CONSERVATIVE TREATMENT FOR SYNDROMAL FORM OF ORONAL CHEST DEFORMITY IN CHILDREN

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Abstract*. Pectus excavatum deformity (PCD) is one of the complex pathological conditions characteristic of the pediatric orthopedic spectrum. According to a number of studies mentioned in the literature, it is observed in 0.4-2.25% of children, which accounts for up to 91% of all congenital chest deformities [3, 4 , 10]. Despite significant advances in the treatment of this disease, problems related to its diagnosis and treatment remain relevant. As the child grows, these problems can worsen, leading to compression of the internal organs of the chest and disruption of their functioning. Obvious cosmetic defects and deterioration in cardiorespiratory condition observed in older children with CAD can cause feelings of isolation, inadequacy and difficulty in social adaptation, which in turn negatively affects the mental development of the child [4, 9].*
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However, treatment with VDHA and the high incidence of complications are significantly associated with the manifestations of chondrodysplasia of the costal cartilages. Collagen, the main element of connective tissue, plays an important role in the body, providing structural support for skin, bones, tendons, cartilage, blood vessels and teeth [1,2,5,6]. Its association with other proteins, such as elastin, is stabilized by covalent cross-links, including intracellular (within a single transcollagen unit) and intermolecular (between individual transcollagen units) [2, 5, 7 , 8]. Glycine, proline and lysine are the main amino acids that make up collagen, and hydroxyproline and hydroxylysine , rarely found in other proteins, are also present in its structure. Collagen biosynthesis depends on proteolytic activity, mainly on proteinglycan , the second main component of connective tissue, consisting of polysaccharide and protein components [6]. Protein glycans, which are the main substance of connective tissue, determine its viscoplastic properties.

Changes in collagen maturation can be caused by various metabolic disorders, including structural defects and changes in the process of post-translational maturation [2, 6, 7, 8]. However, data on the impact of these abnormalities on collagen in the case of VDHA are limited, and an important question remains how to effectively restore proteolytic activity through corrective therapy.

The purpose of the work is to quantitatively study amino acids in the blood and urine in the syndromic form of VDHA in children with the development of anti-relapse therapy.

Material and methods: We examined 150 children aged 4 to 18 years suffering from pectus excavatum deformity (PCD). Of these, 99 (66%) are girls, and 51 (34%) are boys. Interestingly, the ratio between girls and boys was 1:1.6. 64 (42.6%) patients were diagnosed with stage II VDHA, including 5 patients with relapses after previous operations (sternochondrotomy with external fixator fixation). 86 (57.4%) patients were diagnosed with stage III VDHA. During the examination, various clinical studies were carried out: a complete blood count, biochemical tests using tandem mass spectrometry (TMS) and gas chromatography-mass spectrometry to quantify proline in the blood, hydroxyproline and glycosaminoglycan in the urine, as well as

morphological and radiation methods, including magnetic resonance imaging (MRI) and chest radiography, spirography, electrocardiogram and echocardiogram.

To study hydroxyproline, we analyzed both the free and bound forms of this component, the latter including peptides with a mass of 700 D. The total content of hydroxyproline was expressed in milligrams per 100 ml of urine, and the content of each of its forms was expressed as a percentage of the total content. For analysis, we used a morning urine sample, which was fractionated on a 50x70 column with Sephadex. The optical density of urine was recorded at the exit of the column at a wavelength of 280 nm. Normative values for hydroxyproline were established based on a urine test of 24 healthy children of similar age. For statistical analysis, we used the Medstat program with Student's t test, but no statistically significant differences in hydroxyproline excretion were found.

Results and discussion: The research results revealed (Table 1) that between the isolated and syndromic forms of VDHA, significant differences were found in the content of free hydroxyproline, which was lower in Marfan syndrome ($p < 0.05$) than in cases of isolated forms and in the ratio of free hydroxyproline to peptide-bound (>700D) with the same statistical significance. Initially obtained data, analyzed in the aspect of connective tissue dysfunction, indicate an increase in the release of hydroxyproline in children with VDHA, motivated by changes in metabolic processes (Table 1). Compared with healthy children of the same age, the content of free hydroxyproline, and in terms of creatinine, both in isolated and in syndromic forms of VDHA was significantly lower ($p < 0.01$ and 0.05, respectively) the relative content of free hydroxyproline (Table 2) when isolated

Table 1

Initial indicators of hydroxyproline in urine in children with VDHA (M ± m)

Age	Norm	Boys	Girls	R
4-7	36.76 ± 0.16	51 ± 1.4	65.21 ± 1.4**	>0 , 0 5
8-1 8	58.8 2± 0.15	76.47 ± 1.3***	90.04 ± 1.3	>0 , 0 5

Note: * - p; ** - $p < 0.1$

In the form of VDHA and VDHA, against the background of Marfan syndrome - lower ($p < 0.05$ and <0.01, respectively). Relative content of bound hydroxyproline in peptides (<700D) and ratio of peptide bound hydroxyproline in peptides with molecular weight <7000 and peptide-bound ratio hydroxyproline (<700D/<700D) for isolated VDHA and VDHA against the background of Marfan syndrome remained within normal limits.

In children with an isolated form of pectus excavatum (PVD), the ratio of free hydroxyproline to peptide-bound (<700D) remained within the normal range. However, in children with CDHA accompanied by Marfan syndrome, this ratio was lower than normal ($p < 0.001$). The data obtained indicate a reduced content of total hydroxyproline in children with CDHA, regardless of the form. This indicates a possible decrease in collagen synthesis in this pathology.

However, according to the available data in the literature, in patients with Marfan syndrome, but without pectus excavatum (PVD), hydroxyproline excretion is either increased or within the normal range [5]. The results of our studies indicate that reduced excretion of hydroxyproline in urine in Marfan syndrome is associated specifically with the presence of VDHA. Changes in free and peptide-bound hydroxyproline in syndromic forms of VDHA indicate a specific disruption of the process of collagen degradation in these patients. This may be caused by

both changes in the activity of collagenolytic proteases and the structural features of collagen fibrils. It is interesting to note that disturbances in the ratio of free and peptide-bound hydroxyproline are associated with the presence of the syndromes under consideration, and, apparently, do not depend on the presence or absence of VDHA.

Table 2

Initial indicators of hydroxyproline in urine in children with VDHA (M ± m)

Group number	Total hydroxyproline (mg/10ml)	Ratio of hydroxyproline to creatine (mmol per 1 mol)	Free hydroxyproline (% of total hydroxyproline)	Bound hydroxyproline (% of total hydroxyproline)	Ratio of free and bound hydroxyproline (>700 D)	Peptide bound ratio hydroxyproline (>700 D)
1	2.6 ± 0.2	16.2 ± 1.5	1.6 ± 0.2	25.3 ± 2.4	0.06 ± 0.009	0.36 ± 0.05
2	2.4 ± 0.4	11.1 ± 2.7	1.0 ± 0.07	30.2 ± 2.9	0.03 ± 0.005	0.44 ± 0.07
3	4.9 ± 0.4	33.4 ± 3.4	2.6 ± 0.1	26.6 ± 1.4	1.0 ± 0.007	0.38 ± 0.03
Healthy children	4.9 ± 0.8	32.2 ± 1.8	2.6 ± 0.4	32.0 ± 2.4	0.08 ± 0.006	0.49 ± 0.05

These results are confirmed by the indicators of hydroxyproline excretion obtained in patients with Marfan syndrome without pectus excavatum (Pectus excavatum) and their comparison with the indicators in patients suffering from Marfan syndrome against the background of this syndrome. With the exception of significant differences in the total hydroxyproline content and the ratio of hydroxyproline to creatinine ($p < 0.05$), the excretion rates of hydroxyproline in children in the second group and in those who do not suffer from this syndrome were similar. A higher content of free hydroxyproline was found compared to the norm ($p< 0.001$), as well as a lower content of peptide-bound hydroxyproline (<700D) ($p<0.001$ and $p<0.05$). Accordingly, the ratio of free to peptide-bound hydroxyproline was 4-5 times higher than normal ($p< 0.001$ and $p<0.01$), and the value of the peptide-bound ratio hydroxyproline (<700D/<700D) was below normal ($p<0.05$).

Tandem mass spectrometry was used to analyze amino acid levels in the blood. In the case of this pathology, a decrease in the level of proline (normal 100-645) and glycine (normal 150-150e + 0.03), as well as other amino acids, is most often observed. At an early age, with compensated metabolic disorders and a properly selected treatment strategy, including corrective bandages, massage, therapeutic pine-salt baths, exercises for correcting posture and taking vitamin complexes (such as complivit, oligovitis, vitamin B6), as well as physical therapy. There is a positive trend in the regression of connective tissue changes. However, as you age, longer and more intensive treatment may be required. The use of vitamin preparations (for example, ascorbic acid), chondroitin sulfate, massage, physical therapy, breathing exercises and other methods that stimulate metabolic processes has a beneficial effect on the restoration of ligaments in the area of the sternocostal complex.

Therefore, increased levels of free hydroxyproline and decreased levels of peptide-bound (<700D) hydroxyproline are likely characteristic of this syndrome, despite its varied manifestations, and are not associated with the presence of pectus excavatum per se. The indicators of hydroxyproline excretion in the urine in patients with an isolated form of VDHA 6-8 months after thoracoplasty (group 3) did not differ statistically significantly from the indicators of healthy children of the same age, which indicates restoration of collagen metabolism. After conservative treatment, normalization of the level of amino acids in the blood (proline , lysine, glycine, etc.) was observed, which was accompanied by normalization of collagen formation. This can probably be explained either by a “switching” of the genetic apparatus of chondrocytes to normal activity, or by competitive replacement of dysplastic cartilage cells with normal ones.

The conducted studies are a reliable diagnostic tool for determining Marfan syndrome and contribute to the correct prescription of drug correction in the postoperative period of treatment of children with pectus excavatum deformity (PCD). The use of drug correction for the syndromic form of VDHA after surgery helps to strengthen the sternocostal complex and reduce the risk of relapse after removal of the metal plate.

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