Volume 20 Issue 32
Originally issued as F6



Global Journal of Medical Research: F
Diseases
Volume 20 Issue 6 Version 1.0 Year 2020
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

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GJMR-F Classification: NLMC Code: QS 532.5.C7



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Relationship of Clinical Manifestations of Heart Connective Tissue Dysplasis with Indicators of Hydroxyprolin Level and Mineral Imbalance

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Abstract- **Connective tissue dysplasia is a unique ontogenetic anomaly in the development of the body, which is one of the complex, far from studied questions of modern medicine, and is the morphological basis of 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 was revealed for the syndrome of dysplasia of the connective tissue of the heart and stigma of embryogenesis. An increase in the average level of hydroxyproline in blood serum in children with small abnormalities of the development of the heart in combination with cardiovascular pathology and patterns characterizing the relationship of the clinical manifestations of the disease and mineral imbalance has been established.**

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I. Introduction

Despite the great interest in recent years in the connective tissue dysplasia syndrome, many issues regarding the formation of cardiovascular pathology in children with cardiac manifestations of connective tissue dysplasia remain to date poorly understood. The development of many heart abnormalities is based on dysplasia of the connective tissue of the heart. Connective tissue dysplasia is a unique ontogenetic anomaly of the body's development, which is one of the complex, far from studied questions of modern medicine [10, 12]. These anomalies are the morphological basis of functional changes in cardiac activity, and with organic lesions of the heart can aggravate their prognosis [4, 8].

One of the most comprehensive definitions of connective tissue dysplasia is a genetically determined disorder in the development of connective tissue, characterized by defects in the fibrous structures and the main substance of the connective tissue, leading to a disorder of homeostasis at the tissue, organ and organism levels, in the form of various morphological and functional disorders, visceral and locomotor organs with progressive the course and determining features of associated pathology, as well as pharmacokinetics and pharmacodynamics of drugs [5, 7].

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Small abnormalities of the development of the heart is one of the manifestations of connective tissue dysplasia, so they can be combined with other signs of it. Small abnormalities in the development of the heart in children are a fairly common condition. According to various authors, small abnormalities of heart development occur 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 study is 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 trace elements.

II. Materials and Methods

We studied 115 preschool and school-age children who received inpatient treatment in the departments of cardiac rheumatology of the Central Clinical Hospital No. 4 and the Tashkent Medical Institute, Tashkent Of these, 95 children with connective tissue dysplasia and small abnormalities in the development of the heart and 20 practically healthy children of a similar age who made up the control group. Of the 95 children with connective tissue dysplasia, 55 comprised group I — with cardiovascular pathology against the background of small abnormalities of the heart and 40 children — group II without cardiovascular pathology against the background of small abnormalities of the heart.

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

III. Results and Discussion

The study of the age category in the studied groups of children with small abnormalities of heart development showed that the majority of patients were teenagers from 8 to 12 and 12-16 years old, in the group of practically healthy children were mostly young children and adolescents 12-16 years old (Fig. 1).

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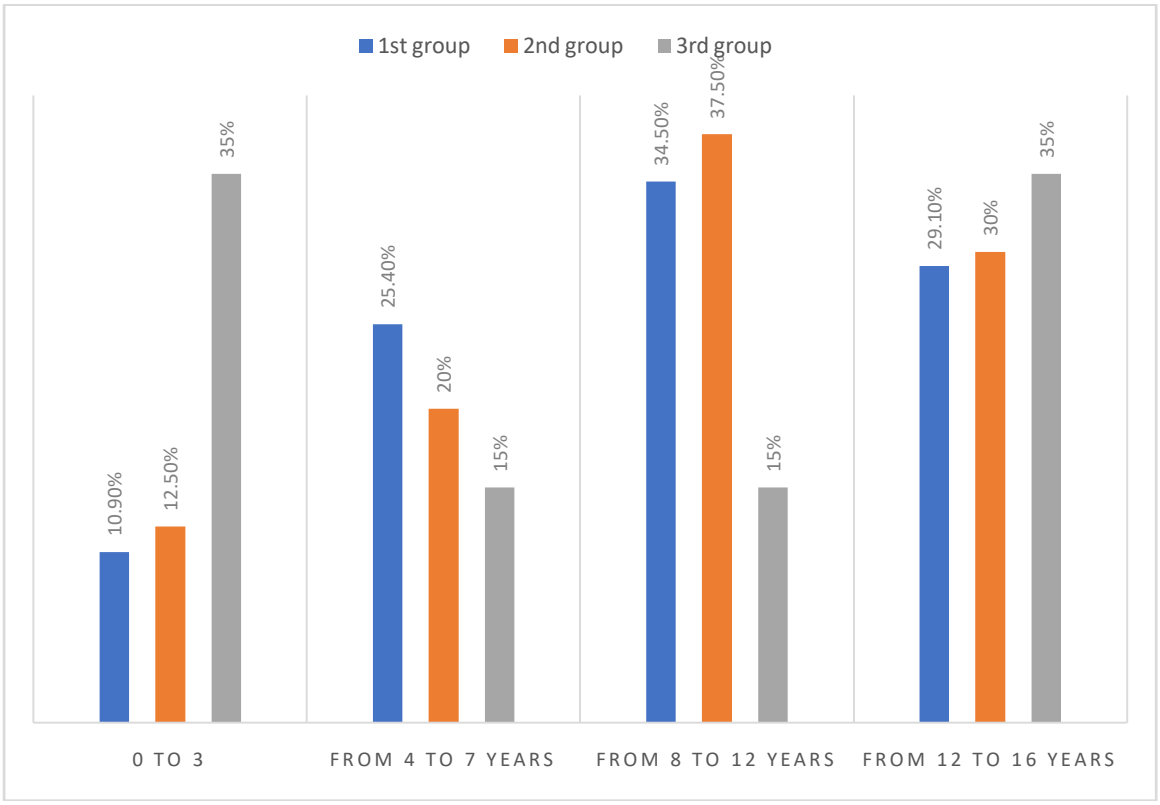


Fig. 1: Age categories of the examined patients

When analyzing gender differences among the examined children with small abnormalities of the heart, in combination with cardiovascular pathology and without cardiovascular pathology, the prevalence of boys was revealed - 60% and 52.5% (Fig. 2).

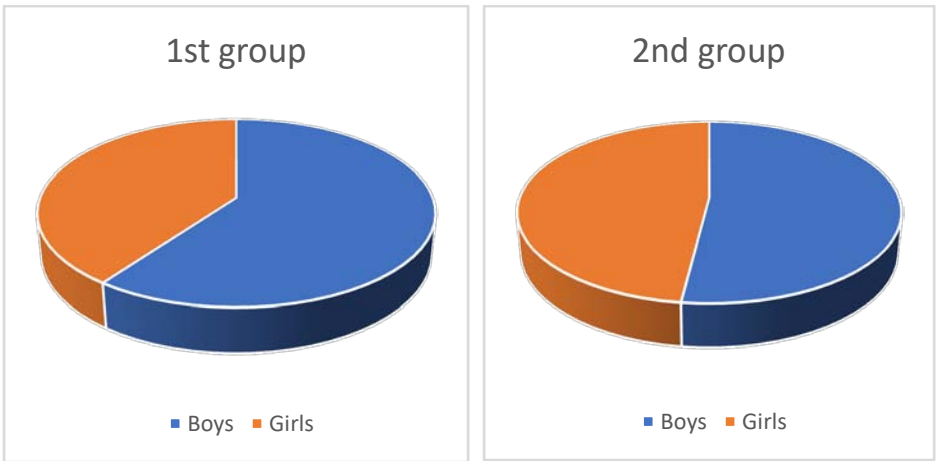


Fig. 2: The distribution of the examined patients depending

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

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Table 1: Characterization of the frequency of complaints in patients with minor abnormalities of the heart

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

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

Children with a combination of mitral valve prolapse and abnormal left ventricular complaints more often complained of “aching” pains in the heart area, a feeling of palpitations, cephalgia and dizziness, fatigue, a feeling of “coldness” and cooling hands, at room temperature. 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 small abnormalities of heart development also had dyspeptic disorders in the form of abdominal pain, not always associated with eating, heartburn, heaviness in the right hypochondrium, fast satiety, constipation.

Pallor of the skin was observed in 41.0% of children with mitral valve prolapse, in 32.0% with abnormal left ventricular passages and 47.4% with a combination of mitral valve prolapse and abnormal left ventricular passages.

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

Table 2: Scoring of external and visceral signs of systemic involvement of connective tissue in children

Signs	Total points in group I	Total points in group II
Osteoarticular		
Funnelchestdeformity	98	84
Keeledchestdeformity	30	22,5
Dolichostenomelia	40	17,5
Scoliosis	96	56
Kyphosis	64	28
joint hypermobility	100	72
Halluxvalgus	30	30
Arachnodactyly	15	0
Otherchestdeformity	16,5	18
Flatfeet	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
"Corns" on the back surface of the feet	21	15
Visiblevenousnetwork	16	15
Teethingabnormalities	14	18
Muscular:		
Musclehypotension	82,5	60
Visceralsymptoms		
Osteopeniasevere / moderate	100	58
Mitral valve prolapse (all types) / other minor abnormalities of the heart	100	62
Other minor abnormalities of the heart	42	31,5
Biliary dyskinesia against the background of an abnormality of the gallbladder	57	39
Refluxdisease	32	25

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An analysis of the obtained data shows that the most characteristic phenotypic signs in children with small abnormalities of the heart and cardiovascular pathology are: funnel chest deformity, keeled chest deformity, dolichostenomelia, scoliosis, kyphosis, hypermobility of joints, muscle hypotension, osteopenia, mitral valve prolapse all types) / other small abnormalities of the development of the heart.

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 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 is found mainly in blood and 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 hydroxyproline in blood serum and urine is the result of catabolic processes in the connective tissue and may reflect the degree of activity of this process [6].

A study of the serum hydroxyproline content showed that the level of free hydroxyproline in the blood in patients with small abnormalities of the heart and cardiovascular pathology was significantly ($P < 0.05$) higher compared with patients with small abnormalities of the heart without cardiovascular pathology and amounted to - 29, 4 ± 2.4 μmol / L and 20.2 ± 1.5 μmol / L, respectively. The indicators of hydroxyproline in healthy children amounted to 16.1 ± 1.2 μmol / L (table. 3).

Table 3: The serum hydroxyproline content in children in the studied groups (M ± m; μmol / L)

Groupofpatients	The average level of hydroxyproline
Small abnormalities of the development of the heart with cardiovascular pathology	29,4 ± 2,4*
Small abnormalities of the development of the heart without cardiovascular pathology	20,2 ± 1,5
Healthychildren	16,1 ± 1,2

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

The content of trace elements of selenium, copper, manganese and magnesium in blood serum was studied in 30 examined children, 12 of them with small abnormalities of the heart and cardiovascular pathology, 8 with small abnormalities of the heart without cardiovascular pathology and 10 practically healthy children. It was found that the microelement profile in children with small abnormalities of the heart, complicated by cardiovascular pathology, compared with children with small abnormalities of the heart 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 trace elements in the blood in the studied groups

(mcg / g)	Se	Cu	Mn	Mg
Children with small abnormalities of the development of the heart and CVP (I-group) (n = 12)	0,052±0,015	0,493±0,076	0,0056±0,0009	0,508±0,092
Children with minor abnormalities of the heart without CVP (group II) (n = 8)	0,067±0,014	0,592±0,071	0,0073±0,0016	0,585±0,083
Controlgroup (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 small abnormalities of the development of the heart 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

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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 immunobiological 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 vital functions, especially during pregnancy. By analyzing the copper content in the compared groups, a comparative copper deficiency was revealed in both groups of children with small heart development abnormalities, with relatively stable rates being normal. In children with small abnormalities of the heart, 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 connective tissue 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 trace 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.

IV. Conclusion

1. The analysis of clinical and phenotypic manifestations of connective tissue dysplasia syndrome in children with small cardiac abnormalities revealed that children with minor cardiac abnormalities burdened by cardiovascular pathology presented significantly more often complaints;
2. A high frequency of occurrence of external phenotypic markers of dysplasia of the connective tissue of the heart 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. There was an increase in the average level of hydroxyproline in blood serum in children with small cardiac abnormalities in combination with cardiovascular pathology, compared 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 dyslementoses 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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