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Features of Diagnosis and Treatment of Articular Syndrome in Undifferentiated Connective Tissue Dysplasia

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Abstract **Background.** The problem of Undifferentiated Connective Tissue Dysplasia (UCTD) has recently aroused great interest of medical practitioners in connection with the increase in the detect ability of patients with this pathology. The damage of dense connective tissue is manifested by changes on the part of the skeleton: disorder of posture in the form of kyphosis and scoliosis of the spine, deformation of the chest. Weakness of the ligament apparatus in patients with dysplasia leads to the development of generalized joint syndrome that occurs 57 - 94%. **Objective.** In this regard, the aim of our study was to develop an algorithm for the diagnosis and treatment of joint syndrome in UCTD. **Study materials.** 105 patients were examined, who were final to anthropometric studies, determination of the level of autoantibodies to collagen of type I, HLA genotyping in blood in patients with UCTD. **Results**. Anthropometric and phenotypic characteristics of the studied patients showed that all patients experienced flat-footedness (flat-foot index-29%), moderate degree of joint hypermobility, scoliosis of 1 and 2 degree (36%), as well as increased level of autoantibodies to collagen type I depending on severity of clinical manifestations of UCTD (5, 9±0.3 μg/l). A statistically significant increase in the frequency of the class II HLA gene, in particular in the first and second line of kinship, was found to be observed among patients with UCTD, the effectiveness of magnesium and chondroprotectors showed that the level of antibodies to collagen of 1 type was statistically significantly decreased in 2.6 (P <0.001). **Conclusion.** Based on the principles of the algorithm, which form the basis of diagnosis of various the forms of UCTD, IT is recommended to check Genetic a predisposition in Patients with signs of internal and external phenotypes of dysplasia of the disease and to the Determine the level of autoantibodies to collagen of the type I of. Application of the proposed method of treatment with magnesium and chondroprotectors makes it possible to restore disturbed collagen synthesis and improve connective tissue structure.

Keywords Undifferentiated Connective Tissue Dysplasia, Joint syndrome, Flat-footedness, Antibodies to collagen of 1 type, HLA II class gene, Magnesium and chondroprotectors

1. Background

In recent years, ideas about connective tissue dysplasia (CTD) have changed significantly. The problem of CTD has recently been of great interest to medical practitioners in connection with an increase in the detection of patients with this pathology [10]. UCTD is a heterogeneous group of diseases, which, in turn, can lead to various chronic diseases with impaired morphology and organ function [3,5,6].

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Clinical manifestations, which depend on the predominant lesion of dense or loose connective tissue, the number and quality of mutations, the nature and severity of the violation of fibrillogenesis [9]. Due to the fact that connective tissue is ubiquitous in the body - bones, skin, cartilage, vascular wall, organ stroma, the disease is poly-systemic in nature with various symptoms [11]. Damage to the dense connective tissue is manifested by changes in the skeleton: impaired posture in the form of kyphosis and scoliosis of the spine, stoop, chest deformity [9]. Weakness of the ligamentous apparatus in patients with dysplasia leads to the development of generalized articular syndrome, which occurs in 57 - 94% (fig. 1).

In the literature, the term “osteodysplasia” is used, which is understood as a malformation of bone tissue caused by stopping, slowing down or distorting osteogenesis at a

certain stage of embryonic or postnatal development [2]. The concept of "bone dysplasia" reflects only locomotor changes with systemic underdevelopment of connective tissue. Most of these works consider arthralgia as a manifestation of joint hypermobility (JHM) developed as a result of UCTD. Therefore, there is a need to study other bone-articular manifestations of UCTD, in which arthralgia occurs.

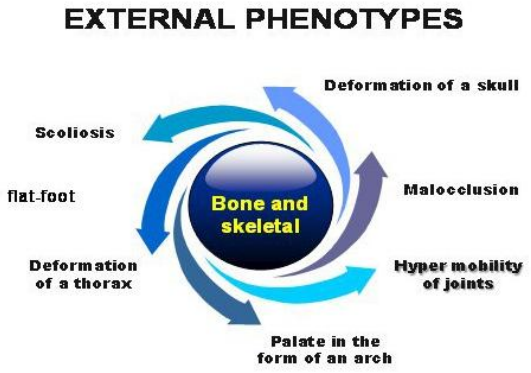

Figure 1. External phenotypes of undifferentiated connective tissue dysplasia: Joint changes

General approaches to the diagnosis of UCTD should be based on a comprehensive analysis of the results of clinical, genealogical and laboratory-instrumental studies [1,11,7,8]. Clinical and genetic examination of the patient's relatives is extremely important, as it allows you to confirm the hereditary nature of the identified pathology and to evaluate the manifestations of connective tissue dysplasia in the family. An important point in the diagnosis will be the identification of small developmental abnormalities in the patient and in relatives of the first and second degrees of kinship, as well as the establishment of estimated risk factors for the development of DST [4].

Based on early diagnosis, it is necessary to timely prevent complications of the articular syndrome in undifferentiated connective tissue dysplasia by treatment with chondroprotectors and magnesium medications.

2. Objective

In this regard, the aim of our study was to develop an algorithm for the diagnosis and treatment of articular syndrome with UCTD.

3. Study Materials

105 patients were examined on the basis of the Samarkand City Medical Association and the clinic of the Samarkand Medical Institute, as well as family members of these patients. Measurements were made of height, body weight, chest circumference, epigastric angle, arm span, length of the upper body segment, hand, foot, fingers, height of the arch of the foot, examination of the back area (in order to detect scoliotic deformity, lumbar hyperlordosis and hyperkyphosis of the thoracic spine, pterygoid scapula), as well as the Beighton test (to detect joint hypermobility). To diagnose longitudinal flatfoot, the calculation of the podometric index (P) = (h×100): L, where h is the height of the foot - the distance measured by the compass from the floor to the upper surface of the scaphoid 1.5 cm anterior to the ankle, mm; L - foot length - distance from the tip of the first finger to the back roundness of the heel, mm (Friedland method).

4. Methods of the Study

Patients were determined the level of titers of autoantibodies to collagen type I before and after treatment. The study of the immunogenetic status of patients with UCTD was carried out using the DNA aplification method of HLA-DNA-TECH kits for HLA typing of class II genes (DRB1, DQA1 and DQB1 loci) and, based on the study, a diagnostic and treatment algorithm was compiled. The determination of titers of autoantibodies to type I collagen in blood plasma was determined by enzyme-linked immunosorbent assay using Imtek kits (Russia). All patients were prescribed magnesium preparations, chondroitin sulfate and glucosamine hydrochloride.

5. Results and Discussions

Studies have revealed the diversity of the clinical condition of the articular syndrome in patients with UCTD.

Anthropometric and phenotypic characteristics of the studied patients showed that the average height of the patients is 168.89±7.96 cm, weight - 62.38±12.24 kg, chest circumference - 89.16±8.15 cm, epigastric angle (in degrees^0) - 87.46±9.74, arm span depending on height - 1.002±0.07, length of the upper body segment 89.36±9.008 cm, brush length –0.106±0.007 cm, foot length depending on height -0.149±0.08, the height of the arch of the foot -7.95±1.15 cm, respectively.

For an objective assessment generalized hypermobility joints (TOS) was used criteria Beighton (P. Beighton). In this case, hypermobility was evaluated in points: 1 point means pathological extension in one joint on one side. The maximum value of the indicator, given the two-way localization, is 9 points. An indicator of 4 to 9 points was regarded as a state of hypermobility. Among the studied patients, the highest were revealed 6 and 8 points (6 points - in 42, 8 points - in 34 patients, respectively).

To identify flat feet in patients, the Friedland method was used (Table 1).

Table 1. Calculation of the submetric index (PI) = I = h/L * 100% according to the Friedland method

Parameters	Indicators (average)
The height of the arch of the foot (h), cm	5.85±1.15
Foot length (L) cm	20.12±2.04
Sub metric index (I),%	29.03±3.54

Where h is the height of the foot - the distance measured by the compass from the floor to the upper surface of the scaphoid by 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 this table, it should be noted that the podometric index is 29%. This suggests that most of the subjects have flat feet.

In addition to flat feet in patients, various spinal deformities were also noted: of these, scoliotic spinal deformity in 36%, lumbar spinal hyperlordosis - 1.9%, thoracic spine hyperkyphosis - 7.6%, pterygo-shaped scapula - 11.4%, finger deformity brushes - 3.8% of the studied, respectively. Based on the above data, it can be concluded that patients with UCTD have various clinical options for the joint syndrome, which in turn complicates the diagnosis and treatment tactics of general practitioners and general practitioners.

In healthy humans in small amounts constantly circulating autoantibodies, which are a particular mechanism of immune regulation and implement a "sanitary" function, binding and transporting the products of metabolism. Delayed or insufficient formation of autoantibodies causes a violation of homeostatic mechanisms. Connective tissue dysplasia is known to be often associated with disorders of homeostasis at the tissue and organ levels. In this aspect, an increase in the levels of autoantibodies to type I collagen with UCTD not only characterizes interstitial collagens as predominantly involved in the formation of dysplastic changes in the musculoskeletal system, but also indicates the "tension" of autoimmunity - a process that is borderline between normal self-recognition and autoimmune pathology.

Therefore, we patients conducted an analysis of a study of the level of autoantibodies to type I collagen, for the purpose of early diagnosis (table 2).

Table 2. The level of autoantibodies to type 1 collagen in the blood plasma of patients with UCTD

Group of patients with articular syndrome	The level of autoantibodies to collagen type I, μg/ml
With scoliosis	5.2±0.6
With flat feet	4.8±0.8
With joint hypermobility syndrome	5.4±0.4
With scoliosis, flat feet and hypermobility of the joints	5.9±0.3

An increase in the concentration of autoantibodies to type I collagen was revealed in groups with scoliosis, flat feet and articular hypermobility. An analysis of the concentrations of autoantibodies to collagen in the blood plasma of patients with joint hypermobility syndrome showed high levels of autoantibodies to type I collagen with maximum values. A study of the level of autoantibodies to collagen depending on the nature of dysplastic manifestations made it possible to identify a number of patterns: an increase in the content of autoantibodies to collagen I ("bone") type in patients with scoliosis, flatfoot, articular hypermobility and the absence of violations of autoimmunity to the studied types of collagen in patients with UCTD with out these dysplasia of the musculoskeletal system.

It was found that, among patients with UCTD, a statistically significant increase in the frequency of class II HLA gene was observed, in particular in the first and second lines of relationship. Indicators for calculating the odds ratio (OR) criterion and the value of the 95% confidence interval indicate that the chance of complications is significantly higher in carriers of these alleles, which determines the predisposing role of these genes in the development of complications in the form of multiple organ pathology in patients with UCTD (fig. 2).

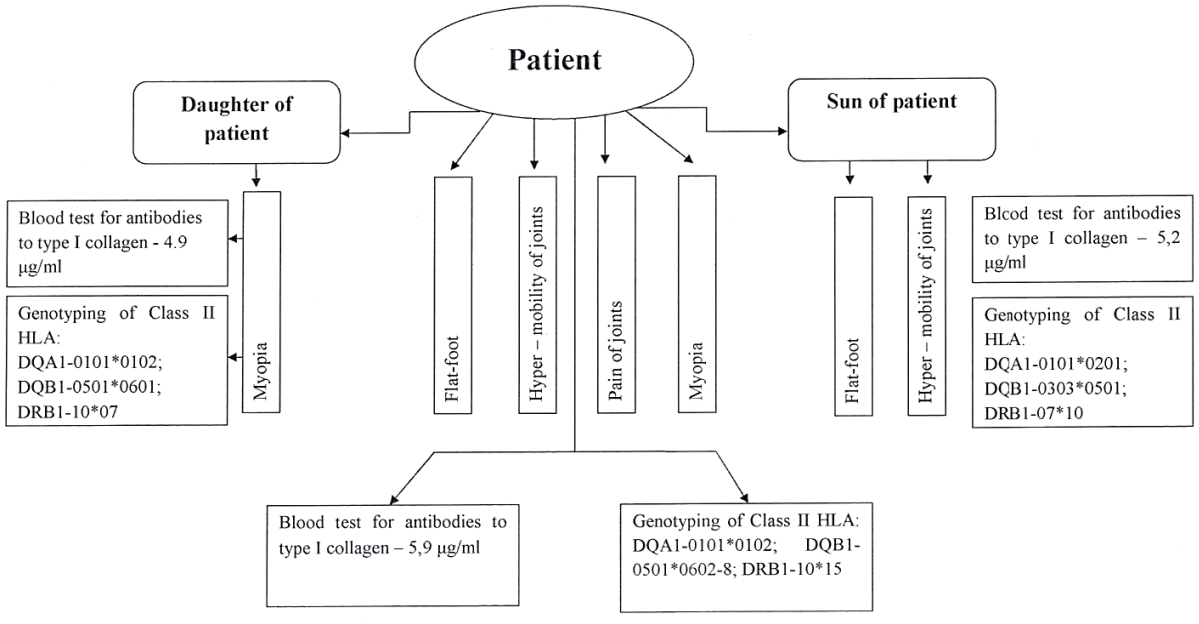

Figure 2. The incidence of UCTD in relatives of the first and second line of kinship

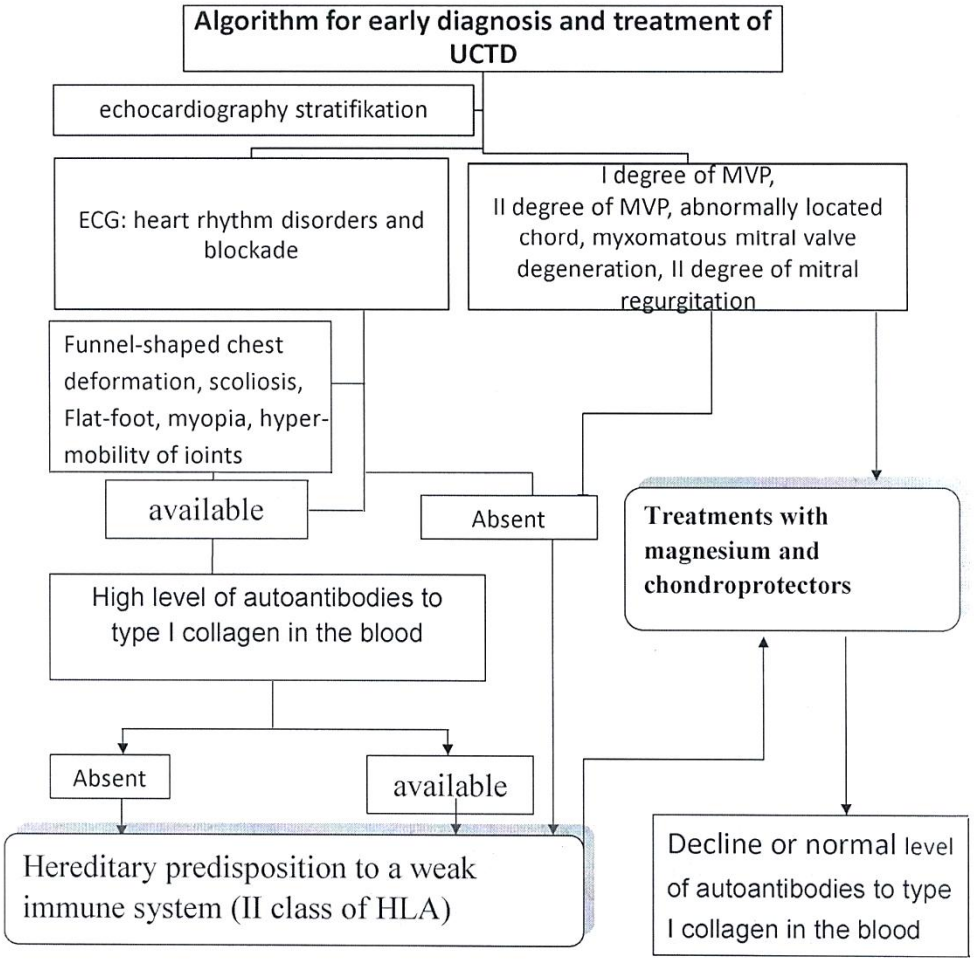

Figure 3. Algorithm for early diagnosis and treatment of UCTD

The clinical and immunological efficacy of drugs containing magnesium, chondroitin sulfate and glycosaminoglycan with UCTD was studied. It is known that Mg^{+2} is part of the main substance of connective tissue and is involved in the regulation of its metabolism. This dictates the need to include Mg^{+2} ions in the course of therapy for patients with UCTD. Chondroitin sulfate has a tropism for cartilaginous tissues initiates the fixation process the sulfur in the synthesis of chondroitin - sulfuric acid, which in turn promotes calcium deposition in bones. Stimulates the formation of proteoglycansand collagen type I and II, and also protects the cartilage matrix from enzymatic cleavage (by suppressing the activity of hyaluronidase) and from the damaging effect of free radicals; maintains viscosity of synovial fluid. Glucosamine makes up for the natural deficiency of glucosamine, stimulates the production of hyaluronic acid and complex proteoglycans. Additional inclusion of chondroitin sulfate and glucosamine glycan preparations to magnesium preparations according to the scheme, it contributed to an even greater increase in the effectiveness of treatment. Studies have shown the high efficiency of the proposed treatment methods UCTD. When using these drugs, the level of antibodies to type 1 collagen was statistically significantly decreased by 2.6 ($P < 0.001$).

Based on the diagnostic and therapeutic methods, we compiled an algorithm for the early diagnosis and treatment of UCTD (fig. 3).

6. Conclusions

Thus, diagnostics UCTD is considered odes them from complex branch of medicine s. To him are not only rare monogenic forms, but also a number of genetically heterogeneous, but close in their phenotypic and clinical manifestations of the disease. Based on the principles of the algorithm underlying the diagnosis of various forms of UCTD, it is recommended to check the genetic predisposition in patients with signs of internal and external phenotypes of dysplasia of the disease and determine the titer of autoantibodies to type I collagen. Application of the proposed a method of treatment with magnesium preparations and chondroprotectors, makes it possible to restore impaired collagen synthesis and improve the structure of connective tissue.

This, in turn, will make it possible to correctly determine the indications for medical consultation of patients, give recommendations on family planning, optimize early diagnosis, predict the outcome of the disease, see a single

systemic defect in connective tissue and conduct dispensary registration.

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