UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA: A CONSTITUTIONAL BASIS FOR MULTIPLE ERGONOMIC DISORDERS IN YOUNG AGE

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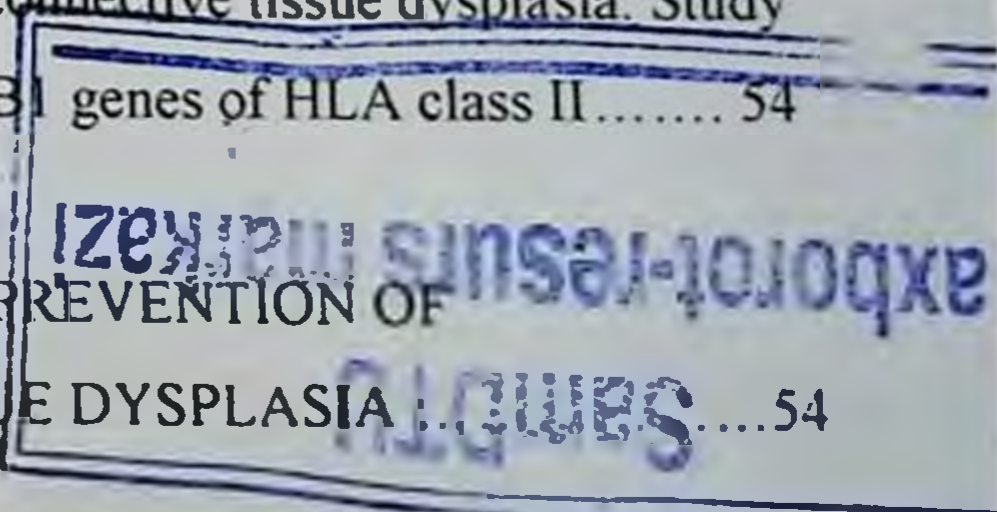
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The book presents various classical and modern aspects of undifferentiated connective tissue dysplasia. The results of scientific and practical studies, as well as our own clinical, instrumental, and functional observations made in a large contingent of patients with various forms of external and internal phenes of undifferentiated connective tissue dysplasia, are presented. The significance of phenotypic, genetic markers for the development and early diagnosis of undifferentiated connective tissue dysplasia, as well as the correction of undifferentiated connective tissue dysplasia using magnesium preparations and chondroprotective, are discussed.

The publication is intended for therapists, rheumatologists, and doctors of related specialties.

CONTENT

A QUICK REFERENCE OF abbreviated terms

ARCH	Abnormally located notochord
VSD	Vegetative-vascular dystonia
GAG	Glucosaminoglycan
GN	Hyaluronidase
HS	Hypermobility syndrome
DST	Connective tissue dysplasia
IBS	Coronary artery disease
IL	Interleukin
ELISA	Linked immunosorbent assay
IFN-y	Interferon
KDR	End-diastolic size
DAC	End-systolic size
LV	Left ventricle
LP	Left atrium
MAC	Minor anomalies of the heart
MMP	Matrix metalloproteinases
NDCT	Undifferentiated connective tissue dysplasia
NIST	Hereditary undifferentiated connective tissue dysplasia
BUT	Osteogenesis imperfecta
ODA	Musculoskeletal apparatus
PG	Prostaglandins
PMK	Mitral valve prolapse
PCR	Polymerase chain reaction
SD	Diabetes

CM	Marfan syndrome
SRO	Free radical oxidation
CVD	Cardiovascular diseases
MTR	Cardiovascular Complications
SED	Ehlers-Danlos Syndrome
FV	Ejection fraction
FC	Function class
TNF-α	Tumor necrosis factor-alpha
HM	Holter monitoring
HP	Chondroprotectors
XC	Chondroitin sulfate
ECG	Electrocardiography
TIMP	Matrix metalloproteinase inhibitors
MASS phenotype	Mitral valve, Aorta, Skeleton, Skin
THIS	Endothelin
Mg2÷	Magnesium ions
HLA	Human Leucocyte Antigens (Major Histocompatibility Complex Molecules)

Introduction

Today in the world, there is an increased interest in the problem of undifferentiated connective tissue dysplasia, this is due both to the enormous medical and social significance, and the insufficient knowledge of practical health care doctors about undifferentiated connective tissue dysplasia as a background condition of various diseases. In the world among young people, to increase the effectiveness of early diagnosis, treatment, and prevention of possible complications of undifferentiated connective tissue dysplasia, numerous scientific studies have been carried out, including the rationale for the formation and course of this disease; improvement of the system of early diagnostics; assessment of the state of collagen formation; development of modern methods of treatment and prevention of possible complications in the light of modern requirements. A detailed search for markers, carried out in the course of recent studies, has a close relationship with the genes that determine the development of this disease, which in turn can be widely applied in practical health care. At the same time, the study of genetic markers contributes to the creation of a reasonable basis for differentiated clinical management in different groups of patients with UCTD.

The lack of modern monographs on undifferentiated connective tissue dysplasia is one of the reasons for the preservation of outdated ideas rooted in practice in the use of modern functional research methods.

The authors of the monograph have been dealing with the issues of pathogenesis, diagnosis, and treatment of this pathology for a long time, and set themselves the task of highlighting its modern aspects. The book reflects the results of scientific research on theoretical and practical issues of undifferentiated connective tissue dysplasia, which are compared with the generalized data of

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special literature, as well as the invaluable experience of the therapeutic departments of hospitals in Samarkand. Samarkand State Medical Institute.

The authors do not claim to be exhaustive of the provisions expressed in the book and admit that some of them may turn out to be controversial, believing that this work will find its reader and will ultimately contribute to a further improvement in the quality of knowledge and skills of medical personnel.

§1.1. Classification, modern views on the diagnosis of undifferentiated connective tissue dysplasia

The definition of connective tissue dysplasia (CTD) is several disorders in the development of connective tissue in the embryonic and postnatal periods from the cause of a violation of fibrillogenesis of the extracellular matrix, due to genetic factors, leading to a disorder of homeostasis at the tissue, organ and organism levels in the form of various morphofunctional disorders of visceral and locomotor organs [59, p.235; 72, p.188]. According to Tvorogov T.M. et al. a huge number of anomalies and diseases, due to genetic defects, create precisely anomalies in the structure and functions of the connective tissue, they have a certain type of inheritance, or are mutations under the influence of adverse environmental factors in the embryonic period (unfavorable environmental conditions, unbalanced nutrition, stress, etp.) [64, p.1215].

Thus, DST is a hereditary disorder of connective tissue development, characterized by breakdowns in the structure of its main substance and fibers [64, p.1215]. Among the main causes of CTD, one can single out a temporary pathology of the synthesis and assembly of collagen and elastin, the creation of immature collagen, breakdown of the structure of collagen and elastin fibers, which are based on their incomplete cross-linking [64, p.1215]. This indicates that a breakdown in the structure of the connective tissue has a variety of manifestations, the diversity of which is expressed in the form of violations of several systems of internal organs.

Scientific research conducted in recent years indicates that DST is divided into the following forms: differentiated, undifferentiated.

Differentiated connective tissue dysplasia has a characteristic type of inheritance, which has a clear clinical picture, and sometimes confirmed and well-studied gene or biochemical damage [30, p.46-50]. Thus, the most common representative of this group is Marfan's syndrome, Ehlers-Danlos syndrome of all

10 types, osteogenesis imperfecta, and flaccid skin syndrome (Cutis laxa) [59, p.235]. In contrast to the above, undifferentiated connective tissue dysplasia (UCTD) is characterized by an indefinite set of phenotypic features, and does not have a clear clinical picture as in cases of differentiated CTD. UCTD is not a whole nosological unit, but a genetically diverse group. Currently, the term "MASS-phenotype" is often used, this is an abbreviation for the first letters of the phenotypic traits that are most often found (Mitral valve, Aorta, Skeleton, Skin). This term characterizes dysfunction or weakness of the connective tissue, as well as mesenchymal insufficiency or the syndrome of "small" connective tissue dysplasias [73, p.117-119]. In the early 1990s, five annual all-Union congresses were held in the city of Omsk, Russian Federation, all of which were devoted to topical issues of the DST. At one of the five congresses, a working classification was adopted, which was proposed by Professor V.M. Yakovlev and G.I. Nechaev. It should be noted that this classification applies to a practitioner and contributes to the division into:

1. Dysplastic-dependent changes in organs and systems in connective tissue dysplasia (locomotor, skin, visceral);

2. Conditions associated with connective tissue dysplasia.

Some scientists (X All-Russian Congress of Cardiologists, 2009) bring to the fore hereditary breakdowns in the development of connective tissue and recognize the need to identify individual dysplastic syndromes and phenotypes [38, p.164-172]. The scientific debate led to the creation in 2008 of an expert council to draw up a national clinical recommendation "Hereditary disorders of the structure and function of connective tissue" for patients with UCTD [38, pp.164-172].

Today, various authors call UCTD differently, it is "connective tissue dysplasia syndrome" or "connective tissue weakness", also "mesenchymal dysplasia" or "connective tissue dysfunction", "unclassified forms of connective tissue dysplasia", which in turn, all this is a synonym for UCST [38, pp.164-172].

Scientific and practical research has been achieved by the allocation of 10 dysplastic syndromes and phenotypes: Marfan-like appearance; Marfan-like

phenotype; MASS-phenotype (Mitral valve, Aorta, Skeleton, Skin), primary mitral valve prolapse; Ehlers-like phenotype (classic or hypermobile); benign joint hypermobility; unclassifiable CTD phenotype; increased dysplastic stigmatization; increased dysplastic stigmatization with predominantly visceral manifestations [76, p.298-320].

Each of the syndromes and phenotypes has certain clinical symptomatology and a certain prognosis of development and outcome [76, p.298-320]. Of all the syndromes, the unclassified phenotype, as well as increased dysplastic stigmatization, are characterized by a minimum of clinical manifestations, and this syndrome is close to normal variants [76, p.298-320].

According to R.O. Demidov et al. (2015), the most common symptom of CTD, namely from 57 to 94% of cases, is skeletal pathology: deformity of the chest and spine, flat feet, joint hypermobility, juvenile osteochondritis [19, p.37-42]. Clinical signs of damage to the muscular system are malnutrition, muscle hypotension, diastasis of the rectus abdominis muscles, abdominal hernias; pathology of the skin, which is manifested by its hyper elasticity, the presence of striate [19, p.37-42]. The defeat of the cardiovascular system is characterized by a low frequency of 3 to 10%. From cardiovascular pathology, mitral valve prolapse occurs (PMC), as well as false chords of the left ventricle [19, pp.37-42]. A frequent symptom is the pathology of blood pressure: in young people, the so-called idiopathic arterial hypotension is more often observed, which turns into arterial hypertension with age [19, p.37-42]. Frequent lesions of the vascular bed, are varicose veins of the upper and lower extremities, varicocele, hemorrhoids, lesions of the elastic type arteries in the form of pathological tortuosity of the arteries, which can reach loop formation [19, p.37-42].

R.O. Demidov et al. (2015) indicate in their article that ophthalmic manifestations are also observed with high frequency, which is about a third of observations. In patients with CTD, the myopia of varying degrees of manifestations, astigmatism, hyperopia, dislocation, and subluxation of the lens can be diagnosed [19, p.37-42]. A frequent component of DST is the pathology of

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the gastrointestinal tract, this is biliary dyskinesia, duodenogastric and gastroesophageal refluxes, sometimes gastro ptosis, esophageal diverticula, hiatal hernia can be observed. Often, nephroptosis is a component of CTD from the urinary system (9.1-20% of cases), anomalies in the structure of the kidneys can also be observed (11.6%). With a small frequency, there is a lesion of the bronchopulmonary system (6%) [19, p.37-42]. Literature data indicate that the pathology of the nervous system in patients with UCTD most often manifests itself in the form of vegetovascular dystonia (VVD) - in 68-87.0% of cases, and sometimes cerebrovascular disorders.

According to the literature data, the occurrence of UCTD depending on gender and age was considered. Of young people, from 26 to 80% are observed, among them 70% are women [35, p.4-8: 44, pp.42-44]. In their work, G. I. Nechaeva et al. (1997), cites data that 74 - 85% of school-age children have various signs of CTD [45, p. 20-24]. Also, Kan N.E et al. (2014), claims that UCTD women are much more likely (85.5%) to have pregnancy pathology compared to healthy women (53.3%) [28, p.7-9]. Literature data indicate a higher risk of developing gynecological, obstetric, and neonatal complications in women with UCTD [29, p.47-52].

A. V. Klemenova et al. (2014) in their studies noted that in women with UCTD, the frequency of occurrence of cardiac disorders is 60.7%, anomalies in the location of the chord of the left ventricle were detected in 12.5%, MVP in 44.6% of the examined patients, atrial septal defect - in 30.4% of cases, kidney anomalies - in 19.7% of the examined and varicose veins - in 16.1% of cases [34, p.127-136].

In the age aspect, UCTD is most clinically manifested by changes in the musculoskeletal system, in particular, joint hypermobility. For many years, HS was associated with arthralgia. However, recent literature data indicate the correlation of HS with pain in the spine, the appearance of extra-articular signs of connective tissue failure. These facts aroused interest in studying the pathology that combines lesions of the musculoskeletal system, including the spine [39, p.3]. One of the most common manifestations of damage to the musculoskeletal system in the

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human population is a pain in the spine, while in 22% of cases it is accompanied by joint hypermobility, as well as other indicators of connective tissue dysplasia in young people [41, p.38-42].

The factor in the formation of prolapse of the valvar apparatus, chords of the heart, and the violation of the elastic properties of the aorta are the pathology of the structure of the valvar apparatus of the heart and the vascular wall due to the violation of the formation of the intercellular matrix of the connective tissue framework [41, p.38-42].

Clinical and echocardiographic indicators of the pathology of DST from the CCC are currently the main ones in the diagnosis of MAS, the frequent use of this method for diagnosing DTS is due to the complexity of the reproduction methods and the lack of developments in the field of molecular genetic analysis in the diagnosis of DTS [12, p.3- 10]. Most often, we observe secondary mitral valve prolapse, which occurs in coronary pathology, rheumatism, cardiomyopathies, myocarditis, which leads to the pathology of the left ventricle and papillary muscles, i.e. mitral valve prolapse develops [11, p.286]. In this regard, practitioners are faced with the problem of whether mitral valve prolapse is a consequence of true diseases. heart or it is an indicator of an existing congenital defect in the connective structure of the heart [11, p.286]. In this regard, the genetic search for markers is relevant, since the defect in the formation of connective tissue has a stable and stable connection with a birth defect [12, p.3-10].

§1.2. Features of the HLA class II system in individuals with UCTD

The hereditary predisposition and resistance of the human body to the pathology of a multifactorial nature, mainly associated with impaired function of the immune system, is determined by the diversity of major histocompatibility complex (HLA) genes. It is important that close interaction with the pathology of the immune system function has been proven for UCTD [12, p.3-10]. Despite numerous studies, the features of determining HLA antigens in patients with

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UCTD are few and are mainly devoted to the study of patients with MVP [12, p.3-10].

HLA (from the English Human Leucocyte Antigens) is a system of human tissue compatibility genes - a group of histocompatibility antigens associated with the human immune system [52, p.54]. Major histocompatibility complex class II molecules (DP, DM, DOA, DOB, DQ, DR). Molecules of this class are located on the surface of antigen-component cells: dendritic cells, macrophages, B-lymphocytes [52, p.54].

At the moment, the HLA complex includes more than 1900 alleles, which provide a mosaic of individual HLA phenotypes and genetic polymorphism of the population. The HLA system is localized on the short arm of the 6th chromosome, and consists of 4 classes, of which the most studied at the moment are classes I and II (Fig. 1.3) [68, p.13-14]. HLA class II molecules, exclusively from HLA class I, are encoded only by the three main loci DP, DR, DQ, and are present only on macrophages and B-lymphocytes [68, p.13-14].
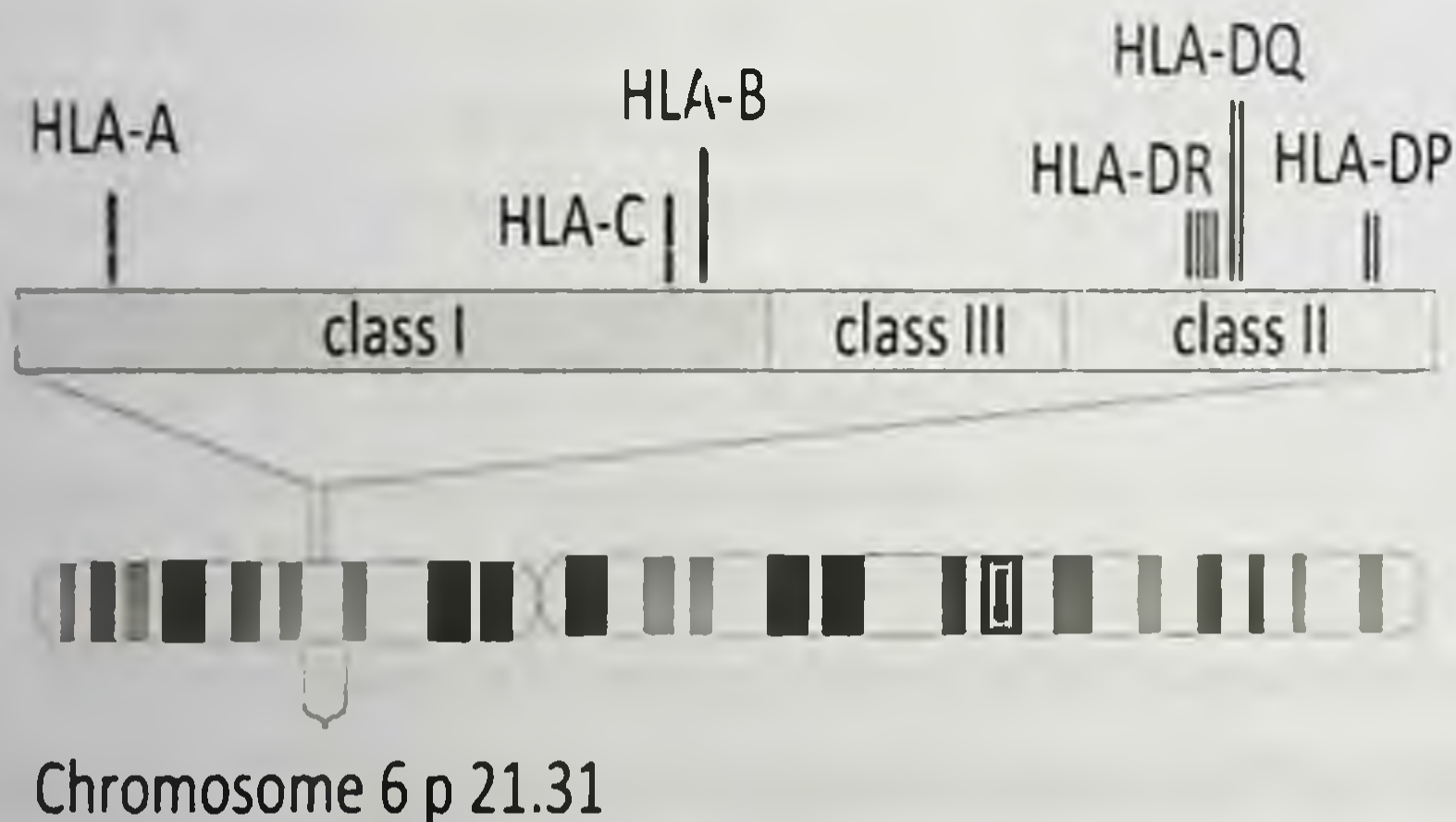
Rice. 1.3. Localization of the HLA system in the chromosome.

The control and regulation of the relationship between body cells are considered to be among the fundamental physiological functions of the major histocompatibility complex, they also include the implementation of the body's

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immune response, the implementation of genetic diversity, and the degree of survival of the individual as a species in conditions of exogenous and endogenous aggression [68, p.13-14]. Allelic polymorphism of the HLA system genes is the fundamental mechanism of "natural selection" diversity, which can provide hereditary predisposition or resistance to multifactorial diseases [68, p.13-14].

At the present stage, the HLA system attracts great interest from various authors who study the relationship between antigenic predisposition and the course of various pathologies [1, p.35]. This problem has not been sufficiently studied to date, but the nature of their association with the most common undifferentiated connective tissue dysplasia in the population has not been determined.

The frequency of occurrence of connective tissue dysplasia in recent years has been increasing all over the world, in particular, among the Uzbek population, which is associated with negative environmental impacts, family marriages, food quality, and frequent stresses of everyday life.

Typing of the HLA system is carried out by PCR analysis. Polymerase chain reaction (PCR) is a technique in molecular biology that allows you to significantly increase the low concentrations of individual nucleic acid fragments (DNA/RNA) in a variety of biological materials (samples) [51, p.7].

Usually, when selecting a donor for organ transplantation, typing of HLA class II genes is mandatory. In addition, some allelic variants of HLA class II genes are associated with an increased risk of several diseases (rheumatoid arthritis, diseases of the endocrine system: autoimmune thyroiditis and type 1 diabetes, as well as predisposition to infectious diseases, etp.) [52, p.54]. Also, the determination or typing of HLA class II genes is applicable for the diagnosis of certain forms of infertility and miscarriage, which may be due to the high similarity of HLA class II genes in a married couple with normal fertility of partners [52, p.54].

To date, there are few scientific works devoted to the ratio of DST to various HLA antigens, and they are often contradictory. This fact is explained by the different methods used (serological or DNA typing) and, to a greater extent, by the

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observed differences in the frequency of manifestations of individual antigens or alleles in various populations. After all, the fact is known that in populations that differ in HLA genetic characteristics, different HLA markers can be observed in the same disease [69, p.15].

It should be noted that the prevalence of HLA antigens in the population of Uzbekistan has not been studied. PCR research allows modern medicine to predict the course and occurrence of various diseases among the population.

Another important problem in the development of dysfunctions on the part of organs and systems in UCTD is the pathology of collagen synthesis, which is observed in most patients. When collagen is exchanged in the body, an immune response occurs in the form of circulating autoantibodies, that is, it is a physiological process that consists of the utilization of metabolic products of connective tissue structures - a characteristic of which is the level of activity of the immune system, a decrease or creation of autoimmune phenomena, as well as persistent immune reactions that indirectly indicate the individual types of collagen included in the pathological process [79, p.61-68]. How intense the metabolism of collagen in the body is most often determined by the level of diversity of forms of hydroxyproline in daily urine.

Thus, determining the role of regulatory mediators of interactions between cells and autoantibodies to collagen in UCTD is undoubtedly interesting both from a theoretical and practical point of view. This will make it possible to specify some of the mechanisms for the development of UCTD, which determine the clinical polymorphism of this pathology and enrich the knowledge of practical health care physicians with new methods for diagnosing undifferentiated forms of connective tissue dysplasia. The study of these indicators is also used to calculate the risk of undifferentiated forms of CTD and is applicable to improve the treatment tactics for this sample of patients and determine the treatment program for possible complications.

It is known that 42 genes are involved in the process of collagen synthesis (27 types), 1300 mutations are noted, and 23 of them have a variety of mutations

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and their phenotypic manifestations, which are factors in the complexity of diagnosis, this category of pathologies often complicates the course of diseases of organs and systems, the most common of which are minor heart anomalies, joint hypermobility, flat feet, etp. [63, p.57-64]

Thus, the study of genetic markers in UCTD is of scientific and practical interest, because, this provides an opportunity to study the mechanisms of development of UCTD, the characteristics of the course, the formation of possible complications, which, in turn, allows practitioners to most correctly differentiate this pathology, choose treatment tactics and carry out timely prevention of complications.

§1.3. The main measures for the prevention of complications of undifferentiated connective tissue dysplasia

The definition of UCTD is its manifestation as a systemic disease, with damage to various organs and tissues, which includes numerous manifestations of a violation of the cardiovascular system: minor anomalies of the heart, mitral valve prolapse, additional chords of the left ventricle, impaired peripheral circulation, as well as diseases of the musculoskeletal system, motor apparatus (hypermobility of the joints, scoliosis, flat feet, etp.), skin extensibility, keloid scars, vegetovascular dystonia, myopia, astigmatism, impaired reproductive function, and menstrual cycle. [31, p.1]. UCTD is a disease with medical and social significance and is associated with a limited choice of profession, the risk of complications during pregnancy and childbirth, unsuitability for military service, a high incidence of disability, as well as the observation of cases of early and sudden death. [31, p.1]. This is because doctors underestimate the phenotypic criteria of "weakness" of the connective tissue, on the other hand, the cause of diagnostic errors is the polymorphism of clinical symptoms [34, p.127-136; 49, pp. 89-92]. The interdependence of "weakness" of the connective tissue with the development of complications indicates the need to include drugs that affect collagen metabolism in the complex pathogenetic therapy.

An analysis of the literature data indicates an association of connective tissue dysplasia with hemostasis disorders at the cellular, tissue, and organ levels [10, p.28-32; 13, pp.107-110; 26, p.271].

According to the authors, this is due to regulatory systems and their interrelated work. Regulatory systems affect the main links of physiological and pathological processes in the body of an individual. So, they include cytokines, mediators of intercellular interactions, and growth factors [47. p.2-7].

Carrying out therapeutic measures to prevent complications is largely determined by the clinical form of UCTD [47, p.2-7]. The problem of treating various clinical forms of UCTD is extremely complex and requires consideration of the clinical manifestations of UCTD. With generalized forms of UCTD involving various organs and systems in the pathological process, a comprehensive therapeutic approach is required using non-drug and drug treatments.

In the literature, UCTD therapy is carried out in the form of a non-drug and drug-based way. A non-drug method of treatment is used for mild forms of UCTD. These include proper nutrition, exercise therapy, and massage.

The medical method of treatment is substitutional. First of all, it is the stimulation of collagen formation, pharmacological correction of violations of the synthesis of glycosaminoglycans, a decrease in the breakdown of these compounds. We must not forget about the stabilization of mineral metabolism, maintaining a sufficient level of free amino acids in the blood serum, and improving the bioenergetic state of the body. Drugs that stimulate collagen formation include ascorbic acid, chondroitin sulfate, glucosamine sulfate, and their analogs, the vitreous body, vitamin D, carnitine chloride, etp. [36, p.147-152; 38, pp.164-172]. These drugs, in combination with microelements and B vitamins (copper, zinc, magnesium, manganese, etp.), have a much better effect on the synthesis of the structure of collagen molecules, as well as other structural elements of connective tissue. To correct violations of the synthesis and catabolism of glycosaminoglycans, chondroprotectors (CP) are used: chondroitin sulfate (structure), glucosamine sulfate (dona), etp. [36, p.147-152]. In patients with hereditary collagenopathies, to

normalize mineral metabolism, it is necessary to use drugs that normalize phosphorus-calcium metabolism, especially vitamin D2 (its active forms are alfacalcidol, oxide it (alfacalcidol).

As noted earlier, patients with UCTD have autonomic dysfunction Therefore, in the drug therapy of this pathology, an important place is occupied by its correction. So, according to K. A. Scordo (2007), the treatment regimen for children with MVP differs depending on the severity of leaflet prolapse, as well as the type of vegetative-vascular and cardiac changes [104, p. 58-71]. According to the author, if there is a pathology of repolarization on the ECG, then a course of therapy with drugs that improve metabolism in the myocardium is necessary [40, p.30]. If frequent group early ventricular extrasystoles (type R to T) are observed, in particular against the background of prolongation of the QT interval and persistent repolarization disorders, Obzidan is used at a dosage of 0.5-1.0 mg/kg of body weight per day, for 2-3 months [6, p.15-23; 7, p.37; 21, p.13].

It should also be remembered that it is necessary to carry out preventive measures for various complications of UCTD. In particular, prevention of bacterial endocarditis in patients with MVP, systemic thromboembolic complications in non-occlusion of the foramen ovale, and aneurysm of the interatrial septum, hip joint dislocation, bone fractures, multiple organ failure due to HA deformation.
In the formation of DST, the leading role belongs to the violation of magnesium and collagen metabolism in the body of patients [2, p.677-684; 18, pp. 230-239; 17, pp. 23-32; 20, pp.76-81; 33, pp.2-4; 47, p.2-7; 55, pp.19-22; 66, pp.10-14]. Therefore, we decided to specifically discuss the role of magnesium in the body and the need for therapy with drugs containing magnesium, chondroitin sulfate, and glucosamine sulfate.

Magnesium, as one of the trace elements of the body, is a component of more than 300 enzymes. It is a participant in the intra- and extracellular maturation of collagen and other elements of the connective tissue structure, is involved in the transmission of nervous excitation, regulates calcium metabolism in the body, and many others. Magnesium ion deficiency is extremely common among the world's

population [9, p.12-16; 15, p.44; 43, p.28; 56, pp.54-60; 61, p.272; 73, pp.119-122].

In the studies of N. A. Korovina et al. (2006), it was shown that the administration of magnesium preparations to children with MVP according to the scheme for 6 months showed the normalization of collagen formation in the valve leaflets, an increase in its elasticity [37, p.17-30]. Upon re-examination, 79.7% of the children had a complete disappearance of the MVP, and the rest had a significant decrease in the depth of leaf deflection. The use of magnesium preparations in children with idiopathic MVP at a dose of 50 mg/kg during the first week and 25 mg/kg subsequently leads to a fairly good effect on objective and subjective clinical data of the disease, with their complete or partial elimination in more than half of the patients. Among all the cations present in the human body, the magnesium ion (Mg2+) is in fourth place in terms of distribution frequency (after sodium, potassium and calcium) [67, p.230-238].

Mg2+ ions are involved in adhesion, cell migration, energy metabolism, are involved in the processes of DNA replication, transcription and stabilization of RNA, translation and post-translational modification of proteins, and are involved in other cellular functions [67, p.230-238].

At least 290 genes are known in the human genome, the work of which requires the presence of magnesium ions, there are many proteins in which the Mg2+ ion acts as a co-factor [77, p.28].

Magnesium ions are distributed in the body in different ways. This is due to the physiological functions of organs and tissues. The largest proportion of this element (up to 53%) is found in bone tissue, dentin, and tooth enamel, in tissues with a high metabolism (brain, heart, muscles, adrenal glands, kidneys, liver) containing about 20% [66, p.10-14; 77, p.28]. 90% of magnesium ions are concentrated inside the cell in the form of

$Mg2 + ATP$. therefore magnesium is an intracellular element (30% in mitochondria, 50% in the cytosol, and 10% in the nucleus) [66, p.10-14; 77, p 28]. At the same time, 10% of the total magnesium content in the human body is in the extracellular space. In a healthy individual, the content of magnesium in the blood serum is in the range from 0.7 to 1.1 mmol / l. This blood element is constantly exchanged with magnesium reserves in bones and muscles [66, p.10-14; 67, p.230-238]. For an adult, the daily intake of magnesium is 400 mg/day. However, its absorption in the intestine is limited and only about 200 mg of consumed magnesium is adsorbed [67, pp.230-238]. There is a certain relationship between intake, sorption, and excretion. According to the literature, with magnesium deficiency, a secondary deficiency of potassium, calcium, and phosphates is observed. The clinical picture of chronic magnesium deficiency is characterized by anorexia, tachycardia, nausea, periodic weakness, a general decrease in muscle tone, muscle cramps, pronounced asthenia, and the formation of chronic fatigue syndrome [67, p.230-238; 109, p.1291-1296].

According to many authors, magnesium deficiency is caused by genetic (constitutional) factors, as well as environmental influences, such as chronic emotional stress, unbalanced nutrition, etp. [89, p.288-295; 93, p.757-764]. Genetically determined hypomagnesemia is relatively rare.

In several studies, the authors determined the participation of magnesium in the metabolic processes of connective tissue [66, p.10-14; 77, p.28]. With a decrease in the level of magnesium in the connective tissue, histological changes were detected, which was manifested by a deterioration in its mechanical properties. Its mechanism of action is quite complex. In general terms, we can say that the main effect of $Mg2+$ on all tissues and cells of the body is to stabilize RNA, in particular, tRNA (Fig. 1.4) [67, p.230-238]. Thus, magnesium deficiency in connective tissue is I am the reason for the slowdown in the synthesis of all its structural molecules (collagen and elastin, glycosaminoglycans, and proteoglycans) [67, p.230-238].

However, other mechanisms of hypomagnesemia on connective tissue are also known. So, in particular, the action of hyaluronidase inhibitors depends on the concentration of magnesium ions, the decrease of which leads to a deterioration in the quality of the extracellular matrix.

Rice. 1.4. The main functions of magnesium in the body of a healthy person [66, p.10-14]

The effect of Mg^{2+} on the connective tissue is not only the effect on the synthesis of collagen protein and collagenase enzymes. Thus, it has been proven that microfibrils and elastin are the main components of flexible fibers. In the presence of Mg^{2+}, the destruction of elastin fibers increases by 2–3 times. Lack of Mg^{2+} causes a decrease in the activity of elastase and an increase in the number of flexible fibers in the connective tissue. But the work of some authors testifies the leading role in these processes of calcium ions. So, in particular, Ca^{2+} is a necessary component for the active centers of elastase, and interaction with fibrillin-1 stabilizes the structure of microfibrils [67, p.230-238] and binds to glycoprotein-1 (MAGP-1) - microfibrils. Given that Mg^{2+} deficiency leads to a secondary Ca^{2+} deficiency, it can be assumed that magnesium deficiency has an indirect effect on the structure of elastin. Therefore, a decrease in magnesium in the blood contributes to the activation of collagens and elastins. This process, combined with the activation of MMPs, will lead to granularization of the connective tissue.

Thus, literature data allow us to conclude that Mg^{2+} deficiency negatively affects the synthesis of connective tissue, due to the mechanisms of destruction of collagen and elastin fibers. The introduction of Mg + 2 into the course of treatment

will have a positive effect on the restoration of disturbed heart rhythm, echocardiographic phenomena of prolapse, and will significantly reduce the depth of prolapse of the affected valve cusps.

Chondroitin sulfate has a high specific effect on cartilage tissue by fixing sulfur for the synthesis of chondroitin-sulfuric acid. All this improves the formation of proteoglycans, type I and II collagen, protects the cartilage matrix and maintains the normal composition of the synovial fluid. Glucosamine replenishes the natural deficiency of glucosamine, stimulates the production of hyaluronic acid and complex proteoglycans.

In the works of Oesser S. and Seifert J. 2003, a direct stimulating effect of collagen hydrolyzate on collagen synthesis in chondrocytes was indicated. It has been established that collagen hydrolyzate belongs to chondroprotective, which in turn promotes the regeneration of cartilage and bone tissues [101, p. 393-399].

In recent studies, the theory of the anti-inflammatory action of cholesterol and GA has been proven. They directly affect the CD44, ICAM1, TL-4 cell receptors, which in turn are responsible for cell infiltration, the production of inflammatory mediators, and angiogenesis. In addition, cholesterol and GA block signaling pathways and reduce the activation of pro-inflammatory factors.

Thus, the literature data allow us to conclude that the development of UCTD is associated with genetic disorders in the synthesis and breakdown of collagen, the presence of autoantibodies to various types of collagen, changes in magnesium concentrations in substrates. The above violations lead to changes in electrical conduction and heart rhythm. In severe cases, they determine the risk of aortic aneurysm and sudden death. The optimal concentration of Mg^{2+} reduces collagen degradation and stimulates the synthesis of new collagen molecules. The introduction of Mg + 2 and CP into the course of treatment has a positive effect on the restoration of disturbed heart rhythm, hemodynamics, and articular manifestations of UCTD.

All clinical studies were conducted for the period 2017-2019. Based on the Samarkand City Medical Association and 1 clinic of the Samarkand State Medical Institute. There were 105 patients under observation, including 47 (44.8%) men and 58 (55.2%) women, aged: up to 18 years about 10.5%, from 19-23 years old - 73.3%, 24 and above - 16.2%, respectively, and 20 practically healthy volunteers of comparable age and gender.

The distribution of patients depending on age and gender are presented in Table 2.1.

Table 2.1

Distribution of patients with UCTD by age and sex

Age, years	Women		Man		χ^2	P
	abs.	%	abs.	%		
Under 18	5	8,6	6	12,8	0,48	>0,05
19-23	43	74,1	34	72,3	0,04	>0,05
Older 24	10	17,2	7	14,9	0,11	>0,05
Total	58	55,2	47	44,8	2,30	>0,05

Studies have shown that the distribution of men and women was approximately the same, there was only a slight predominance of females. The disease was typical for the age group of 19-23 years (73.3%). But, some distinctive features were analyzed that were associated with different periods of transition of girls and boys from puberty and adolescence to a young age, as well as the maturity of the hormonal background.

The severity of UCTD was assessed in points based on certain phenotypic and visceral criteria. To confirm UCTD, we used - 6-8 or more signs of UCTD, external manifestations (skin extensibility, joint hypermobility, flat feet) damage to some internal organs; impaired connective tissue metabolism confirmed by laboratory studies (increased excretion of hydroxyproline, decreased magnesium levels, increased titer of antibodies to type I collagen, indicators of HLA class II) [26, p.271; 27, p.714].

The diagnosis of MAS, MVP was established on the basis of clinical and laboratory, and instrumental studies according to the recommendations of Yu. M. Belozerov et al. (2011) [5, p.63-67; 6, p.15-23]. The inclusion criteria were complaints, ECG, and EchoCG data. The classification of myxomatous degeneration of the mitral valve was carried out according to the recommendations of G. I. Storozhkov et al. [62, p.48-53]: myxomatous degeneration 0 (no lesions); myxomatous degeneration I stage. (minimally pronounced) (cusp thickness more than 3 mm); myxomatous degeneration II stage. (moderate) (more than 6 mm); myxomatous degeneration III stage. (sharply pronounced) (more than 9 mm) [5, p.63-67; 6, p.15-23]. Classification of MVP according to the degree of regurgitation was carried out according to the classification of N. M. Mukharlyamov, MVP of the 1st degree was established in 44 (41.9%) patients, MVP of the 2nd degree - in 15 (14.3%) of the examined patients.

We measured growth; body weight; chest circumference; length of the upper body segment; arm span; brushes; epigastric angle; feet; the height of the arch of the foot; fingers of the hand; examination of the back area (to detect scoliotic deformity, hyperlordosis of the lumbar and hyperkyphosis of the thoracic spine, pterygoid scapulae), as well as the Beighton test (to detect hypermobility of the joints). To diagnose longitudinal flat feet, the iodometric index (PI) = (h × 100) was calculated: L; where h is the height of the foot - the distance measured by a compass from the floor to the upper surface of the navicular bone 1.5 cm anterior to the ankle joint, mm; L - foot length - the distance from the tip of the first finger to the back roundness of the heel, mm (Friedland's method) [65, p.6].

According to the treatment plan, the patients were divided into the following groups:

- subgroup "A" consisted of 16 patients who received traditional treatment in the form of metabolic and vitamins for 10 days;- subgroup "B", 16 patients who have prescribed a course of therapy for preventive and therapeutic purposes for 6 months - traditional treatment + preparations containing magnesium in a daily dose of 3 g (2 tablets 3 times a day);

- subgroup "C" 16 patients treated with traditional treatment + magnesium preparations + chondroprotectors (chondroitin sulfate sodium at a daily dose of 500 mg or glucosamine sulfate sodium chloride at a daily dose of 750 mg for 2 months daily in the morning 1 time, followed by an interval after 2 months repeated three times).

The examination was carried out in dynamics: at admission, after 3 and 6 months from the start of treatment. Efficacy was evaluated based on clinical, laboratory, and instrumental studies.

The control for all compared groups was data from 30 healthy individuals (20.1±1.3 years old) who gave informed consent to the study.

§2.2. Research methods

All methods are well known and widely used in clinical or scientific laboratories of the Republic of Uzbekistan. The main criteria for inclusion of patients in the UCTD group were clinical complaints and changes in ECG and Doppler echocardiography. ECG was carried out according to the generally accepted method on the apparatus Mindray BeneHeart R3 (China). The degree of respiratory dysfunction was assessed according to the WHO recommendation: 1st degree of DN - detected only with significant physical activity (respiratory rate 22-26 per min), 2nd degree - with little physical activity (respiratory rate up to 30 per min) and 3rd degree - at rest (respiratory rate breathing over 30 per minute).

Indicators of clinical manifestations of cardiovascular changes were also the parameters of central hemodynamics, which were assessed using Aloka Doppler echocardiography [3, p.58-69]. Determined: left ventricular ejection fraction

26

(LVEF, %); the final systolic size of the left ventricle (CSR, cm), the anteroposterior size of the left atrium (LA, cm), end-diastolic size of the left ventricle (EDV, cm); area of the mitral orifice (measured by Doppler methods according to the spectrum of the transmitral blood flow, cm2); anteroposterior size of the right ventricle (RV); minute volume of blood circulation (in l/min); systolic pressure in the pulmonary artery (SPPA, mm Hg) - as the sum of the gradient of tricuspid regurgitation and pressure in the right atrium; the pressure value in the right atrium was determined by the change in the lumen of the inferior vena cava [3, p.58-69]. Anthropometric indicators were evaluated, body mass index (BMI) was calculated according to the generally accepted method. The physique of the examined was assessed by the degree of the epigastric angle recommended in textbooks on propaedeutics of internal diseases: an angle of less than 90° - asthenic, 90° - normosthenic, more than 90° - hypersthenip.

Biochemical studies were carried out in the central GMO laboratory of the city of Samarkand and the 1-clinic of SamMU.

Determination of titers of autoantibodies to type I collagen.

Type I collagen is a fibrillar protein that forms the basis of the connective tissue of the body. Most of all is found in the skin, bones, tendons, cornea, etp. The assessment of the titer of autoantibodies to collagen I in blood plasma was studied by enzyme immunoassay using the Imtek kit (Russia) (ELISA ELISA) [78, p.41-45].

The test system is intended for qualitative determination of the level of autoantibodies to type I collagen in human plasma (serum). An analytical method used to determine specific proteins in a sample. At the first stage, protein electrophoresis in a polyacrylamide gel was used to separate denatured polypeptides by length (usually in the presence of SDS) or by the three-dimensional structure of the protein (in the native state). Next, the proteins were transferred to a nitrocellulose or PVDF membrane, then detected using antibodies specific to a given protein (Fig. 2.1).

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SDS-Page электрофорез препарата H C11
(восстановленный)

1   2   3

250 кДа

130 кДа

95 кДа

72 кДа

55 кДа
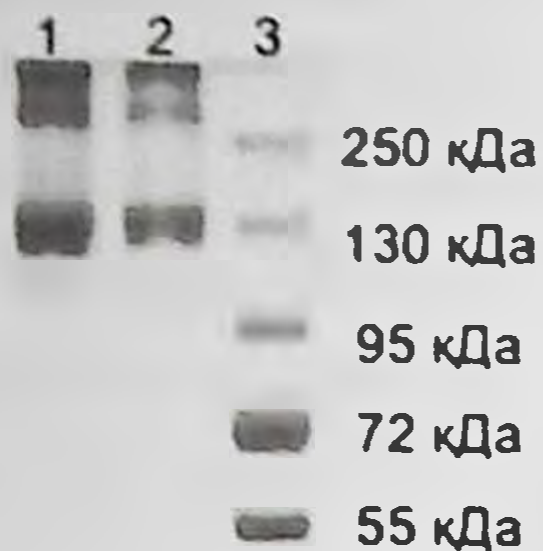
1 - Коллаген человека I типа (H C11). 3 мкг
2 - Коллаген человека I типа (H C11). 1 мкг
3 - PageRuller™Plus. Thermo Fisher

Rice. 2.1 ("Imtek"). Distribution of collagens on polyacrylamide gel electrophoresis

HLA typing class II by DNA application.

Analysis of DQA1 and DQB1 gene typing. For the study, whole peripheral blood of the studied patients was used in vacuum plastic Vacuette tubes with a volume of 4.0 ml with the addition of 2.0 mg/ml of the anticoagulant disodium salt of ethylenediaminetetraacetate (EDTA) [24, p.9-20].

After taking the material in the tube. turn the tube over 2-3 times.

Rice. 2.2. Isolation of DNA from material

Rice. 2.3. Labeling of tubes for amplification.

The next step was to extract the DNA. PROBA-RAPID-GENETICS reagents were used for DNA extraction. According to the instructions for DNA determination, six tubes for amplification with a volume of 0.2 ml were labeled for each analyzed sample, as well as negative and positive control samples (K−), (K+ DQ FAM), (K+ DQ HEX) [25, p.13].

After the tubes with amplification mixtures were shaken for 3–5 s, the tubes were placed in a centrifuge for 1–3 s. Next, 20 μl of the amplification mixture was added to the tubes. Thus, the DQB1-1 mixture was added to the labeled tube 1, the DQB1-2 mixture was added to the labeled tube 2, etp.). The tubes with PCR buffer and TechnoTaq MAX polymerase were shaken for 3–5 s and placed in a centrifuge for 1–3 s on a microcentrifuge-vortex [25, p.13-14].

Rice. 2.4. Preparation of the PCR buffer mixture

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To prepare a mixture of PCR buffer, we mixed - $10 \times (N + 1)$ μl of PCR buffer and - $0.5 \times (N + 1)$ μl of TechnoTaq MAX polymerase, where N corresponded to the number of labeled tubes, taking into account "K-", "K+ DQ FAM", "K- DQ HEX". Next, we shook the resulting mixture in a test tube and centrifuged for 1-3 s on a microcentrifuge vortex. After that, we added 10 μl of the mixture (PCR buffer and TechnoTaq MAX polymerase) and one drop (about 20 μl) of mineral oil to each tube with the amplification mixture and closed the tubes with lids [25, p.13].

Next, 5.0 μl of the DNA preparation isolated from the samples was added to the test tubes for the test samples (6 pcs. for each sample), while no DNA was added to the test tubes "K–", "K+ DQ FAM", "K+ DQ HEX".

After that, 5.0 μl of the negative control sample, which passed the stage of DNA extraction, was added into the "K–" tubes, and 5.0 μl of the positive control sample into the "K+ DQ FAM" tubes. For a positive control sample, 5.0 μl of "K+ DQ HEX" was added to tubes labeled "K+ DQ HEX" [24, p.9-10].

The tubes were placed on a vortex centrifuge for 1–3 s.

Rice. 2.5. Installing test tubes in the block of the detecting cycler

Installed all test tubes in the detection cycler unit. In the "Working with the device" mode, the Real Time_PCR software was used. The "HLA.ini" file was

loaded during the first PCR test. Subsequently, the DQB1 test was added to the protocol, the number and identifiers of the samples, and the location of the test tubes on the thermoblock matrix in accordance with their installation were noted [25, p.13-15].

Analysis of DRB1 gene typing. This method differs from the others in that, during PCR, marking is carried out in 4 strips A and B, as well as 1 strip A and one strip B for "K-", 1 strip A and one strip B for "K +" , the total number consisted of 12 strips. Taq polymerase solution was used as a mixture for amplification.

Registration and accounting of PCR data was automatically carried out by the software for detecting cyclers. The specificity of the HLA DQB1, DQA1, DRB1 gene was also carried out automatically, taking into account the summation of the results for each [24, p.20].

Determination of the level of hydroxyproline in the blood serum. Connective tissue metabolism was determined by assessing the total hydroxyproline (OO) in the blood serum. The simplest and most accurate method for determining RO according to Bergman and Loxley, which is a modification of the Stegeman method [53, p. 212].

In addition to the above research methods, the following were determined:

- Mg + 2 ions (in mmol/l) on an atomic absorption spectrophotometer brand AF-610-A (LTD, China) using a standard test system from ELISA PO (Novosibirsk) [66, p.10-14]. From a physiological point of view, up to 53% of magnesium is concentrated in bone tissue, dentin and tooth enamel, and about 20% in tissues with high metabolic activity (brain, heart, muscles, adrenal glands, kidneys, liver) [16, p.89-94] . Magnesium is one of the regulators of vascular tone, promotes dilatation of the vascular wall [32, p.285]. A low concentration of extracellular magnesium leads to vasospasm or increases their sensitivity to pressor agents [32, p.285].

Statistical research methods

The results obtained were subjected to statistical processing using the Excel, Statistica for Windows 6.0 software package. The normality of the distribution of

quantitative parameters was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests [42, p.12]. The arithmetic mean (M), mean square deviation (δ), arithmetic mean error (m), and sample standard deviation (S) were calculated. Comparison of parametric options after a preliminary assessment of the correctness of the distribution of samples (correspondence to its normal distribution) was carried out on the basis of the Student's criterion (t) with the calculation of the error probability (p) [42, p.12]. Data were considered significant at $p < 0.05$. The analysis of prognostic factors (P) was performed by determining the sensitivity (N), specificity (C), diagnostic accuracy (DT), relative risk (RR) of the predicted outcome in the group of factor-positive patients, RR of a different outcome in the group of factor-positive patients, coefficient asymmetry calculated on the basis of the Bays theorem. Statistical processing was performed by a nonparametric method. The a posteriori probability of an event was calculated using Bayes' theorem, according to the following formula: P=P(D1) P(S1/D1) P(Sn/D1): Numerator + (P(D2) P(S1/D2) P (Sn/D2),

Where:

P is the probability of correct diagnosis or prognosis;

P(D1) - the frequency of the disease in the examined group;

P(S1/D1) -P(Sn/D1) – frequency of S1-Sn– signs in the examined group;

(P(D2) – disease frequency in the comparison group;

P(S1/D2) P(Sn/D2) - frequency of signs S1-Sn- in the comparison group;

numerator - the numeric value of the expression represented in the numerator. The probability of correct diagnosis and prognosis is considered reliable if it is equal to or greater than 0.8 [64, p.1215].

Statistical hypotheses about differences for quantitative and ordinal variables were tested using the Kruskell–Wallis test; in cases of categorical variables (absolute and relative frequencies, shares), the chi-square test (χ^2) with Yates correction, taking into account the degrees of freedom (df) [64, p.1215]. To assess the relative risk, an analysis of contingency tables was carried out: odds ratio (OR) and two-sided 95% confidence intervals (CI). The achieved level of significance

(p) is given as p<0.0001, calculated taking into account its critical value of 5% (p<0.05) [64, p 1215].

The dependence between the indicators was determined using the Pearson correlation analysis (p) [56, pp.54-60, 42, pp.10-15]. The correctness of laboratory data results was determined using the formula:

A =	$\dfrac{\text{Set value- Actual value}}{\text{Set value}}$	- 100

The deviation of the results within ± 3σ was considered acceptable, and the results of laboratory tests were regarded as satisfactory.

Prognostic criteria were evaluated by indicators:

Sensitivity (in %) = true positive 100% / true positive + false negative;

Specificity (in%) = true negative 100% / true negative + false positive;

Diagnostic Accuracy = True Positive + True Negative · 100% / False Positive + True Positive + False Negative.

The design of the conducted studies is shown in fig. 2.2-2.5.

The data obtained were subjected to statistical processing in the Microsoft Windows software using the Microsoft Excel-2007 and Statistica, V6 software packages. The obtained data were processed in the form M±m. Significance of differences was determined by Student's t-test and considered significant at P<0.05. The correlation coefficient (r) between anthropometric groups was calculated according to Pearson.

Chapter 3

ASSOCIATION OF PHENOTYPICAL TRAITS AND GENETIC MARKERS

§3.1. Features of the clinical course of the disease in patients with undifferentiated connective tissue dysplasia

According to the design of the study, all patients with UCTD, depending on phenotypic signs, were divided into 2 large groups to improve early diagnosis; 1st - 57 patients who underwent general clinical studies, and 2nd - 48 patients who underwent general clinical studies + analysis of HLA class II + level of titers of autoantibodies to type 1 collagen. In this regard, we will consider all manifestations of UCTD comparatively, in these groups. As mentioned earlier, the clinical signs of UCTD in the studies were mainly characteristic of young people (Table 3.1).

Table 3.1

Sex and age indicators in the examined groups of patients

Signs	Indicators, n=105		
	M±m		Mmax-Mmin
Age, г	21,78±0,95		45,0-5,0
Woman	58	55,2%	
Teenegers	47	44,8%	
Weight, kg	60,92±3,81		101-16
Growth, sм	167,0±0,35		185-102
IMT	21,84±0,37		29,51-1,54

Our results are somewhat different from the literature, which shows the predominance of females. These differences may be due to ethnic and regional characteristics, as well as the contingent of patients, in particular, the surveys included recruits who were examined at SamSMO and students of SamMU. The distribution of patients by place of residence showed approximately the same distribution, living both in the city and in the countryside.

Weight-height parameters and BMI differed in the studied groups of patients, since their weight and height depended on the age of the patients. Anthropometric and phenotypic characteristics of the studied patients showed that

the average chest circumference was 87.69±8.15 cm, the epigastric angle (in degrees 0) was 88.29±9.74, the length of the foot, depending on height, was 0.151±0, 08, the height of the arch of the foot - 7.75±1.15 cm, respectively.

According to the literature, UCTD is characterized by an asthenic physique, but in some cases, the presence of overweight was revealed. These changes are due to ethnic characteristics, since carbohydrate components predominated in the diet of patients.

With UCTD, the main external manifestations are hypermobility of the joints of the upper and lower extremities; various changes in the spinal column in the form of scoliosis or kyphosis; chest deformity; pathology of the oral cavity, manifested by a high location of the palate, abnormal growth of teeth and supernumerary teeth; flat feet and hallux valgus, sandal gap; pronounced extensibility of the skin and the vascular (venous) network on the skin and a tendency to the formation of hematomas; eye pathology in the form of astigmatism and myopia; protruding ears with attached earlobes; asthenic physique, etp.

Given the above, it was of interest to study the external manifestations of UCTD in patients of varying severity. Articular manifestations of UCTD are flat feet and joint hypermobility.

For an objective assessment of generalized joint hypermobility (HS), the P. Beighton criteria were used in points, where 1 point corresponded to pathological hyperextension in one joint on one side.

Bayton Criteria:

1. Passive flexion of the metacarpophalangeal joint of the 5th finger in both directions.

2. Passive flexion of the 1st finger towards the forearm while flexing at the wrist joint.

3. Overextension of the elbow joint over 10 degrees.

4. Overextension of the knee joint over 10 degrees.

5. Tilt forward with fixed knee joints, while palms reach the floor.

Hypermobility is evaluated in points: 1 point means pathological hyperextension in one joint on one side. The maximum value of the indicator, taking into account bilateral localization, is 9 points (8 for the first 4 points and 1 for the 5th point). An indicator from 4 to 9 points is regarded as a state of hypermobility.

With bilateral localization, the maximum value of the indicator was 9 points [54, p.70]. The state of hypermobility corresponded to indicators from 4 to 9 points. Among the studied patients, 4 and 6 points were most identified: 4 points - in 25 (23.8%) patients, 6 points - in 27 (25.7%), 8 points - in 7 (6.67%) patients, respectively.

The Friedland method was used to detect flat feet in patients (Table 3.2) [61, p.200-203]. Based on this table, it should be noted that the podometric index in patients on average consists of 28.87%. This suggests that most of the subjects have flat feet.

In addition to flat feet, patients also had various spinal deformities: among them, scoliosis of the 1st degree in 21 (20%), 2nd degree - in 21 (20%); kyphoscoliosis of the 1st degree - 15 (14.29%), 2nd degree - 5 (4.8%); hyperlordosis - 8 (7.6%), deformity of the chest: 1st degree ADHD occurred in 20 (19%), 2nd degree - 10 (9.52%) of the examined persons with UCTD.

Table 3.2

Calculation of the submetric index (PI) $= I = h * 100\% / L$

according to the Friedland method

Parameters	Indicators (average)
Arch height (h), cm	5,81±1,15
Foot length (L), cm	20,12±2,04
Podometric index (I), %	28,87±3,54

Where h is the height of the foot - the distance measured with a compass from the floor to the upper surface of the navicular bone 1.5 cm anterior to the

ankle joint, mm; L - foot length - distance from the tip of the first finger to the back roundness of the heel, mm.

Based on the above data, it can be concluded that patients with UCTD have various clinical variants of the articular syndrome, which in turn complicates the diagnosis and treatment tactics of general practitioners and therapists.

Skin manifestations of UCTD in patients in the form of varying degrees of skin extensibility were observed in 48 (45.7%) patients (Fig. 3.1).
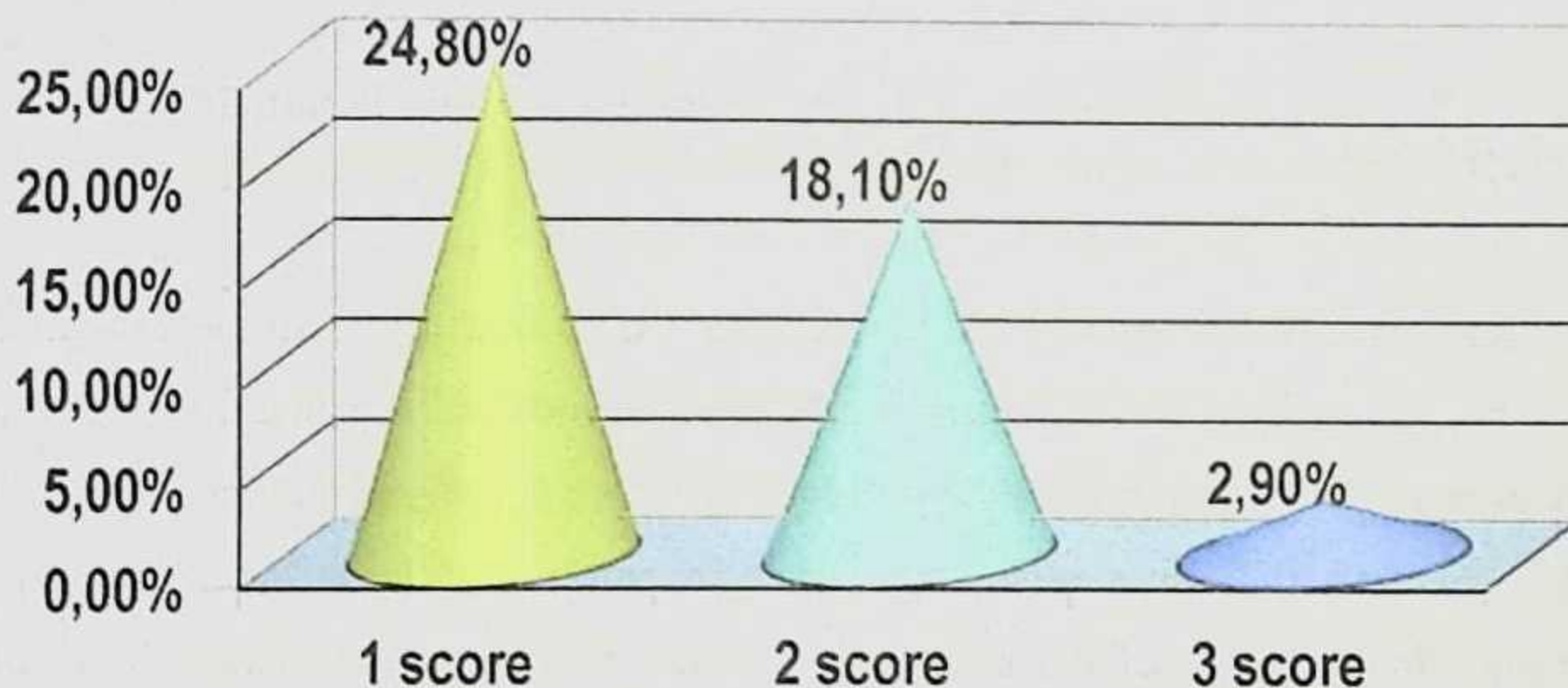
Rice. 3.1. The frequency of skin extensibility of varying degrees in patients with UCTD

In patients, skin extensibility was mainly detected in 1 and 2 points in 26 (24.8%) and 19 (18.1%) examined patients, 3 points were found in 3 (2.86%), respectively. Muscle hypotension was noted in 28 (26.7%) patients.

Another external phenomenon in patients with UCTD is small developmental anomalies, which are manifested by large protruding ears and adherent earlobe

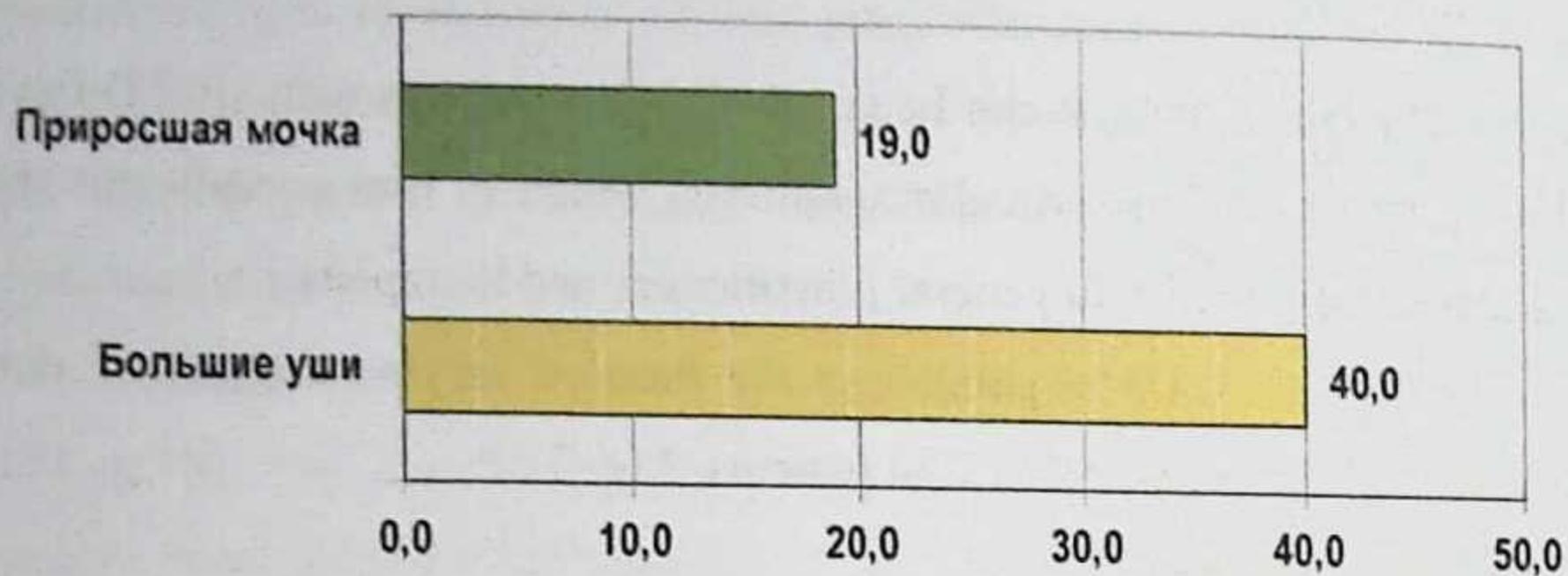(Fig. 3.2). We detected these signs in 42 (40%) and 20 (19%) patients.

Rice. 3.2. The frequency of small developmental anomalies in patients with UCTD. *Приросшая мочка\ Ingrown earlobe.* Большие уши big ears

As can be seen from the above data, external UCTD hair dryers in the examined patients were manifested by disorders of the musculoskeletal system, changes in the skin and joints, as well as the presence of minor developmental anomalies. In terms of severity, they were manifested by hypermobility of the joints (100%), changes in the shape of the spine (41.9%), chest (40.9%), skin extensibility of varying severity (45.7%), minor developmental anomalies (59%) and flat feet (50.5%). The frequency of combinations of different hair dryers in patients was different. The frequency of combination of 6 external hair dryers was found in 18 (17.1%), 5 - in 21 (20.0%), 4 - in 29 (27.6%), 3 - in 18 (17, 1%), 2 - in 15 (14.3%) examined, and in 4 (3.8%) patients one hair dryer was detected (Fig. 3.3). It should be noted that many patients had more severe manifestations of external phenes.
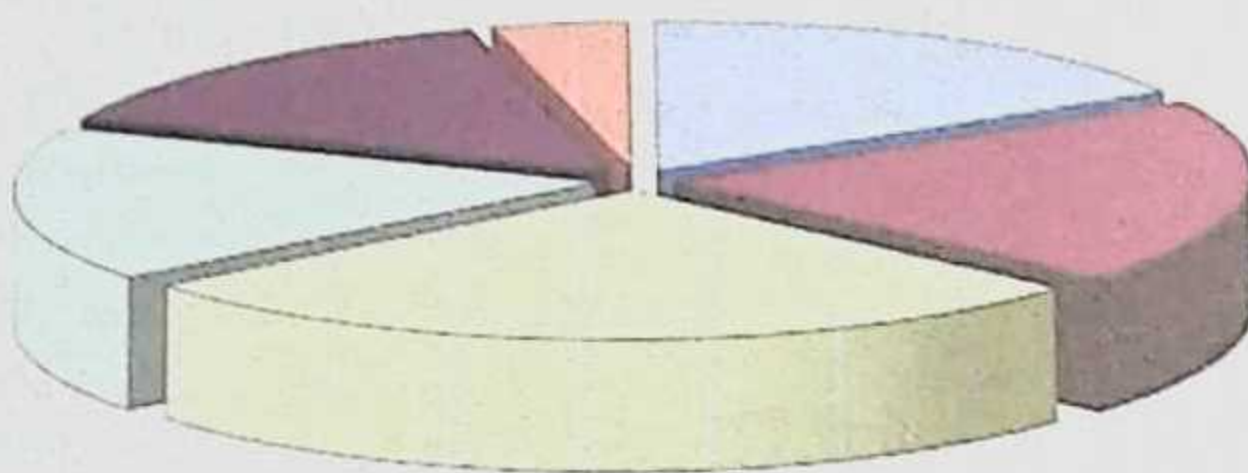
Rice. 3.3. The frequency of occurrence of combinations of various external hair dryers in patients with UCTD (*фен \ hair dryer*)

It is known that a genetic defect in the synthesis or catabolism of the connective tissue, clinically manifested by damage to various organs and systems, which are usually referred to as internal dryers, underlies the development of UCTD [79, p.62]. These changes affect various systems, including the cardiovascular and respiratory systems, abdominal organs, kidneys, visual impairment, and the nervous system [64, p.1215]. The analysis of internal hair dryers in patients with UCTD showed that ocular manifestations are characterized by the development of myopia of varying degrees in 39% of patients.

At the same time, astigmatism was detected in 14 (13.3%) patients, however, anisometropia and retinal degeneration were not detected in the examined individuals. At the same time, in patients, the 1st degree of myopia was found in 20 (19.0%, P<0.01), the 2nd degree - in 21 (20.0%, P<0.01) patients examined. As can be seen from the above data, damage to the organs of vision was detected in many patients, which indicates a severe course of the underlying disease. This is confirmed by the presence of comorbidities. Chronic bronchitis was detected in 14 (13.1%) patients, pyelonephritis in 3 (2.9%), nephroptosis of both kidneys of the 1st and 2nd degree in 20 (19.1%), biliary dyskinesia in 36 (34 .3%), vegetative-vascular dystonia 61 (58.1%), respectively.

Of particular note is the presence in patients of gastroduodenal pathology (4.8%), liver pathology (1.9%), osteochondrosis of the lumbar vertebra (3.8%), anemia (9.5%), osteoarthritis (6.7%) and others (Fig. 3.4).

Legend:
- ☐ ДЖП
- ☐ ВСД
- ☐ гастро
- ☐ печень
- ☐ Остеохондроз
- ☐ анемия
- ☐ Остеоартроз
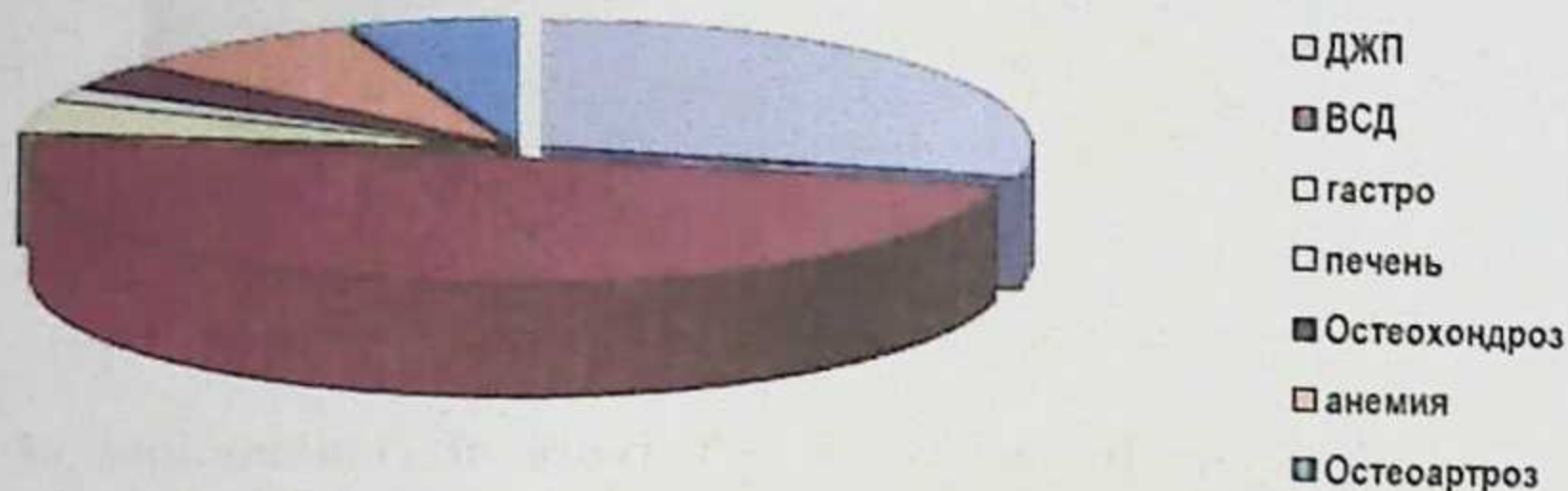
Rice. 3.4. The frequency of comorbidities in patients with UCTD

Thus, when analyzing the clinical manifestations of UCTD, it can be said that external UCTD phenes were characterized by the presence of small developmental anomalies, skeletal, skin and articular forms, and internal ventilators were characterized by a violation of the organs of vision, pathology of the cardiovascular and pulmonary systems, abdominal organs and kidneys. , and especially VNS.

§3.2. Features of electrocardiographic and hemodynamic disorders in patients with undifferentiated connective tissue dysplasia

Features of electrocardiographic disorders depended on the damage to the cardiovascular system. The surveyed revealed MVP, abnormally located chord, myxomatous degeneration of the heart valves. According to the study, among the examined MVP of the 1st degree, regurgitation was diagnosed in 41 (39.0%), with MVP of the 2nd degree - in 14.3%, ARC - 4.8%, MAC - 2.9%.

Many patients complained of increasing weakness and rapid fatigue, in connection with which chronic fatigue and decreased performance were noted. Along with this, patients complained of memory impairment and difficulty in concentrating attention, which was especially negatively reflected in the

educational process. They often experienced dizziness, fainting, and headaches. Autonomic dysfunctions were manifested by difficulty falling asleep, heavy sleep, feelings of anxiety and nervousness. Often this turned into a feeling of inner tension and anxiety. According to patients, the above complaints became more frequent and more pronounced during the period of mental and physical activity.

It was of interest to clarify the nature of the above complaints in the examined groups of patients. If in the first place, the majority of the patients surveyed indicated a stabbing pain at the apex of the heart and discomfort in the region of the heart in the form of constriction. In second place, patients complained of periodic attacks of palpitations and a feeling of uneven rhythm of the heart. Often in patients, all these complaints were combined with a feeling of lack of air during a deep breath, that is, difficulty in breathing.

Clinical manifestations of CVD in UCTD vary from minimal to maximal signs, depending on the severity of myxomatous changes. Given that the patients mainly complained of shortness of breath, the gradation of these indicators was carried out in accordance with the WHO recommendations.

Thus, 39 (37.1%) patients complained of shortness of breath, during the study, over time, as the pathological process progressed, already 66 (62.9%) patients made these complaints, which indicates that the condition worsens and the quality of life of these patients is reduced.

74 (70.50%) patients complained of lack of air, and 83 (79.0%) patients complained of headaches, 80 (76.2%) pains in the joints, the intensity of these complaints increased depending on the general condition and concomitant diseases. In patients with UCTD, the presence of rhythm and conduction disturbances is not always confirmed by an ECG study. Such patients need to carry out Holter monitoring in order to clarify individuals with varying degrees of connective tissue dysplasia.

The studies carried out in this regard have shown that in many cases, CVD with UCTD is accompanied by certain changes in the ECG (Table 3.3).

The automatism function of the sinus node was impaired in the form of sinus tachycardia, which indicates an increased work of the sympathetic nervous system. In the patients examined by us, the heart rate varied widely: from 45 to 150 beats/min, on average, these values were 83.0±0.37; minimum - 45 bpm, maximum - 150 bpm. respectively. The data obtained by us are similar to the literature, which shows a wide variability of heart rate on the ECG at rest and in half of the cases may not exceed normal values. In our studies, there was a tendency to an increase in heart rate as the pathological process worsened. It should be noted that patients often complained about episodes of increased heart rate during the day, especially during active physical activity, which affected the quality of life of patients. To a greater extent, this was characteristic of patients with comorbidities on the background of UCTD.

We have established sinus tachycardia in 17.1%, sinus bradycardia in 5.7% of the examined, in one examined bradycardia was noted against the background of sick sinus syndrome. This condition was more often observed in patients with initial vagotonia.

Table 3.3

The frequency of cardiac arrhythmias in patients with UCTD

Signs	Patients, n=105	
		%
Sinus tachycardia	19	18,1
Sinus bradycardia	6	5,7
sinus arrhythmia	2	1,9
Atrial extrasystole	6	5,7
Extrasystole of the ventricles	2	1,9

Repolarization disorder	12	11,4
Metabolic changes	37	35,2
LV hypertrophy	8	7,6
Diffuse hypoxia	8	7,6
AV block I degree	1	1,0
SSSU	1	1,0
Blockade of Hiss	3	2,9

Sinus tachycardia was usually observed in patients with signs of sympathicotonia and hypersympathicotonia, and was mainly associated with physical exertion. It was combined with moderate shortness of breath, moderate or severe lack of air, which significantly affected the quality of life of patients.

According to N. I. Nechaeva et al. (2011), atrial and ventricular extrasystole is the most common cardiac arrhythmia among patients with UCTD [48, p.43-47].

According to our observations, in patients with severe manifestations of UCTD, cardiac arrhythmias during rest were 5.7% and during exercise 15%, and ventricular extrasystoles were rare, 1.9% of cases. Along with this, autonomic dysfunctions, minor anomalies in the development of the heart, as well as a decrease in tissue magnesium content play an important role in the development of extrasystole. Clinically, cardiac arrhythmia was combined with spinal deformity in the form of scoliosis, in laboratory studies, a decrease in magnesium and an increase in the level of autoantibodies to type I collagen in the blood of the examined.

The examined patients had atrioventricular paroxysmal tachycardias. It should be said that the frequency of paroxysms, according to our observations, varied widely depending on the severity of the pathology. The frequency of paroxysms was mainly characteristic of patients who did not tolerate arrhythmias.

According to ECG data, changes in the terminal part of the ventricular complex were detected in 10.5% of patients.

Thus, the clinical manifestations of UCTD depend on the state of the cardiovascular system and the addition of another pathology. This is due to changes in electrical conduction and heart rate. In severe cases, they can determine the risk of aortic aneurysm and sudden death. Early detection of CVD disorders in UCTD, as well as the study of the mechanism of their development in adolescents and young people, will allow for dispensary registration, treatment and prevention of complications.

As noted earlier, in some patients with CVD against the background of UCTD, ECG revealed some changes in the myocardium. According to the literature, in order to more clearly identify changes in cardiac hemodynamics in patients, Doppler echo or Holter monitoring is necessary. Considering these conclusions, we studied the parameters of cardiac hemodynamics in patients with UCTD.

Conducted in this regard, studies have shown violations of cardiac hemodynamics. The values of KDR and KSR tended to increase, while they had values within the upper limits (average 4.89 ± 0.77; 3.28 ± 0.135). We noted an increase in normative indicators in 23.4% of the sample of patients. EF indicators tended to decrease in relation to the control group. The EF index on average consists of 62.9 ± 0.143, respectively. We observed a decrease in this indicator in 16.19% of the examined. It should be said that the values of SBP and DBP in many remained within the age norm, but in 12 (11.4%) it increased to 140-150 / 90-100 mm Hg, in 28 (26.7%) it decreased 90-100/50-60 mmHg examined, respectively. Changes in cardiac hemodynamic parameters were detected in many patients with UCTD. At the same time, it should be said that deviations in cardiac hemodynamics were manifested in patients with comorbidities against the background of this disease, which, in our opinion, is associated with changes in the valvular apparatus, prolapse of the leaflets and an increase in blood ejection back into the left atrium. In conclusion, I would like to note that in the examined

patients, most often external hair dryers were characterized by skin, articular, skeletal, forms and the presence of small developmental anomalies. Internal hair dryers were manifested by damage to the cardiovascular and pulmonary systems, organs of vision, pathology of the abdominal organs and kidneys, and especially the ANS. In patients, arrhythmias, sinus tachycardias, extrasystoles, impaired repolarization, and others are detected. According to the ECG data, metabolic disorders are detected in 13-15.7% of patients. Changes in cardiac hemodynamic parameters are detected in a larger number of patients with grade 2 prolapse compared to grade 1 MVP. As CVD progresses, cardiac hemodynamic parameters worsen. Patients with UCTD showed a more pronounced violation of cavity dilatation and a decrease in cardiac output. Under these conditions, to maintain an adequate pumping function, myocardial systems of neurohumoral regulation are activated, causing the development of tachycardia and hypertrophy, and as a result, systolic dysfunction. In severe cases, they can determine the risk of aortic aneurysm and sudden death. Early detection of CVD disorders, as well as the study of the mechanism of their development in adolescents and young people, will allow for dispensary registration, treatment and prevention of complications.

§3.3. Features of changes in the main laboratory parameters in patients with connective tissue dysplasia

One of the main reasons for the increase in the pathology of connective tissue dysplasia are violations of the connective tissue structure, extracellular matrix, collagen and elastin structure [78, p.41-45]. Leading world scientists have recently emphasized the relevance of studying the regulation of fibrillar proteins of the extracellular matrix, that is, magnesium ions [23, p.80]. Deficiency of Mg + 2 contributes to the disruption of the joints, bones, cardiovascular system and valvular apparatus of the heart, the frequency of myxomatous degeneration of the prolapsing leaflets of the mitral valve, cardiac arrhythmia [27, p.714; 78, pp. 41-45]. One of the significant manifestations of UCTD is a violation of collagen synthesis in patients. In the process of collagen metabolism, an immune reaction occurs - circulating autoantibodies. They represent a physiological process in

which waste products of the connective tissue are screened out, its decrease leads to the activation of immune responses that indicate certain types of collagen involved in the pathological process.

In this regard, we also studied the level of magnesium, hydroxyproline, titers of autoantibodies to type I collagen in the blood serum of patients with UCTD. The studies carried out in this regard have shown a trend towards a decrease in the level of magnesium; we have identified a significant decrease in the magnesium content in patients with concomitant diseases, in particular, in combination with CVD. In this group of patients, its level in blood serum decreased by 1.2 times ($P<0.001$) relative to the values of practically healthy individuals (Table 3.4).

Table 3.4

The content of Mg + 2 ions, titers of autoantibodies to type I collagen in blood serum and excretion of hydroxyproline in patients with UCTD, M±m

Researched	Control, n=30	Patients with UCTD
Indicators	0,912±0,022	0,81±0,038*
Mg+2, mol/l	3,2±0,398	4.88±0,095***
Titer Auto ATCol Type I	21,79±0,55	27.2±0,63***

Note: * - differences relative to the data of the control group are significant (* - $P<0,05$, *** - $P<0,001$

A decrease in the level of magnesium leads to pathology of the endothelium, a violation of the volumetric organization of collagen and elastin, which is the cause of the violation of the formation of the components of the extracellular matrix. Thus, a low magnesium level in patients with UCTD is a trigger for the progression of CVS.

Against the background of a decrease in Mg + 2 ions in the blood, an increase in the activity of proteolytic enzymes is noted, in particular, a significant

increase in the excretion of total hydroxyproline in patients with UCTD by 24.3%, relative to the values of practically healthy individuals.

To study the titers of autoantibodies to type I collagen, depending on the phenotypic signs of UCTD, we divided the clinical signs into several groups, depending on the change in the level of autoantibodies. This has an important clinical significance and makes it possible to carry out early diagnosis, to identify the progression of the musculoskeletal system - scoliosis, ADHD, flat feet and joint hypermobility syndrome, as well as minor anomalies of the heart.

Indicators of the level of autoantibody titers in disorders of the musculoskeletal system, MAC are indicated in Table 3.5. Based on this table, it is possible to compare autoantibody titers in various combinations of lesions of the musculoskeletal system, joint hypermobility syndrome, and minor cardiac anomalies.

Table 3.5

Indicators of the level of autoantibody titers in disorders of the musculoskeletal system

Groups of phenotypic traits (n=48)	Level of titers of autoantibodies to type I collagen (mcg/ml)
The level of AAT to type I collagen with impaired ODA (n=12)	4,35±0,73
The level of AAT to type I collagen with impaired ODA + GS (n=11)	4,84±0,81
Level of AAT to type I collagen with signs of MAC (n=8)	4,60±0,59*
The level of AAT to type I collagen with signs of ODA + GS + MAC (n=17)	5,08±0,56**
Control (n=30)	3,2±0,398

Note: * - *differences relative to the data of the control group are significant (* - P<0,05, ** - P<0,01*

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A high level of concentration of titers of autoantibodies to type I collagen (5.08±0.56 µg/ml) (P<0.01) was established, as well as a sample of patients (n=17) who had complex clinical manifestations of UCTD, in particular the combination disorders of the musculoskeletal system, pronounced hypermobility of the joints (having more than 2 points) and MAC (PMC I, II degree + ARC) compared with the control group.

These data indicate that there is a relationship between the clinical manifestations of UCTD and the level of titers of autoantibodies to type I collagen in the plasma of the examined. Thus, an increase in the level of antibodies suggests the importance of the autoimmune component in the pathogenesis of this disease, which will help us to make an early diagnosis and prevent possible complications.

§3.4. Immunogenetic status of undifferentiated connective tissue dysplasia. Study of allelic variants of the DRB1, DQA1 and DQB1 genes of HLA class II

The hereditary predisposition and resistance of an individual to dysfunction of the immune system depends on the diversity of genes of the major histocompatibility complex (HLA) [12, p.3-10]. It should be noted that UCTD has a significant relationship with immune system dysfunction [12, p.3-10]. It has been established that among patients with UCTD there is a statistically significant increase in the frequency of occurrence of the HLA class II gene, in particular in the first and second lines of kinship.

Specificity of the HLA system of class II loci DQA1 (0101, 0102, 0103, 0201.0301, 0401, 0501, 0601), DQB1 (0201.0301, 0302, 0303, 0304, 0305, 0401, 0501, 0502, 0504, 0503 , 0602), DRB1 (01, 02, 03, 04, 07, 08, 09, 10, 11, 13,14,15) were typed in 48 (22 men, 2 boys, 22 women, 2 girls) patients with internal and external hair dryers UCCT.

An analysis of the frequency of occurrence of alleles of the HLA-II DRB1, HLA-DQA1 and HLA-DQB1 genes (Table 3.6-3.7) was carried out in a sample of patients with UCTD (main group) and healthy people (control group).

When examining the HLA-II DQA1 gene, it was noted that *0101 alleles were significantly more common in the group of patients with UCTD (RR=1.58,

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CI 95% - 1.05-2.37; OR=2.50, CI 95 % - 1.01-6.19), *0102 (RR=2.00, CI 95% - 1.38-2.90; OR=5.00, CI 95% - 1.66-15.03) , *0501 (RR=7.69, 95% CI - 3.30-17.92; OR=28.26, 95% CI - 9.38-85.10) compared with the control group.

The study of the HLA-II DQB1 gene also showed a significantly higher incidence of *0201 alleles in patients with UCTD (RR=4.07, CI 95% - 2.45-6.76; OR=17.50, CI 95% - 6.57 -46.60), *0501 (RR=1.81, CI 95% - 1.23-2.67; OR=3.71, CI 95% - 1.30-10.57), *0602 (RR \u003d 1.69, CI 95% - 1.09-2.61; OR \u003d 3.23, CI 95% - 0.93-11.24) in comparison with the frequency of occurrence of alleles in the examined control group.

Table 3.6

The occurrence of allelic variants of HLA class II phenotypes in individuals with

UCTD

Gene	Allele	Frequency (%)		χ^2	P
		Fundamentals. gr. (n=48)	Control (n=60)		
DQA1	*0101	33,3	16,7	4.05	<0,05
	*0102	31	8,3	9.28	<0,01
	*0103	8,3	3,3	1.27	>0,05
	*0201	16,6	16,7	0,00	>0,05
	*0301	27	20	0,75	>0,05
	*0401	2,0	1,6	0,03	>0,05
	*0501	89,5	23,3	46.96	<0,001
	*0601	0	0		
DQB1	*0201	72,9	13,3	39.51	<0,001
	*0301	27	20	0,75	>0,05
	*0302	18,7	8,3	2.56	>0,05
	*0303	12,5	10	0,17	>0,05
	*0304	0,0	3,3	1,63	>0,05
	*0305	0	0		
	*0401	6,25	1,6	1,57	>0,05
	*0501	29,1	10	6,49	<0,01
	*0502	8,3	8,3	0,00	>0,05
	*0503	4,16	6,6	0,32	>0,05
	*0601	10,4	6,6	0,49	>0,05
	*0602	18,7	6,6	3,68	<0,05
DRB1	*01	4,16	10,0	1,32	>0,05

Allele				
*02	0,0	1,6	0.81	>0,05
*03	58.3	0,0	47.25	<0,001
*04	16.6	18,3	0,05	>0,05
*07	22,9	16,6	0,67	>0,05
*08	4,16	1,6	0,62	>0,05
*09	4,16	0,0	2,55	>0,05
*10	10,4	1,6	3,89	<0,05
*11	27,0	3,3	12.58	<0,001
*13	18,75	8,3	2,56	>0,05
*14	16,6	0,0	10,80	<0,001
*15	35,4	1,6	21,87	<0,001
*16	0,0	20	10,80	<0,001
*17	0,0	8,3	4,19	<0,05

Note: χ^2 test was calculated at 95% CI

Table 3.7

Relative risk (RR, CI 95%) and odds ratio analysis (OR, CI 95%) of various alleles of the HLA class II genes in the examined

Gene	Allele	Frequency (%)		RR	Lower gr. 95%CI	Upper gr. 95%CI	OR	Lower gr. 95%CI	Upper gr. 95%CI
		Fundamentals. gr. (n=48)	Counter. gr. (n=60)						
DQA1	*0101	33,3	16,7	1.58	1,05	2.37	2,50	1.01	6.19
	*0102	31	8.3	2.00	1.38	2.90	5,00	1.66	15.03
	*0103	8.3	3.3	1.55	0.84	2.84	2.64	0.46	15.05
	*0201	16,6	16,7	1,00	0.57	1.76	1.00	0.36	2.77
	*0301	27	20	1,23	0.78	1.94	1.49	0,61	3,65
	*0401	2,0	1,6	1,13	0.28	4.58	1.26	0.08	20,61
	*0501	89,5	23,3	7,69	3.30	17.92	28.26	9,38	85.10
	*0601	0	0	-	-	-	-	-	-
DQB1	*0201	72,9	13,3	4.07	2.45	6.76	17.50	6.57	46,60
	*0301	27	20	1.23	0.78	1.94	1.49	0,61	3,65
	*0302	18,7	8.3	1.55	0.98	2,45	2.54	0.79	8,16
	*0303	12.5	10	1,14	0.62	2.10	1.29	0.39	4,27
	*0304	0,0	3.3	0.00	0.00	-	0.00	0.00	-
	*0305	0	0	-	-	-	-	-	-
	*0401	6,25	1,6	1.73	0.95	3.18	3.93	0.40	39.08
	*0501	29,1	10	1,81	1.23	2.67	3.71	1.30	10.57
	*0502	8,3	8.3	1,00	0.47	2.15	1.00	0.25	3.95
	*0503	4,16	6,6	0.74	0.23	2.34	0.61	0.11	3,47
	*0601	10,4	6,6	1,28	0.68	2.39	1.63	0.41	6,43
	*0602	18,7	6,6	1,69	1.09	2.61	3.23	0.93	11.24
DRB1	*01	4,16	10,0	0.54	0,16	1.84	0.39	0.08	2,03
	*02	0,0	1,6	0.00	0.00	-	0.00	0.00	-
	*03	58,3	0,0	4,00	2,74	5.85	-	-	-
	*04	16,6	18,3	0,94	0.53	1.67	0.89	0.33	2.43
	*07	22,9	16,6	1,23	0.77	1.98	1.49	0.57	3,87
	*08	4,16	1,6	1,52	0.66	3.49	2.57	0.23	29.18

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	*09	4.16	0.0	2.30	1.85	2.86	-	-	-
	*10	10.4	1.6	1.98	1.29	3.02	6.86	0.77	60.86
	*11	27.0	3.3	2.30	1.66	3.20	10.77	2.29	50.58
	*13	18.75	8.3	1.55	0.98	2.45	2.54	0.79	8.16
	*14	16.6	0.0	2.50	1.97	3.18	-	-	-
	*15	35.4	1.6	2.74	2.02	3.72	32.35	4.11	254.66
	*16	0.0	20	0.00	0.00	-	0.00	0.00	-
	*17	0.0	8.3	0.00	0.00	-	0.00	0.00	-

Examination of the HLA-II DRB1 gene showed that patients with UCTD had a significant increase in the frequency of occurrence in alleles *03 (RR=4.00, CI 95% - 2.74-5.85; OR=5.85), *10 (RR=1.98, CI 95% - 1.29-3.02; OR=6.86, CI 95% - 0.77-60.86), *11 (RR=2.30, CI 95% - 1.66-3.20; OR=10.7, 95% CI - 2.29-50.58), *13 (RR=1.55, 95% CI - 0.98-2.45; OR =2.54, CI 95% - 0.79-8.16), *14 (RR=2.50, CI 95% - 1.97-3.18), *15 (RR=2.74, CI 95% - 2.02-3.72; OR=32.35, CI 95% - 4.11-254.66) in comparison with the subjects of the control group. At the same time, during the survey, it was found that 2 alleles of the HLA-II DRB1 gene were not found in patients with UCTD, which was significantly significant in comparison with the control group in alleles * 16 (RR = 2.00, CI 95% - 1.64 -2.44; OR=2.54, 95% CI - 0.79-8.16) and *17 (RR=1.87, 95% CI - 1.56-2.24).

Thus, the study made it possible to establish the alleles of genes predisposing to the development of UCTD: DQA1*0101, *0102, *0501; DQB1 *0201, *0501, *0602; DRB1 *03, *10, *10, *11, *14, *15, and alleles of genes that are protective for the development of UCTD: DRB1 *16, *17.

The occurrence of class II HLA genes in patients with UCTD, predominantly lesions of the musculoskeletal, cardiovascular system, and their combination with ocular manifestations is presented in Table 3.8.

The most identified haplotypes were identified in the examined patients (Table 3.9), while in patients with UCTD there was a significant increase in the frequency of occurrence of haplotypes DQA1*0501 DQB1*02 DRB1*03 ($\chi2$=8.52; P<0.01), DQA1*0301 DQB1*0501 DRB1*15 ($\chi2$=12.19; P<0.01), DQA1*0101 DQB1*0301 DRB1*13 compared with the control group, the total

frequency in the study population was 23.1%, 11.1% and 4.6% respectively. Thus, the analysis allows us to conclude that the detection of DQA1*0501 DQB1*02 DRB1*03, DQA1*0301 DQB1*0501 DRB1*15 or DQA1*0101 DQB1*0301 DRB1*13 haplotypes indicates a risk of developing UCTD.

Statistical processing of the genetic material included the calculation and analysis of the following indicators: antigen distribution frequency (F), χ^2 test (Chi-square), relative risk (RR), etiological fraction (EF), preventive fraction (PF).

Table 3.8

Association of Genes with Clinical Course in Patients with UCTD

Clinical	Alleles Genes	A	RR	EF	PF	χ^2	P
Signs and their combinations (%)	DQA1*0301 DQB1*0501 DRB1*11	25,1	5,00	0,20	0,00	1,1	0,310
NCD by cardiac type	DQA1*0102 DQB1*02 DRB1*07	25,0	8,2	0,05	0,00'	8,2	0,004
(6.25)	DQA1*0501 DQB1*02 DRB1*03	37,5	0,20			0,4	0,523
NDC+Myopia	DQA1*0301 DQB1*0501 DRB1*15	0,0	0,16			4,0	0,045
PMK I degree (37,50)	DQA1*0501 DQB1*02 DRB1*03	0,0	2,14	0,07		0,0	0,992
PMK II degree (10.40)	DQA1*0101 DQB1*0301 DRB1*13	12,5	2,14	0,07	0,00	0,0	0,992

Table 3.9

The most common haplotypes among the studied groups

Haplotypes	Fundamentals. gr.	Control (n=60)	χ^2	P	% in

	(n=48)						research. popul.
	n	%	n	%			
DQA1*0501 DQB1*02 DRB1*03	17	37,5	8	13.3	8.52	<0,01	23,1
DQA1*0301 DQB1*0501 DRB1*15	11	22.9	1	1.7	12.19	<0,01	11,1
DQA1*0101 DQB1*0301 DRB1*13	5	10,4	0	0.0	6.55	<0,05	4,6

Thus, UCTD showed positive correlations with higher RR values of the DQA1, DQB1, and DRB1 genes. Studies have shown that associations of these genes were detected most often in patients with HA and spinal deformity, myopia, flat feet, MVP, ARC, and myxomatous MV degeneration. Which, in turn, suggests that by conducting these studies, it is possible to conduct early diagnosis and prevent possible complications.

Based on the foregoing, we were interested in the study of hereditary manifestations. The study of probands showed a certain dependence of genetic factors in the formation of UCTD (Fig. 3.5-3.6). So, if in the 1st group of patients the frequency of occurrence of signs of UCTD in the 1st, 2nd and 3rd lines of kinship was detected in 6 (8.5%), 9 (13%) and 5 (7%) patients from 71 examined, then in the 2nd group they were detected in 13 (18.3%, P<0.01), 14 (20%, P<0.05) and 11 (15.5%, P<0.01) of the examined persons.

According to this figure, similarities between the genetic parameters of all HLA loci of the class II system are noticeable.

Thus, I would like to note that in the examined patients, most often external phenes were characterized by skin, articular, skeletal, forms and the presence of small developmental anomalies. Internal hair dryers were manifested by damage to the cardiovascular and pulmonary systems, organs of vision, pathology of the abdominal organs and kidneys, and especially the ANS. In patients, arrhythmias, sinus tachycardias, extrasystoles, impaired repolarization, and others are detected. According to the ECG data, metabolic disorders are detected in 13-15.7% of patients. Changes in cardiac hemodynamic parameters are detected in a larger

number of patients with grade 2 prolapse compared to grade 1 MVP. As CVD progresses, cardiac hemodynamic parameters worsen.

Patients with UCTD showed a more pronounced violation of cavity dilatation and a decrease in cardiac output. Under these conditions, to maintain an adequate pumping function, myocardial systems of neurohumoral regulation are activated, causing the development of tachycardia and hypertrophy, and as a result, systolic dysfunction.

In severe cases, they can determine the risk of aortic aneurysm and sudden death. Early detection of CVD disorders, as well as the study of the mechanism of their development in adolescents and young people, will allow for dispensary registration, treatment and prevention of complications. According to the results of laboratory studies, it can be concluded that an increase in the level of antibodies suggests the importance of the autoimmune component in the pathogenesis of this disease, as well as positive relationships with higher RRs of the DQA1, DQB1 and DRB1 genes in UCTD. Studies have shown that associations of these genes were detected most often in patients with HA and spinal deformity, myopia, flat feet, MVP, ARC, and myxomatous MV degeneration. Which, in turn, suggests that by conducting these studies, it is possible to conduct early diagnosis and prevent possible complications.

Chapter 4

ASPECTS OF PHARMACOTHERAPY AND PREVENTION OF UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA.

§ 4.1. The effectiveness of therapy with chondroprotectors and magnesium preparations in individuals with undifferentiated connective tissue dysplasia

The above data indicate that one of the factors in the development of dysplasia on the part of the connective tissue is a decrease in the level of

magnesium and an increase in the titers of autoantibodies to type I collagen in the blood serum.

In this regard, according to the treatment plan, the patients were divided into three subgroups:

- subgroup "A" consisted of 16 patients who were prescribed a course of therapy for preventive and therapeutic purposes, traditional treatment + preparations containing magnesium in a daily dose of 3 g (2 tablets 3 times a day) for 6 months;

- subgroup "B", 16 patients treated with traditional treatment + magnesium preparations + chondroprotectors (chondroitin sulfate sodium at a daily dose of 500 mg or glucosamine sulfate sodium chloride at a daily dose of 750 mg for 2 months daily in the morning 1 time, followed by an interval after 2 month repeated three times).

- subgroup "C" 16 patients who received traditional treatment in the form of metabolites and vitamins for 10 days;

The examination was carried out at admission and 6 months after the start of treatment. Efficacy was evaluated on the basis of clinical, laboratory and instrumental studies. The control for all compared groups were data from 30 apparently healthy individuals who gave informed consent to the study.

According to the study, the proposed treatment methods for UCTD showed high efficiency (Fig. 4.1). In group "A", in patients, complaints of shortness of breath decreased by 2.86 (P<0.001) times, for lack of air by 7.35 (P<0.001) times.
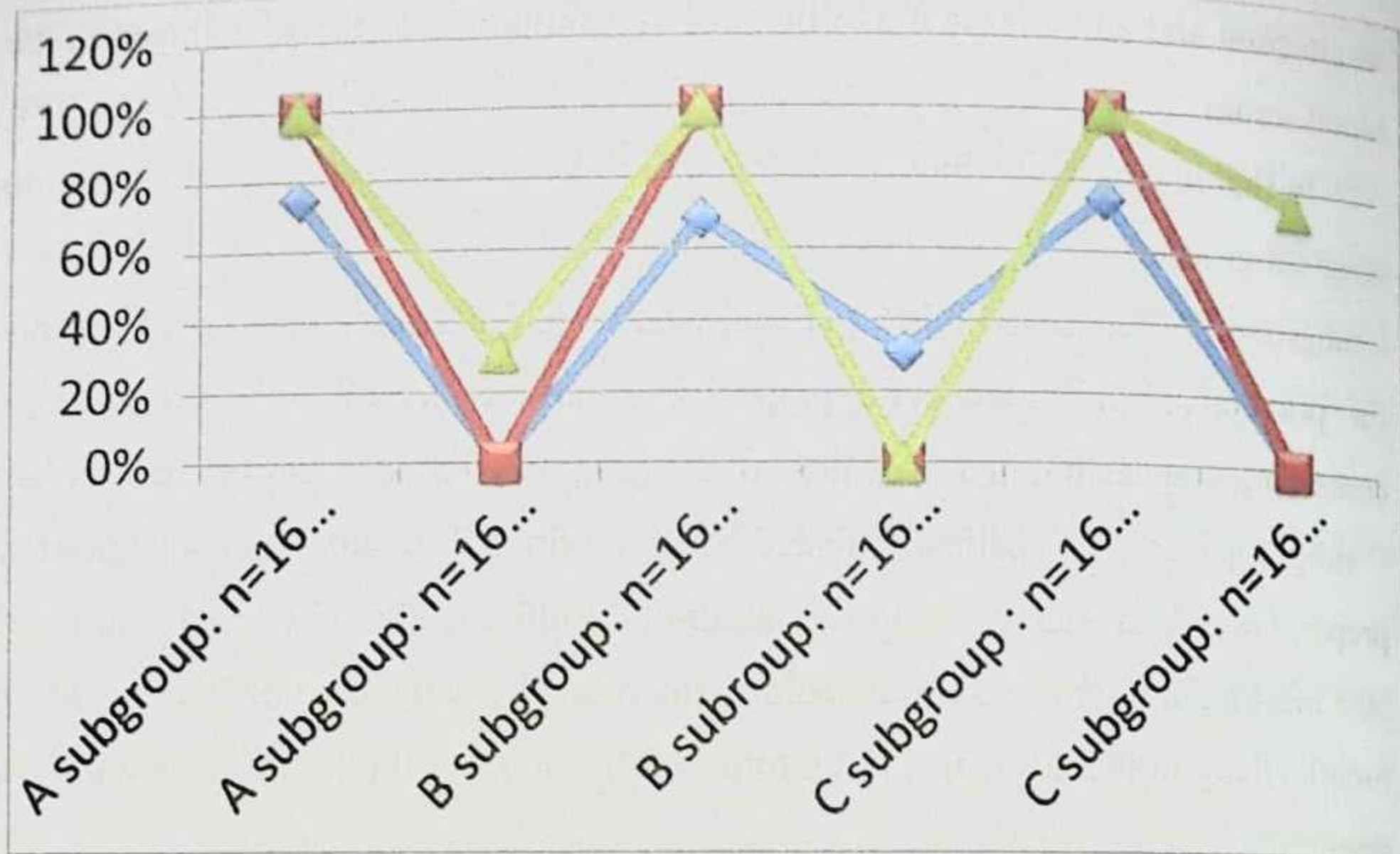
Rice. 4.1. Dynamics of regression of clinical manifestations of UCTD during treatment. *Headaches Shortness of breath. Pain in the joints.*

Nevertheless, 18.2% of patients continued to complain of mild dyspnea and moderate lack of air, joint pain persisted in 31%, almost no complaints of headaches, ECG disturbances after treatment with magnesium preparations in group A did not occur (table 4.1).

Table 4.1

Electrocardiogram dynamics in UCTD during treatment, %

Groups	Before		After	
	abs.	%	abs.	%
A Group: n=16	14	87.5	0	0
B Group: n=16	15	93.8*	1	6.25***
C Group: n=16	15	93.8*	8	50.0***

Note: ** - differences relative to pre-treatment group data are significant (* - $P<0.05$, ** - $P<0.01$, *** - $P<0.001$)*

According to this table, it can be concluded that the appointment of magnesium preparations has a beneficial effect, contributing to a significant reduction in the clinical manifestations of UCTD.

Additional inclusion of chondroprotectors to magnesium preparations according to the scheme (group B) led to an even greater increase in the effectiveness of treatment. The frequency of complaints of shortness of breath decreased by 3.2 ($P<0.001$) times, relative to the values before treatment; 2.2 ($P<0.05$) times compared with the sample of patients who received only traditional treatment. After treatment, in group "B" patients had practically no complaints of joint pain, while in group "A" they were preserved in 31% of patients, and in group "C" in 75% of patients, respectively. Complaints of headaches decreased by 2.2 ($P<0.05$) times compared to before treatment, and in contrast to traditionally treated patients by 2.6 ($P<0.05$). After treatment, in group "B" ECG changes were almost not detected, while in the group of patients who received only traditional treatment, they persisted in 87.5% of those treated. It should be noted that changes in EchoCG parameters were detected in patients with UCTD. The treatment of these patients with the use of magnesium preparations showed a positive trend, a decrease in EDR, EFR, blood pressure, heart rate against the background of an increase in ejection fraction parameters, cardiac output.

Another important symptom of UCTD is joint hypermobility. We conducted a study on HS scores, according to the Beighton test. According to our data, after the treatment, there was an improvement in the condition of patients, which are listed in Table 4.2.

Based on this table, we concluded that with the help of magnesium preparations there is a relative improvement in the condition of the joints, since, in group "A", 44% of patients who had 3 points, of which 25% switched to 2 points, and out of 2 points (31.2% of patients) switched to 1 point 6.25%, respectively. A more improved indicator was in the "B" group, since 44% had a high HS score, but in 56% after the use of magnesium and CP preparations in a complex, it decreased to 1 point, in contrast to the "C" group. This, in turn, led to a regression of the clinical manifestations of the articular syndrome in UCTD.

Table 4.2

Dynamics of regression of joint hypermobility after treatment in patients with UCTD

score	8 points before/after treatment	6 points before/after treatment	4 points before/after treatment	2 points before/after treatment
Group "A" n=16	-/-	7/3	5/4	4/5
Group "B" n=16	2/-	5/2	6/5	3/9
Group "C" n=16	1/1	-	3/2	12/13

All the data obtained by us indicate the high efficiency of the complex use of magnesium preparations and chondroprotectors for the treatment of UCTD. This is due to a significant improvement in the synthesis of collagen and elastin in fibroblasts under the influence of magnesium ions. According to the literature, our results are consistent, since a six-month course of therapy with magnesium preparations provides a significant reverse dynamics of the clinical symptoms of UCTD manifestations. The best indicator of clinical efficacy was shown by the combination of magnesium preparations and chondroprotectors on the regression of clinical symptoms of the musculoskeletal system, articular syndrome, joint hypermobility, MAP. This, in our opinion, is associated with an improvement in the processes of regeneration of cartilage and bone tissues, as well as a slowdown in degenerative changes. The anti-inflammatory effect of CP is positive on the musculoskeletal system, which leads to a reduction in pain and restoration of function.

§ 4.2. The results of pharmacotherapy on biochemical parameters in patients with UCTD

According to our data, it turned out that the use of magnesium and CP preparations is the main pathogenetic method for the treatment and prevention of UCTD. The

appointment of magnesium to patients with UCTD showed an increase in the level of magnesium in the blood of patients.

As can be seen from this figure, in patients of group "A", the level of magnesium in the blood serum increased statistically significantly from 0.79 ± 0.018 mol/l to 0.86 ± 0.010 mol/l ($P<0.05$). In patients of group "C", the level of magnesium in the blood serum was initially significantly lower compared to the values of the previous group. Despite the increase in the magnesium content in the blood of the examined, the level remained below the values of practically healthy individuals (0.912 ± 0.022 mol/l).

In patients of group "B" who received magnesium and CP preparations, the level of magnesium in blood serum increased statistically significantly from 0.78 ± 0.008 mol/l to 0.901 ± 0.007 mol/l ($P<0.05$). However, as well as in the previous group, the values of the magnesium level were statistically significantly different from the normative values.

Thus, the prophylactic and therapeutic use of magnesium alone or in combination with CP increases the level of magnesium in the blood serum of the examined patients.

As mentioned earlier, one of the main reasons underlying the insufficiency of the functions of organ systems in UCTD is considered to be violations in the process of collagen synthesis, determined by the autoimmune activity of the body, through the production of autoantibodies.

During the metabolism of collagen, an immune reaction appears in the form of circulating autoantibodies, where we previously conducted a study and showed that the level of titers of autoantibodies to type I collagen increases in the blood of these patients.

With the use of magnesium, CP patients with UCTD, there was a tendency to reduce the level of autoantibodies to type I collagen (Fig. 4.3).

Rice. 4.3. Titers of autoantibodies to type I collagen before and after treatment in patients with UCTD

The level of autoantibodies to type I collagen in the examined subgroups before and after treatment (ug/ml)

Group «B»
4.94/3.69

Group «A»
4.91/3.71

Group «C»
4.79/3.95

This was more pronounced in patients in group "B". So, in these patients, statistically significantly decreased by 1.25 ($P<0.05$) times. These studied indicators approached the values of practically healthy individuals. The results obtained indicate the effectiveness of magnesium and CP for the correction of autoimmune state indicators in UCTD.

Features of pharmacotherapy of patients with UCTD showed that during the treatment period, the group of patients who had allelic variants *02 and / or *0501 of the DQB1 gene, as well as *15/03 of the DRB1 gene had a complex clinical course and, accordingly, they responded poorly to treatment, which in in turn, required a longer use of magnesium and CP preparations (table 4.3).

Table 4.3

Features of pharmacotherapy in patients with UCTD depending on HLA class II alleles

Clinical	Alleles	Before %	After (3 mounths course) %	After (6 mounths course) %
signs and their combinations (n=48)	DQB1*02 DRB1*03	16.70	16.70	15.37***

flat feet	DQB1*0501 DRB1*15	22.90	20.53*	19.81**
Deformity of the HA and spine	DQB1*02 DRB1*03	37.50	37.50	37.50

Note: * - *differences regarding data between groups are significant * - P<0.05,* ** *- P<0.001 *** - P<0.001*

It has been proven that autoimmune conditions are an essential factor in supporting collagen homeostasis. When collagen is metabolized, an immune response appears, which reflects the vital activity of the connective tissue [79, p.61-68]. In the presence of inflammatory processes in UCTD, the ability of fibroblasts to secrete collagen and elastase, which are responsible for the formation of the components of the extracellular matrix, changes. It can be assumed that the elevated level of autoantibodies to type I collagen identified in our studies in UCTD also justifies the need to include CP in the course of therapy for these patients. The use of magnesium and CP preparations leads to the activation of the synthesis of high-molecular hyaluronic acid by synoviocytes, masks secondary antigenic factors in relation to collagens, and reduces the activity of enzymes that disrupt cartilage and the synthesis of interleukins.

§4.3. Algorithm for early diagnosis and treatment of UCTD

After analyzing the data obtained, we can say that already in childhood and adolescence, it is necessary to conduct comprehensive studies for the early diagnosis of UCTD. At the primary level, in adolescent examination rooms, doctors should pay attention to the presence of external and internal hair dryers in adolescents and young people, especially recruits, in order to exclude UCTD, and prepare them for the necessary preventive measures.

According to our scientific work, a program was developed to determine the likelihood of developing complications of cardiovascular diseases of undifferentiated connective tissue dysplasia in young people. This program is designed for early determination of the risk of developing CVD complications in young people with undifferentiated connective tissue dysplasia. Functionality of

the program: drawing up a card of the examined patient, collecting, entering, saving data on the factors of occurrence and distribution among relatives of the risk of developing UCTD. The program allows you to assess the risk of developing complications of CVD, the musculoskeletal system and other organs, predict an unfavorable course and prevent possible complications of this pathology. The program can be used in such areas as therapy, family medicine and in outpatient practice, for early diagnosis, prognosis of the course and prevention of complications of UCTD in young people (Table 4.5)

Table 4.5

A program for determining the likelihood of developing complications of cardiovascular diseases of undifferentiated connective tissue dysplasia in young people.

Phenotypes	№	signs	Manifestations	score	Manifestations	score	Manifestations	score
IN E S H N I E 1.	IN E S H N I E 1.	Bone-skeletal: Scoliosis	Up to 2 signs	0	Up to 3 signs	0,5	More than 3 signs	1
	2.	Chest deformity, arched palate, skull deformity		0		0,5		1
	3.	Skin: hyperelasticity of the skin, weakness of the abdominal muscles, wrinkling, tenderness or velvety skin, a symptom of "cigarette paper".	Up to 2 signs	0	Up to 3 signs	0,5	More than 3 signs	1
Up to 3 signs 2 to 3 signs	4.	Minor developmental anomalies: eye hypertelorism, protruding ears, attached earlobes, zygomatic hypoplasia	Up to 2 signs	0	Up to 3 signs	0,5	More than 3 signs	1
HUTRE ENNIE	5.	Ocular: ectopic lens, astigmatism, myopia, blue sclera	Up to 2 signs	0	Up to 3 signs	1	More than 3 signs	2

No.	Description						
6.	Cardiovascular: mitral valve prolapse, abnormally located chords, myxomatous degeneration of the mitral valve.	Up to 2 signs	0	Up to 3 signs	2	More than 3 signs	3
7.	Pulmonary: spontaneous pneumothorax, apical bullae, tracheobronchomegaly.	Up to 2 signs	0	Up to 3 signs	2	artificial	3
8.	Organs of the abdominal cavity and kidneys: gastroptosis, hepatoptosis, nephroptosis.	Up to 2 signs	0	Up to 3 signs	2	More than 3 signs	3
9.	Nervous system: lumbosacral ectasia, autonomic dysfunction.	Up to 2 signs	0	Up to 3 signs	2	More than 3 signs	4
	Combination of external and internal features	NOT	0	Up to 3 signs / 2 to 3 signs	2	More than 3 signs	6

The signs are evaluated, after which the scores are summed up and the result is interpreted as follows:

- 0-4 points - the risk of complications from the cardiovascular system is minimal or absent.

- 5-15 - the risk of complications from the cardiovascular system is insignificant, there is a tendency to develop mitral valve prolapse of I - II degree, arrhythmias, it is necessary to carry out a set of preventive measures, apply magnesium preparations, chondroprotectors, it is recommended to be examined by a therapist every 6 months.

- 15-21 - high risk of complications from the cardiovascular system (within 3 months), it is necessary to carry out a set of preventive measures, apply magnesium preparations, chondroprotectors, it is recommended to be examined by a therapist every 3 months.

The use of the BROSCVS scale will allow for an objective assessment of the likelihood of developing CVD complications in young people with UCTD, will reveal the risk of developing complications such as mitral valve prolapse, cardiac arrhythmias, severe scoliosis, pyelonephritis, gastritis, etp.

In addition, it is necessary to conduct R-studies to identify disorders of the musculoskeletal system, such as deformities of the chest, spine, flat feet, determine HS, identify reflux esophagitis and other pathologies of the gastrointestinal tract, as well as consult an ophthalmologist to identify pathologies from the side vision. It is recommended to conduct an ECG and EchoCG study to study heart rhythm, cardiac conduction disorders and the presence of MAC, as well as biochemical studies to determine magnesium ions in the blood serum, the level of titers of autoantibodies to type I collagen (Fig. 4.4).

If these disorders are detected, patients should be registered as a risk group for further thorough examination and treatment and preventive work. It is desirable to carry out gene diagnostics in the primary stage, for the presence of a predisposition to a weak immune system, by determining HLA class II antigens, in order to maintain the immune status against the background of UCTD. This will lead to early prevention of complications of ODA, CVS, etp. These studies will reveal hidden violations in the formation of connective tissue

Patients of the risk group, if there is a deficiency in the body of magnesium, it is necessary to prescribe magnesium preparations in a daily dose of 3.0 (2 tablets 3 times a day for 3 and 6 months). With an increase in the level of titers of autoantibodies to type I collagen, it is necessary to additionally prescribe CP (sodium chondroitin sulfate at a daily dose of 500 mg or glucosamine sodium chloride sulfate at a daily dose of 750 mg for 2 months daily in the morning 1 time, followed by an interval of 2 months repeated three times) . This will reduce the risk of complications, improve the quality of life of patients and promote recovery.

After reviewing all the data obtained, it should be said that the use of magnesium, especially in the CP complex, for the treatment of UCTD is reasonable and effective. Since, an increase in the synthesis of collagen and elastin in fibroblasts under the influence of magnesium and HP ions improves the quality of connective tissue. However, treatment must be carried out for a long time (within 6 months). Indeed, studies on UCTD therapy have shown an earlier and more pronounced restoration of balance in the collagen formation system, especially with the use of magnesium and CP. The combination of these properties, apparently, leads to an improvement in the metabolism in the connective tissue, general cardiac hemodynamics and clinical manifestations of UCTD in the examined patients.

Conclusion

Connective tissue dysplasia combines a large group of diseases, including both genetically determined factors (differentiated CTD) with proven gene disorders, as well as non-syndromic forms or undifferentiated CTD with diverse developmental paths. The clinical manifestations of genetically determined diseases suggest significant genetic diversity.

UCTD is one of the most common connective tissue anomalies. This sample of patients has a high risk of complications such as severe scoliosis, bone fractures, joint dislocations, infective endocarditis, thromboembolism, arrhythmia, and heart failure. Currently, clinicians propose to isolate diseases of the ODA, MAS as an independent dysplastic syndrome. Considering these pathologies as a syndrome requires solving its connection with CTD, i.e. in terms of understanding the pathogenesis of connective tissue disorders. However, these problems have not been fully resolved and are in search of their solution. Algorithms for diagnosing lesions of other organs and systems have not yet been approved, and most mechanisms for disrupting the structure and function of connective tissue in patients with UCTD also remain unexplored. Studies of this series have not been conducted in Uzbekistan, therefore, there are no recommendations for the management of such patients, in particular, with the involvement of the heart and joints in the pathological process, which leads to significant

differences in the treatment and diagnostic tactics of doctors of different specialties. All of the above factors were the rationale for this study - search approaches for the diagnosis, treatment and prevention of possible complications of UCTD.

Finally, we note that further solution of the problem of early diagnosis and correction of undifferentiated connective tissue dysplasia in young people still depends on taking into account the anatomical and physiological features, the quality of timely and primary diagnosis of the disease. Only in this case it will be possible to achieve the main goals - minimizing disability, preventing possible complications, as well as reducing both the duration and frequency of hospitalization of young people with this pathology.

The severity of clinical symptoms of UCTD was associated with the frequency of occurrence and the number of combinations of external dryers: connective tissue dysplasia: joint hypermobility (100%), changes in the shape of the spine (41.9%), chest (40.9%), skin extensibility varying degrees of severity (45.7%), minor developmental anomalies (59%), flat feet (50.5%) and internal hair dryers: myopia 39%, heart anomalies 61%, ECG and EchoCG changes were observed in 80% of the examined, where the presence cardiac arrhythmias are associated with connective tissue weakness

In UCTD, positive associations with higher RR values of the DQA1, DQB1, and DRB1 genes were noted. A relationship has been established between HLA class II genes (allelic variants of the DRB1 gene *14 and/or *15, 13/14) and clinical manifestations of UCTD in the

form of changes in external and internal phenes (musculoskeletal system and cardiovascular system).

The predisposing alleles of the HLA genes of the class II system to the development of UCTD were found: DQA1*0101, *0102, *0501; DQB1 *0201, *0501, *0602; DRB1 *03, *10, *10, *11, *14, *15, as well as protective alleles of genes to the development of UCTD gene alleles: DRB1 *16, *17.

In patients with UCTD, a decrease in the level of magnesium in the blood and an increase in titers of autoantibodies to type I collagen were revealed. This led to a deterioration in the formation of collagen and elastin involved in the formation of the extracellular matrix.

On the basis of clinical and genotypic manifestations, a method for early diagnosis of UCTD in adolescents and young people was proposed, which makes it possible to be registered with a dispensary and conduct secondary prevention in a family advisory clinip.

For the prevention of possible complications and treatment of UCTD, it is advisable to prescribe magnesium and CP preparations for a long time. They restore the balance of magnesium in the body, slow down the breakdown of the extracellular matrix

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Recommendation

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In patients with external and internal phenes of connective tissue dysplasia, it is necessary to determine the content of magnesium, a genetic study of the class II HLA system, the level of titers of autoantibodies to type I collagen to carry out appropriate preventive and therapeutic measures.

A comprehensive assessment of the definitions of the state of the connective tissue and intracardiac hemodynamics will contribute to an adequate assessment of the functional state of the musculoskeletal system and myocardium in patients with UCTD.

To improve collagen formation, patients with UCTD are recommended to use magnesium preparations (at a daily dose of 3.0 g for 3-6 months) and chondroprotectors (glucosamine sulfate sodium chloride at a daily dose of 750 mg for 2 months daily in the morning 1 time, followed by at intervals of 2 months).

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