxygenation (procedures in a pressure chamber), massage.

Drug treatment

Modern drug treatment is based on the use of drugs from several groups:

Blockers monoamine oxidase-B and catechol-O-methyltransferase . Thanks to them, obstacles are created to the destruction of the hormone dopamine.

Activators (stimulators) of dopamine receptors.

Medicines that inhibit the actions of peripheral L-amino acid decarboxylase (inhibitors).

Blockers of the action of choline and its analogues (such drugs can directly influence the mechanism of transmission of nerve impulses).

Amantadines are drugs that increase the sensitivity of a number of receptors.

The choice of how to treat Parkinson's disease depends on the stage of the disease. If at the 1st stage of the disease the emphasis is on dopamine receptor stimulants, then at the 5th stage the treatment is as comprehensive as possible, and it is impossible to do without peripheral decarboxylase inhibitors .

Surgery

Since the 50s of the 20th century, surgery has also been used in the treatment of Parkinson's disease. At the same time, the techniques of neurosurgeons have undergone significant changes. Initially, operations were aimed at destroying the pathways in the thalamus. Alas, the result of such operations was often unsatisfactory, but there were a lot of side effects.

A more progressive method is neuroprosthetics (neuroimplantation) or installation of neurostimulators . A person is given special implants. They activate nerve cells in the brain, improve the brain's ability to process information and control movements.

After surgery, further supportive medical treatment may be required, but the amount of medication required by the patient is significantly reduced. Immediately after the operation, tremors are significantly reduced, balance and the ability to concentrate are improved.

Treatment with folk remedies

Many folk remedies are used for Parkinson's disease:

Juice therapy (from fresh vegetables, fruits).

Oils (externally).

Baths from herbal decoctions (oregano, jasmine).

Use of bee products (especially propolis).

Taking tinctures and decoctions based on lemon balm, eleutherococcus, and ginseng.

But folk remedies are not basic treatment. This is an addition to the main therapy.

Juice therapy is a good general tonic. Massage with jasmine oil, baths with sage relieve tremors, and with oregano reduce muscle tension. Decoctions and tinctures have good general strengthening and tonic properties.

But folk remedies themselves do not produce any effect. They can only be considered as part of a comprehensive treatment.

Nutrition and diet

A proper diet helps maintain the desired balance and consolidate the effect of drug and neurosurgical treatment.

A special diet for Parkinson's disease is not required, but the diet of a person suffering from Parkinson's disease must include fermented milk products, grains, herbs, vegetables, fruits, and grains. They should be the main part of the diet.

At the same time, we must not forget about fish and poultry. Animal protein is essential. Vegetarianism is not recommended for Parkinson's disease . At the same time, doctors (due to the specifics of the disease) recommend leaving meat dishes for dinner.

The food intake schedule must be clearly coordinated with the medication intake schedule . Many medications prescribed for Parkinson's disease can only be taken two hours after a meal.

It is important to observe the drinking regime. It is advisable to adhere to the following scheme: at least 7 glasses of water per day. At the same time, a third of the water you drink should come at meals.

Physiotherapy

An important element in the fight against Parkinson's disease is therapeutic exercises. It is useful for maintaining muscle tone, developing joints, improving coordination of movements, and strengthening ligaments.

Exercises for the shoulder girdle, neck muscles, torso, arms, legs are especially useful:

bending, turning the head to the right and left (the main principle is that the exercises are performed very slowly);

raising, spreading the shoulders;

circular movements in the shoulder joints;

straightening the legs at the knees (alternately);

flexion of toes, hands;

straightening the back, bending the torso.

Facial gymnastics is also shown. Doctors recommend that patients start every day with the following exercises:

Pull out your tongue and move it in different directions.

Raise and lower eyebrows.

Purse your lips.

At first glance, the exercises are simple but effective. If exercises are done regularly, then a number of symptoms, especially those affecting muscles and joints, are significantly less disturbing.

In addition to classical exercise therapy for Parkinson's disease, dancing is useful. Argentine tango provides a particularly good effect. After all, when performing this dance, different muscle groups and joints are maximally involved. With severe progression of the disease, this method of combating the disease is difficult to use, but at the 1st and 2nd stages of the disease, its use is very advisable.

Forecast

The prognosis for Parkinson's disease is unique to each person. The main difficulty is that it is impossible to predict what symptoms will appear and when.

But the patient himself can significantly slow down the course of the disease. This requires a clear treatment plan and a positive outlook. Reducing stress significantly worsens each symptom, when the desire to get better activates the body and increases the chances of recovery.

Also, the prognosis is extremely different for those patients who are treated purely with folk remedies, and those who undergo medication, neurosurgical treatment, and engage in physical therapy under the supervision of a doctor. But the most favorable prognosis is for those who not only struggle with symptoms, maintain existing skills, but also learn new things. These can be both new movements and intellectual processes (learning foreign languages, drawing).

An integrated approach to treatment and rehabilitation allows a person not only to not lose his legal capacity, but to live a full life.

To prevent Parkinson's disease, prevention is very important. These are not just measures to prevent the disease, but the elimination of a number of risk factors from your life

7.3.Huntington's disease

Huntington's disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition).

Adult-onset Huntington's disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington's disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking

and reasoning abilities. Individuals with the adult-onset form of Huntington's disease usually live about 15 to 20 years after signs and symptoms begin.

A less common form of Huntington's disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington's disease tends to progress more quickly than the adult-onset form: affected individuals usually live 10 to 15 years after signs and symptoms appear.

Huntington's disease affects an estimated 3 to 7 per 100,000 people of European ancestry. The disorder appears to be less common in some other populations, including people of Japanese, Chinese, and African descent.

Causes

Variants (also called mutations) in the *HTT* gene cause Huntington's disease. The *HTT* gene provides instructions for making a protein called huntingtin. Although the function of this protein is unclear, it appears to play an important role in nerve cells (neurons) in the brain.

The *HTT* variant that causes Huntington's disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with Huntington's disease, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington's disease, while people with 40 or more repeats almost always develop the disorder.

An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington's disease.

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. An affected person usually inherits the altered gene from one affected parent. In rare cases, an individual with Huntington's disease does not have a parent with the disorder.

As the altered *HTT* gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. A larger number of repeats is usually associated with an earlier onset of signs and symptoms. This phenomenon is called anticipation. People with the adult-onset form of Huntington's disease typically have 40 to 50 CAG repeats in the *HTT* gene, while people with the juvenile form of the disorder tend to have more than 60 CAG repeats.

Individuals who have 27 to 35 CAG repeats in the *HTT* gene do not develop Huntington's disease, but they are at risk of having children who will develop the disorder. As the gene is passed from parent to child, the size of the CAG trinucleotide repeat may lengthen into the range associated with Huntington's disease (36 repeats or more).

Symptoms

Huntington's disease usually causes movement, cognitive and psychiatric disorders with a wide spectrum of signs and symptoms. Which symptoms appear first varies greatly from person to person. Some symptoms appear more dominant or have a greater effect on functional ability, but that can change throughout the course of the disease.

Movement disorders

The movement disorders associated with Huntington's disease can include both involuntary movement problems and impairments in voluntary movements, such as:

Involuntary jerking or writhing movements (chorea)
Muscle problems, such as rigidity or muscle contracture (dystonia)
Slow or unusual eye movements
Impaired gait, posture and balance
Difficulty with speech or swallowing

Impairments in voluntary movements — rather than involuntary movements — may have a greater impact on a person's ability to work, perform daily activities, communicate and remain independent.

Cognitive disorders

Cognitive impairments often associated with Huntington's disease include:
Difficulty organizing, prioritizing or focusing on tasks

Lack of flexibility or the tendency to get stuck on a thought, behavior or action (perseveration)

Lack of impulse control that can result in outbursts, acting without thinking and sexual promiscuity
Lack of awareness of one's own behaviors and abilities
Slowness in processing thoughts or "finding" words
Difficulty in learning new information

Psychiatric disorders

The most common psychiatric disorder associated with Huntington's disease is depression. This isn't simply a reaction to receiving a diagnosis of Huntington's disease. Instead, depression appears to occur because of injury to the brain and subsequent changes in brain function. Signs and symptoms may include:

Feelings of irritability, sadness or apathy
Social withdrawal
Insomnia
Fatigue and loss of energy
Frequent thoughts of death, dying or suicide

Other common psychiatric disorders include:

Obsessive-compulsive disorder, a condition marked by recurrent, intrusive thoughts and repetitive behaviors

Mania, which can cause elevated mood, overactivity, impulsive behavior and inflated self-esteem

Bipolar disorder, a condition with alternating episodes of depression and mania

In addition to the above disorders, weight loss is common in people with Huntington's disease, especially as the disease progresses.

Diagnosis

A preliminary diagnosis of Huntington's disease is based primarily on your answers to questions, a general physical exam, a review of your family medical history, and neurological and psychiatric examinations.

Neurological examination

The neurologist will ask you questions and conduct relatively simple tests of your:

Motor symptoms, such as reflexes, muscle strength and balance

Sensory symptoms, including sense of touch, vision and hearing

Psychiatric symptoms, such as mood and mental status

Neuropsychological testing

The neurologist may also perform standardized tests to check your:

Memory

Reasoning

Mental agility

Language skills

Spatial reasoning

Psychiatric evaluation

You'll likely be referred to a psychiatrist for an examination to look for a number of factors that could contribute to your diagnosis, including:

Emotional state

Patterns of behaviors

Quality of judgment

Coping skills

Signs of disordered thinking

Evidence of substance abuse

Brain-imaging and function tests

Your provider may order brain-imaging tests for assessing the structure or function of the brain. The imaging technologies may include MRI or CT scans that show detailed images of the brain.

These images may reveal changes in the brain in areas affected by Huntington's disease. These changes may not show up early in the course of the disease. These tests can also be used to rule out other conditions that may be causing symptoms.

Genetic counseling and testing

If symptoms strongly suggest Huntington's disease, your provider may recommend a genetic test for the nontypical gene.

This test can confirm the diagnosis. It may also be valuable if there's no known family history of Huntington's disease or if no other family member's

diagnosis was confirmed with a genetic test. But the test won't provide information that might help determine a treatment plan.

Before having such a test, the genetic counselor will explain the benefits and drawbacks of learning test results. The genetic counselor can also answer questions about the inheritance patterns of Huntington's disease.

Predictive genetic test

A genetic test can be given if you have a family history of the disease but don't have symptoms. This is called predictive testing. The test can't tell you when the disease will begin or what symptoms will appear first.

Some people may have the test because they find not knowing to be more stressful. Others may want to take the test before having children.

Risks may include problems with insurability or future employment and the stresses of facing a fatal disease. In principle, federal laws exist that make it illegal to use genetic testing information to discriminate against people with genetic diseases.

These tests are only performed after consultation with a genetic counselor.

Treatment

No treatments can alter the course of Huntington's disease. But medications can lessen some symptoms of movement and psychiatric disorders. And multiple interventions can help a person adapt to changes in abilities for a certain amount of time.

Medications will likely evolve over the course of the disease, depending on overall treatment goals. Also, drugs that treat some symptoms may result inside effects that worsen other symptoms. Treatment goals will be regularly reviewed and updated.

Medications for movement disorders

Drugs to treat movement disorders include the following:

Drugs to control movement include tetrabenazine (Xenazine) and deutetrabenazine (Austedo), which have been specifically approved by the Food and Drug Administration to suppress the involuntary jerking and writhing movements (chorea) associated with Huntington's disease. These drugs don't have any effect on the progression of the disease, however. Possible side effects include drowsiness, restlessness, and the risk of worsening or triggering depression or other psychiatric conditions.

Antipsychotic drugs, such as haloperidol and fluphenazine, have a side effect of suppressing movements. Therefore, they may be beneficial in treating chorea. However, these drugs may worsen involuntary contractions (dystonia), restlessness and drowsiness.

Other drugs, such as olanzapine (Zyprexa) and aripiprazole (Abilify), may have fewer side effects but still should be used with caution, as they may also worsen symptoms.

Other medications that may help suppress chorea include amantadine (Gocovri, Osmolex ER), levetiracetam (Keppra, Elepsia XR, Spritam) and clonazepam (Klonopin). However, side effects may limit their use.

Medications for psychiatric disorders

Medications to treat psychiatric disorders will vary depending on the disorders and symptoms. Possible treatments include the following:

Antidepressants include such drugs as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac) and sertraline (Zoloft). These drugs may also have some effect on treating obsessive-compulsive disorder. Side effects may include nausea, diarrhea, drowsiness and low blood pressure.

Antipsychotic drugs such as quetiapine (Seroquel) and olanzapine (Zyprexa) may suppress violent outbursts, agitation, and other symptoms of mood disorders or psychosis. However, these drugs may cause different movement disorders themselves.

Mood-stabilizing drugs that can help prevent the highs and lows associated with bipolar disorder include anticonvulsants, such as divalproex (Depakote), carbamazepine (Tegretol, Carbatrol, Epitol, others) and lamotrigine (Lamictal).

Psychotherapy

A psychotherapist — a psychiatrist, psychologist or clinical social worker — can provide talk therapy to help with behavioral problems, develop coping strategies, manage expectations during progression of the disease and help family members communicate with each other.

Speech therapy

Huntington's disease can significantly impair control of muscles of the mouth and throat that are essential for speech, eating and swallowing. A speech therapist can help improve your ability to speak clearly or teach you to use communication devices — such as a board covered with pictures of everyday items and activities. Speech therapists can also address difficulties with muscles used in eating and swallowing.

Physical therapy

A physical therapist can teach you appropriate and safe exercises that enhance strength, flexibility, balance and coordination. These exercises can help maintain mobility as long as possible and may reduce the risk of falls.

Instruction on appropriate posture and the use of supports to improve posture may help lessen the severity of some movement problems.

When the use of a walker or wheelchair is required, the physical therapist can provide instruction on appropriate use of the device and posture. Also, exercise regimens can be adapted to suit the new level of mobility.

Occupational therapy

An occupational therapist can assist the person with Huntington's disease, family members and caregivers on the use of assistive devices that improve functional abilities. These strategies may include:

Handrails at home

Assistive devices for activities such as bathing and dressing

Eating and drinking utensils adapted for people with limited fine motor skills.

MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is a severe degenerative muscle disease. It was initially described by Meryon in 1857, and named after Duchenne

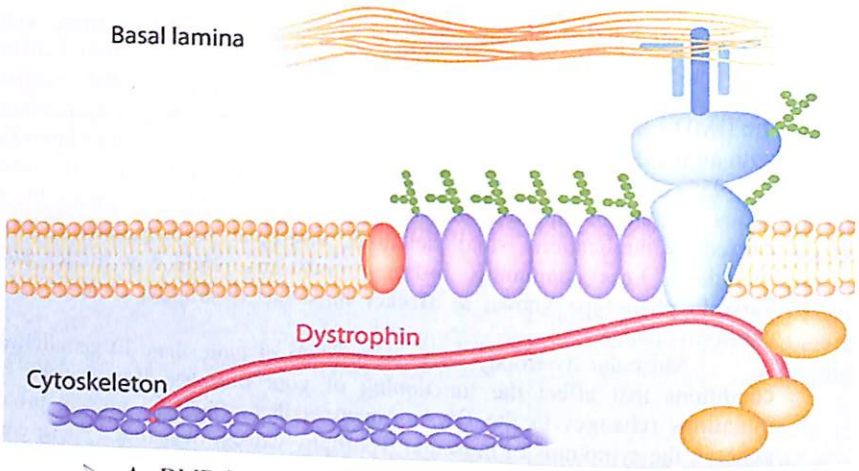
de Boulogne based on his report of a young boy suffering from "congenital hypertrophic paraplegia," a condition characterized by early onset weakness and muscular hypertrophy [1]. The biological basis was later attributed to mutations of the DMD gene on Xp21 [2]. DMD is the most common type of dystrophinopathy, with an incidence of 1 in 3500 live male births [3], and an estimated prevalence of 4.8 (95% CI 1.9–11.8) per 100,000 males worldwide [4]. Deletions of one or more exons account for approximately two-thirds of all DMD mutations; the rest are caused by duplications, small deletions, insertions, point mutations, or splicing mutations. Less commonly, in-frame mutations produce a milder and more variable phenotype known as Becker muscular dystrophy, or X-linked dilated cardiomyopathy.

Muscular dystrophy refers to a group of more than 30 genetic(inherited) conditions that affect the functioning of your muscles. It is caused by gene mutations (changes in the DNA sequence) that affect the muscle proteins. In general, the symptoms of muscular dystrophy worsen over time. These conditions are a type of myopathy, a disorder of your skeletal muscles.

- There are more than 30 types of muscular dystrophy. Most common type include:

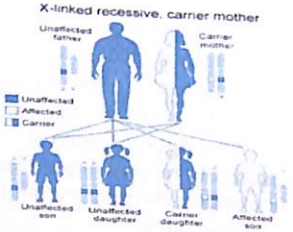
1. Duchenne muscular dystrophy (DMD)
2. Becker muscular dystrophy (BMD)

- DMD and BMD are inherited in an X-linked recessive pattern due to the DMD gene being located on the X chromosome.DMD is a genetic disease due to the mutation of the dystrophin gene, located on chromosome Xp21. It is inherited as an X- linked recessive trait however, approximately 30% of cases are due to new mutations.
- Mutations in the dystrophin gene result in diseases known as dystrophinopathies , which encompass Duchenne muscular dystrophy, Becker muscular dystrophy, and an intermediate form. Mutations result in a limited production of the dystrophin protein, which results in loss of the myofiber membrane integrity with repeated cycles of necrosis and regeneration. Fibrous connective tissue and fat progressively replace muscle leading to clinical features.
- Dystrophin act as a shock absorber within the muscle cells, reducing any damage caused by muscle contractions.
- Patient with Duchenne, the muscles lack a protein called dystrophin, which is critical for muscle function and repair.



- As DMD is inherited as an X-linked recessive manner, boys are more frequently affected than girls. The estimated incidence is 1 in 3600 male live-born infants. It is one of the most common and most severe congenital myopathies.
- 1/3 of these with previous family history
- 2/3 sporadic.
- It is more severe.

Duchenne Muscular Dystrophy (DMD)



EARLY SIGNS AND SYMPTOMS OF DMD:

- **Delays in reaching developmental milestones.**

A delay in meeting developmental milestones may be the first noticeable sign of a muscle problem. Milestones are the skills or tasks a child can do by a certain age.

Milestones will vary from child to child, but most children follow a similar order and pattern. Children with DMD may have a delay in the following milestones:

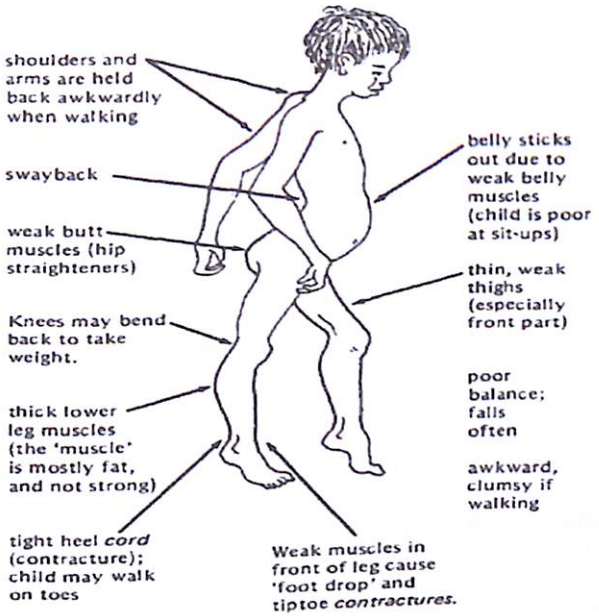
- lifting their head while lying on their tummy
- rolling over on their own
- sitting or standing without assistance

- walking well by 18 months

➢ **Gower's sign**:

Difficulty rising from a sitting position.

- When getting up from a sitting position, your child may first start on their hands and knees and then slowly walk their hands up the shins, knees, and thighs until standing.
- This is called Gower's sign trusted source(or **Gower's maneuver**). Gower's sign is common in children with DMD and is caused by weakness in the pelvic and lower limb muscles.



LATE SIGNS AND SYMPTOMS OF DMD :

Over time, weakness in the muscles progresses until the use of a wheelchair is necessary.

Some of the later signs and symptoms may include:

➢ curvature of the spine (scoliosis)

➢ contracture, which occurs when your muscles, tendons, or joints, which are normally stretchy, tighten or shorten and become non-stretchy; a contracture is usually permanent and can cause significant disabilities

➢ loss of the ability to walk, typically around 12 to 14 year of age.

By the late teens, DMD may also cause serious, life threatening complications affecting the heart and the muscles used for breathing.

➢ ***Effects on the heart:***

Problems with the heart muscles can make it harder for the heart to pump blood (cardiomyopathy). The heart can become enlarged. This may eventually lead to heart failure.

- ***Effects on the lungs:***

Another complication of DMD is weakness of the muscles in the rib cage. This can make it harder to breathe. The weakness also increases the risk of serious respiratory infections like pneumonia. At this stage, a ventilator might be necessary to help with breathing.

- ***Effects on digestion:***

if the muscles of the gastrointestinal tract are affected, food may move through the digestive tract slowly. This can cause constipation or diarrhoea . At advanced stages of DMD it might also become difficult to swallow (dysphagia)

7.4. BECKER MUSCULAR DYSTROPHY

- Becker muscular dystrophy (BMD) is an X-linked recessive disorder involving dystrophin gene mutation, resulting in progressive muscle degeneration. The proximal lower limb muscles are most often affected, while heart failure is a frequent complication among individuals with this condition.
- BMD is less common and less severe than Duchenne muscular dystrophy (DMD).
- Becker muscular dystrophy is rare. It occurs in about 3 to 6 out of every 100,000 births and mainly affects children assigned male at birth.
- Symptoms of Becker muscular dystrophy (BMD) most often start between the ages of 5 and 15 years but may begin later.
- BMD causes muscle weakness that gets worse over time, so common symptoms include:
  - Difficulty walking up stairs.
  - Difficulty walking that gets worse over time.
  - Low tolerance for exercise.
  - Muscle pain and/or spasms.
  - Frequent falls.
  - Toe walking.
  - Fatigue.

Table.Duchenne Muscular Dystrophy and Becker Muscular Dystroph		
	DMD	**BMD**
Dystrophine gene	Absent or nonfuctional	Partially functional
Incidence	1/3.600 male births	3 to 6/100,000 Male births
Mean age at onset	3-5 years	12 years
Disease progression	Fast	Slow
Meanage at becoming nonambulatory	12 years	27 years
Mean life expectancy	Mid 20 s	40s
Oset of cardiomyopathy	Usually follows skeletal progression	May present before Skeletal symtoms

DIAGNOSIS

- High creatine kinase
- Mutations in dystrophin

DNA test

Western blot

- Muscle biopsy

TREATMENT

Investigational therapies for Duchenne dystrophy and Becker dystrophy include:

- Gene therapy.
- Creatine.
- Myostatin inactivation.
- Skeletal muscle progenitors.
- The antioxidant idebenoness.

Treatments can include steroid medications to maintain muscle strength as long as possible; stretching and other exercises specifically designed for people with muscular dystrophy; braces and splints; assistive devices such as wheelchairs, computer technology, and lifting devices to help people with DBMD continue their daily activities; and surgery to prolong walking.

MEDICAL AND GENETIC COUNSELLING

Medical and genetic counselling is a type of specialised medical care aimed at preventing the most frequent hereditary pathologies in society. The main goal of medical and genetic counselling is to prevent the birth of children with severe hereditary diseases. Genetic counselling performs the following tasks:

1. Determination of health prognosis for future offspring in families where there was, is or is expected to be a patient with hereditary pathology.

2 Explaining genetic risk in an accessible way to parents and helping them to make decisions about childbearing.

3. Helping doctors to make a diagnosis of hereditary disease, if this requires special methods of investigation.

4. Dispensary surveillance and identification of a high-risk group among relatives of an individual with an inherited disease.

5. Propaganda of medical and genetic knowledge among doctors and the population.

The reason for medical and genetic counselling may be:

- Birth of a child with congenital malformations, mental and physical retardation, blindness and deafness, seizures, abnormal sexual development.
- Repeated spontaneous abortions, miscarriages, stillbirths, detection of pathology during screening programmes.
- Blood marriages.
- Unfavourable course of pregnancy.
- Exposure to known or possible teratogenic factors in the first three months of pregnancy.

The methodology of medical and genetic counselling includes several stages:

1. Clinical and genealogical examination of the patient and his relatives:
2. Obtaining genetic risk assessments.

At the first stage of counselling, the diagnosis of the disease is clarified. The diagnosis is clarified with the help of genetic analysis, for which genealogical, cytogenetic, biochemical and other methods of modern genetics are used. The second step is to determine the degree of risk of having a sick child. Genetic risk can be determined either by theoretical calculations based on genetic patterns or by empirical data. Determination of the degree of risk in different forms of hereditary pathology is different. In monogenic mendelating diseases, the prognosis is based on the calculation of the probability of offspring according to genetic patterns. In this case, if the type of inheritance of the disease is known and the genotype of the parents can be determined from the pedigree, the risk assessment is reduced to the analysis of Mendelian cleavage. If the proband is found to have a new mutation, the risk of having a child with the same pathology is low. Risk calculation in monogenic disease can be complicated in case of reduced expression or incomplete penetrance of the gene, late manifestation of the genetic abnormality, genetic heterogeneity of the disease and in general in case of inaccurate diagnosis. In chromosomal diseases, determining the risk of second birth of offspring with chromosomal abnormalities depends on whether the karyotypes of the parents are normal, whether they have no mosaicism, and whether there is no familial form of structural chromosome abnormalities. If there are no abnormalities in the karyotype of the parents, the probability of a second child with a chromosomal anomaly is estimated using empirical data for each type of anomaly, taking into account the age of the parents. In multifactorial diseases, i.e. diseases with an inherited predisposition, the basis for risk assessment is empirical data on the population and familial frequency of each disease. At low risk, pathological changes can be expected in 5 % of offspring. In this situation, there are no contraindications for further childbearing. Medium risk is registered if the probability of giving birth to a sick child is 6-20 %. In this case, fertility planning

depends on the severity of the suspected disease and the possibility of prenatal diagnosis. A high genetic risk is defined when the probability of giving birth to a child with a hereditary pathology is more than 20%. Such an assessment of the risk of giving birth to a sick child is rather conditional, as the severity of the hereditary disease plays an important role. *The possibility of prenatal diagnosis* is decisive for a favourable decision regarding the completion of the pregnancy. Genetic risk calculations are not an end in themselves for counselling. The risk values obtained serve as a basis for making a decision regarding the planning of childbearing. At the final stage of medical and genetic counselling, the geneticist explains to the family in an understandable way the genetic risk of having a sick child.This is one of the most responsible stages. A genetic counsellor should always take into account the motives that may guide people (emotional, socio-economic and others), assess the intellectual and educational level of the spouses or the proband, and the psychological climate in the family. In the future, the family independently makes a decision acceptable for it regarding reproductive behaviour at the risk of hereditary disease.

REFERENCES:

1. Rizayev J.A., Muxamadiyeva L.A., Mamatkulova D.X., Bosimov .Klinik genetika.Дарслик.Samarqand 2023.

2.K.N.Njshonboev, O.E.Eshonqulov, M.Sh.Bosimov. Tibbiyot genetikasi. Darslik.

Toshkent.. "Geo fan poligraf". 2011 y.

3. L.A.Muxamadiyva, N.O.Turayeva, B.I.Zokirova, K.T.Azimova, G.R.Rustamova. Monogen va xromosoma kasalliklari, o`quv qo`llanmaSamarqand 2022

4.Клиническая генетика : учебник / Н. П. Бочков, В. П. Пузырев, - 4-е изд., доп. и перераб.М. : ГЭОТАР-Медиа, 2013.+ 2006г. - 592 с. : ил. + Приложение ДИСК

5. Odam genetikasi. S.S. Fayzullayev. / darslik - T.: "Barkamol fayz media" nashriyoti, 2018, 200 b.

6. Медицинская и клиническая генетика для стоматологов / Янушевич О. - М., 2009

7. Erta yoshdagi bolalar kasalliklari : darslik / N.M. Shavazi, M.R. Rustamov, M.S. Atayeva. Samarqand 2022 y. 400 bet.

8. Bolalar kardiologiyasi asoslari. O.A. Sharipova. O'quv qo'llanma. Samarqand 2023.

9. Болалар кардиоревматологияси / О.А. Шарипова, Т.А. Бобомуратов, Д.Х. Маматкулова, Ж.Н. Абдурахмонов.

10. Детская гастроэнтерология : o`quvqo`llanma / N.M. Shavazi, M.R. Rustamov, M.S. Atayeva, L.M. Garifulina, M.V. Lim, N.O. Turayeva.

11. Алгоритм и критерии оценки практических навыков в педиатрии: учебное пособие / N.M. Shavazi, M.F. Ibragimova, M.V. Lim, M.S. Atayeva, N.O. Turayeva, J.Sh. Gaybullayev.

12. Bolalarda organ va tizimlarning anatomo-fiziologik xususiyatlari: o`quv qo`llanma / D.T. Rabbimova, Sh.M. Ibatova, Sh.M. Uralov, M.M. Qodirova

CONTENTS

RIZAYEV JASUR ALIMDJANOVICH
MUHAMADIYEVA LOLA ATAMURODOVNA
MAMATKULOVA DILRABO HAMIDOVNA
TURAYEVA NAFISA OMANOVNA
RUSTAMOVA GULNOZA RUSTAMOVNA

PEDIATRICS. MEDICAL GENETICS

Textbook for students faculty of denistry

ARTEX NASHRI

Mas'ul muharrir — Madina Mirzakarimova

Musahhih — Madina Mirzakarimova

Texnik muharrir — Raxmonov Shohimardon

Dizayner va sahifalovchi — Raxmonov Shahzod

ARTEX NASHRI bosmaxonasida chop etildi.

Samarqand shahar, Alisher Navoiy ko'chasi 27 - uy

Bichimi 60x84 1/16. Times New Romanl garniturasi. 20 bosma taboq.

Adadi: 200 nusxa. Buyurtma raqami: 107 /06.12.2025

Tel:(97) 897-80-00


9 789910 846717