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Indicators of Hydroxyprolin and Mineral Imbalance in Children with Clinical Manifestations of Connective Tissue Dysplasia

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Abstract: Connective tissue dysplasia (CTD) is a unique ontogenetic anomaly body development, which is one of the complex topics with insufficient number of researches have been done in modern medicine and is the morphological basis of the functional changes in cardiac activity. We studied 115 children of preschool and school age with connective tissue dysplasia and small heart development abnormalities. A high frequency of occurrence of external phenotypic markers of connective tissue dysplasia syndrome (CTDS) and stigma of embryogenesis was revealed. An increase in the average level of HOPof spine in blood serum in children with Minor Cardiovascular Development Abnormalities (MCDA)in combination with cardiovascular pathology and patterns characterizing the relationship of the clinical manifestations of the disease and mineral imbalance has been established.

Keywords: connective tissue dysplasia, small heart developmental abnormalities, hydroxyproline, microelements, children.

Introduction

The basis of the development of many heart abnormalities is heart connective tissue dysplasia (HCTD). Despite the great interest in recent years to the syndrome of heart connective tissue dysplasia, many issues regarding the formation of cardiovascular pathology in children with cardiac manifestations of connective tissue dysplasia (CTD) remain poorly understood to date. CTD is a unique ontogenetic anomaly of the development of the body, which is one of the complex topics with insufficient number of researches have been done in modern medicine [10, 12]. These anomalies are the morphological basis of functional changes in cardiac activity, while organic lesions of the heart can aggravate their prognosis [4,8].

One of the most comprehensive definitions of CTD is - genetically determined disorder in the development of connective tissue, characterized by defects in the fibrous structures and the ground substance of the connective tissue, leading to a disorder of homeostasis at the tissue,

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organ and organism levels, in the form of various morphological and functional disorders of visceral and locomotor organs with a progressive course and defines the features of associated pathology, as well as pharmacokinetics and pharmacodynamics of drugs [5, 7].

Minor Cardiovascular Development Abnormalities (MCDA) are one of the manifestations of CTD, so they can be combined with other signs of it. MCDA in children is a fairly common condition. According to different authors, MCDAoccurs from 2,2 to 10% of cases in children with pathology of the cardiovascular system - in 10–25% of cases (up to 68.9%, depending on the contingent of subjects) [2, 9].

The aim of the researchis to study the relationship of the clinical manifestations of dysplasia of the connective tissue of the heart with indicators of the level of hydroxyproline and an imbalance of microelements.

Materials and research methods

We studied 115 preschool and school-age children who received inpatient treatment in the departments of cardiac rheumatology of the Children's Clinical Hospital №4 of Tashkent city and the Clinic under Tashkent Medical Institute. Of these, 95 children with CTD and MCDA and 20 practically healthy children of a similar age who made up the control group. Of the 95 children with CTD, 55 made up the group I — with cardiovascular pathology against the background of minor abnormalities of the heart and group II was constituted by 40 children —without cardiovascular pathology against the background of minor abnormalities of the heart.

The external and internal phenotypic features, the age-sex structure, the nature of complaints, as well as the characteristics of the markers of connective tissue metabolism were studied.

Results and its discussion. The study of the age category in the studied groups of children with MCDA showed that the majority of patients were teenagers from 8 to 12 and 12-16 years old while the group of practically healthy children was made up of mostly young children and adolescents of 12-16 years old (Fig. 1).

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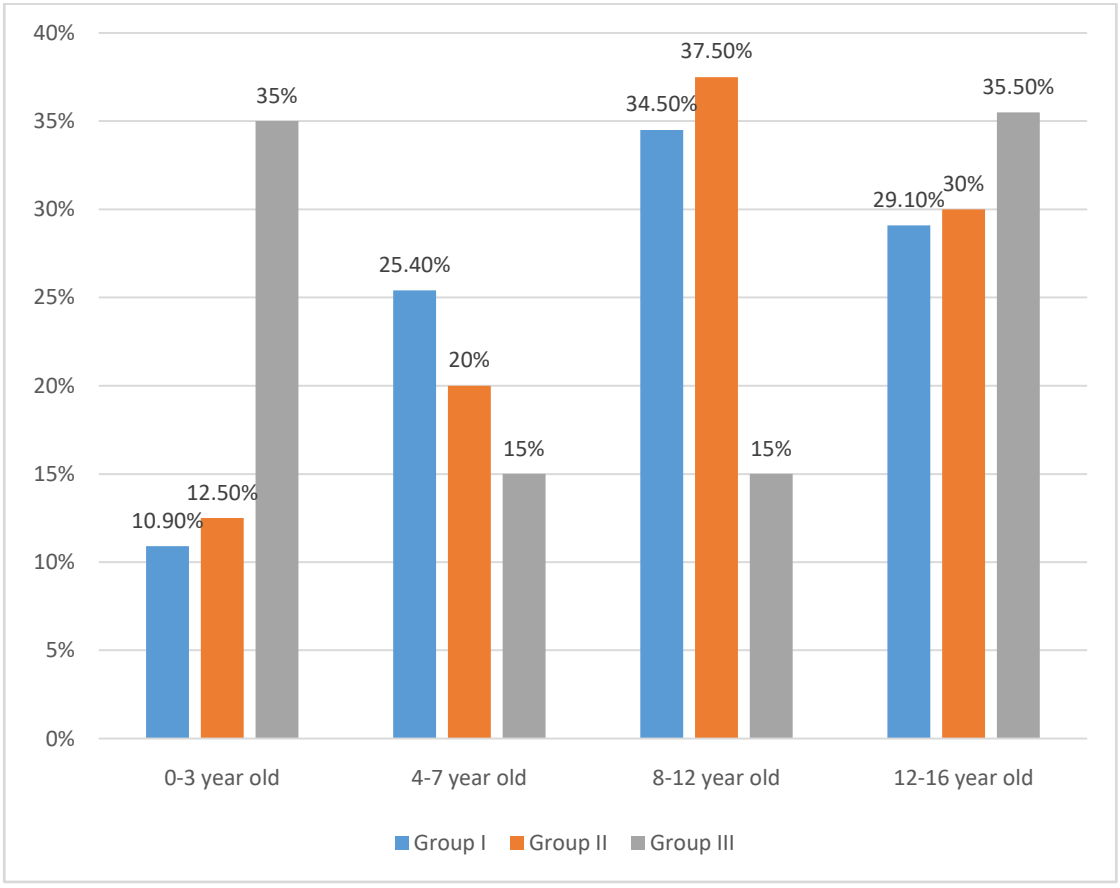

Fig. 1. Age categories of the examined patients

The analysis of gender differences among the examined children with MCDA in combination with cardiovascular pathology and without cardiovascular pathology revealed a predominance of the proportion of boys - 60% and 52.5% (Fig. 2)

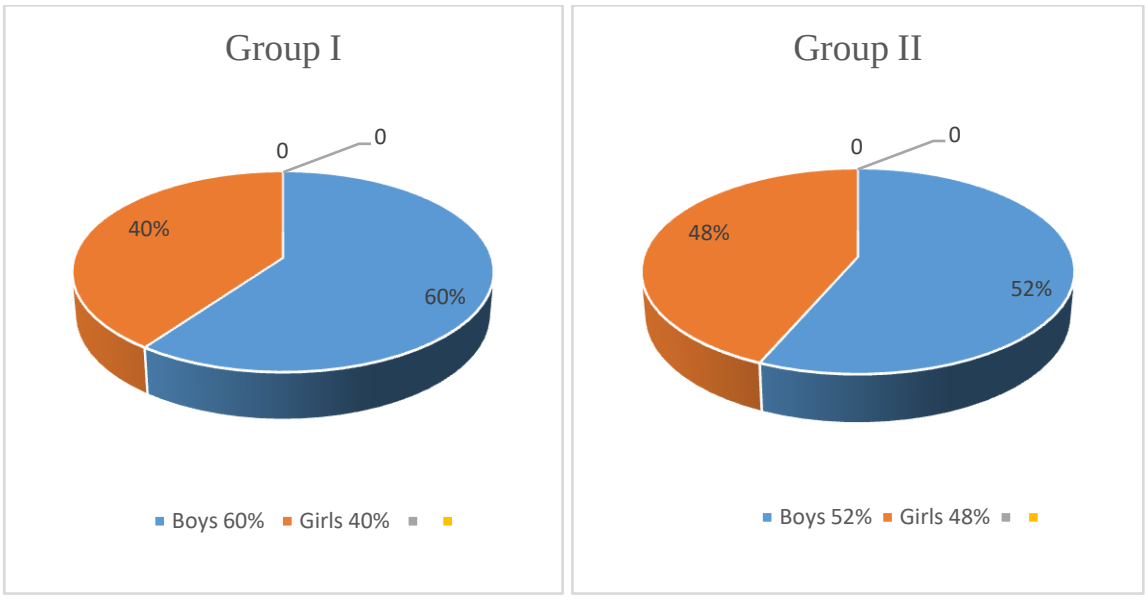

Fig. 2.The distribution of the examined patients depending on gender.

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The clinical picture in children with minor abnormalities in the development of the heart is quite diverse. Its manifestations often begin in adolescence. An analysis of complaints in patients with MCDA shows that children with MCDA, weighed down by cardiovascular pathology, presented significantly more often complaints. The leading cardiovascular pathology in the children with MCDA examined by us was arrhythmic syndrome (Table 1).

Table 1.

Characterization of the frequency of complaints in patients with MCDA

Complaints	I-group(n=55)	II –group(n=40)
Heartfailure	39 (70,9%)	14 (35,0%)
Cardialgia	21 (38,2%)*	9 (22,5%)
Palpitation	40 (72,7%)*	17 (42,5%)
Headache	29 (52,7%)**	9 (22,5%)
Dizziness	16 (29,1%)	8 (20,0%)
Bad appetite	23 (41,8%)	13 (32,5%)
Fatigue	50 (90,9%)*	21 (52,5%)
Apathy	19 (34,5%)**	5 (12,5%)
Thefeelingof "chilliness"	21 (38,1%)*	11 (27,5%)
Cold hands	17 (30,9%)	10 (25,0%)

Note: * - reliability ($p < 0.01$) between group I and II of patients with DST, ** - reliability ($p < 0.05$) between group I and II of patients with DST

Complaints of aching pains in the heart, a feeling of palpitations, cephalalgia and dizziness, increased fatigue, a feeling of "chilliness" and cold hands at room temperature were more often presented by children with a combination of MVP and LVAC. Dizziness appeared when the body position changed (from the wedge to orthosis) and with a sharp turn of the head in 2/3 of the children. Among other complaints, 15.8% of the general population of children with MCDA also had dyspeptic disorders in the form of abdominal pain, not always associated with eating, heartburn, heaviness in the right hypochondrium, fast satiety, and constipation.

Pallor of the skin was observed in 41.0% of children with MVP, in 32.0% with LVAC and in 47.4% with a combination of MVP and LVAC.

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To identify the informative value of phenotypic signs in the diagnosis of cardiovascular pathology, we have made an evaluation of external and visceral signs of systemic involvement of connective tissue in children (Table 2).

Table 2.
Evaluation of external and visceral signs of systemic involvement of connective tissue in children

Signs	Overall score of group I	Overall score of group II
Osteo-articular:		
Pectusexcavatum	98	84
Keeled chest	30	22,5
Dolichostenomelia	40	17,5
Scoliosis	96	56
Kyphosis	64	28
Triple-jointedness	100	72
Halluxvalgus	30	30
Arachnodactyly	15	0
Other chest deformation	16,5	18
Flat feet	50	35
Ectodermal (skin, teeth):		
Hyperpigmentation of the skin over the spinous processes of the vertebrae	56	54
Increasedskinextensibility	58,5	42
Ecchymoses, petechiae, nosebleeds	69	57
Atrophicstriae	24	4,5
"Callosity" on the back surface of the feet	21	15
Visiblevenousnetwork	16	15
Teethingabnormalities	14	18
Muscular:		
Muscular hypotension	82,5	60
Visceral signsReflux disease		
Severe / moderateosteopenia	100	58
MVP (all types) /other MCDA	100	62
Other MCDA	42	31,5
Biliary dyskinesia against the background of an abnormality of the gallbladder	57	39

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Refluxdisease	32	25

Analysis of the obtained data shows that the most characteristic phenotypic signs in children with MCDA and cardiovascular pathology are: funnel chest deformity, keeled chest deformity, dolichostenomelia, scoliosis, kyphosis, joint hypermobility, muscle hypotension, osteopenia, MVP (all types) / others MCDA.

The main component of connective tissue is collagen, accounting for more than 30% of the total mass of body proteins, with 50% of it being in bone and tendon-muscle tissue [5]. The amino acid composition of collagen has been well studied. However, specific markers of this protein are proline and hydroxyproline [7]. As a result of the breakdown of collagen, peptides are excreted in the urine or cleaved by specific enzymes to amino acids. Hydroxyproline (HOP) is an amino acid that is part of collagen, a protein of bone and connective tissue, which is an indicator of their metabolic rate, released from peptides appears mainly in the blood, urine, and part of it is oxidized in the liver [1,7]. Its increase is observed in diseases associated with the breakdown of connective tissue. The appearance of HOP in blood serum and urine is the result of catabolic processes in the connective tissue (CT) and may reflect the degree of activity of this process [6].

A study of the serum hydroxyproline content showed that the level of free HOP in the blood in patients with MCDA and cardiovascular pathology was significantly ($P<0.05$) higher compared to patients with MCDA without cardiovascular pathology and amounted to 29.4±2.4 μmol/l and 20.2±1.5 μmol/l, respectively. HOP values in healthy children amounted to - 16.1±1.2 μmol/l (Tab.3).

Table 3.

The content of HOP in serum in children of the studied groups (M ± m; μmol/l)

Groups of patients	Average level of HOP
MCDA and cardiovascular pathology	29,4 ± 2,4*
MCDA without cardiovascular pathology	20,2 ± 1,5
Healthy children	16,1 ± 1,2

Note: * - reliability between indicators of the compared groups ($P <0.05$).

The content of microelements selenium, copper, manganese and magnesium in blood serum was studied in 30 examined children, 12 of them with MCDA and

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cardiovascular pathology, 8 with MCDA without cardiovascular pathology and 10 practically healthy children. It was established that the microelement profile in children with MCDA complicated by cardiovascular pathology, compared with children with MCDA without cardiovascular pathology, is characterized by a decrease in the concentration of selenium (Se) ($p>0.01$), copper (Cu) ($p>0.01$), manganese (Mn) ($p>0.01$) and magnesium (Mg) ($p<0.05$) in blood serum (Table 4).

Table 4.
Indicators of microelements in the blood in study groups

(mcg/g)	Se	Cu	Mn	Mg
Children with MCDA and cardiovascular pathology (I-group) (n=12)	0,052±0,015	0,493±0,076	0,0056±0,0009	0,508±0,092
Children with MCDA without cardiovascular pathology (II – group) (n=8)	0,067±0,014	0,592±0,071	0,0073±0,0016	0,585±0,083
Control group (III –group) (n=10)	0,178±0,055	0,918±0,172	0,033±0,035	0,845±0,062
P 1:2	> 0,01	> 0,01	> 0,01	<0,05
P 1:3	< 0,05	< 0,05	> 0,01	< 0,05
P 2:3	> 0,01	< 0,05	< 0,05	> 0,01

Note: P is the reliability between the indicators of the examined groups of children.

Analyzing the content of selenium in groups of patients with MCDA and cardiovascular pathology, and the control group, a significant deficiency of this microelement was revealed ($p <0.05$). With a low selenium content in mothers during pregnancy, infant mortality increases and the number of children with various deformities increases. The relationship between the deficit of Se and Cu is noted.

With copper deficiency, disorders of the synthesis of connective tissue, functional disorders of the nervous system, impaired liver function, decreased immune-biological reactivity, damage to the eyes, blood-forming organs, allergic contact dermatitis, and bone formation disorders are noted. It is known that both inadequate and excessive intake of copper in the body can lead to a violation of

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vital functions, especially during pregnancy. Analyzing the copper content in the compared groups, a comparative copper deficiency was revealed in both groups of children with MCDA, with relatively stable rates in the norm. In children with MCDA, weighed down by cardiovascular pathology, a significant ($p < 0.05$) decrease in the level of copper was revealed in comparison with the control group.

The importance of magnesium in the development of connective tissue disorders, in the treatment and rehabilitation of patients with Hip Dysplasia is described in a number of works [3, 11]. Today it is known that magnesium ions are involved in the processes of connective tissue metabolism, control the normal functioning of cardiomyocytes at all levels of subcellular structures, and are involved in the regulation of myocardial contractile function. At the same time, intracellular magnesium deficiency increases the activity of the sinus node, which shortens the time for atrioventricular conduction, reduces absolute refractoriness and lengthens the relative refractoriness, which can lead to the development of various rhythm disturbances. An analysis of the content and dynamics of the levels of magnesium and manganese shows that they are similar to the first two micro-elements and can serve as a kind of indicator of the course of the main process involving the immune system in the pathological process, which indicates the depletion of protective resources and leads to the development or aggravation of the pathological process.

Conclusions

1. The analysis of the clinical and phenotypic manifestations of connective tissue dysplasia syndrome in children with minor heart development abnormalities revealed that children with MCDA, weighed down by cardiovascular pathology, reliably more often complained;
2. A high frequency of occurrence of external phenotypic markers of CTDS and stigma of embryogenesis was revealed. The relationship between the profiles of the external stigma of connective tissue dysplasia and small heart abnormalities has been established;
3. An increase in the average level of HOP in blood serum was noted in children with MCDA in combination with cardiovascular pathology, in comparison with healthy children;
4. The regularities characterizing the relationship of the clinical manifestations of diseases and mineral imbalance are established. Some pathogenetic lines of the development of the pathological process in children with dyselementoses were determined. It is proved that the state of elemental status is an important informative criterion for assessing the severity of the underlying disease.

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