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The Role of Connective Tissue Dysplasia in Post-Treatment Recurrences of Funnel Chest in Children

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Abstract

The article highlights the importance of biochemical investigations in children with thoracic cage whirl-like dysplastic deformities. Quantitative analyses of proline, hydroxyproline and glucosaminoglycans were carried out. The study was based on the examination results of 64 young children. The patients' medical history revealed that a whirlpool deformity was noted from an early age in 30 (58%) children, while in 12 (23%) patients, the disease manifested in the first year of life, In 10 (19%) children, the deformity appeared by the age of 3.

The patients were divided into groups according to age for analysis. It was found that, depending on the degree of connective tissue dysplasia observed in the patients, the biochemical markers shifted in a positive direction following treatment.

Keywords: Chest wall, funnel-shaped deformity, connective tissue dysplasia, child.

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1. Introduction

In children, a pectus carinatum is a complex pathology that negatively affects the internal organs of the chest and is a cosmetic defect. It is considered a pressing issue as it requires surgical intervention in all cases and can lead to postoperative recurrences. According to the international organization Chest Wall International Group (GWIG), chest wall funnel deformity "…accounts for 0.4–2.25% of cases in children and 90% of congenital chest wall deformities." This condition necessitates the development of modern diagnostic and comprehensive treatment measures to prevent postoperative complications of congenital chest wall deformities.

A number of studies are being conducted worldwide to improve the diagnosis and comprehensive treatment of funnel chest deformation (FCD), including determining the various severity levels of FCD by the thoracometric method and multispiral computed tomography (MSCT) by focusing on chest condition and the internal organ effects of deformity, thoracoplasty surgical procedures are being developed. Several surgical techniques for FCD have been proposed, including the D. Nuss operation.

Therefore, despite the variety of surgical treatment methods for FCD and the dynamic development of surgical approaches, recurrences continue to be observed. This is due to the lack of attention to connective tissue dysplasia (CTD) factors during the pre- and post-operative period, the lack of criteria for assessing its biochemical composition

and the morphological state of hyaline cartilage, as well as the absence of clear indications for removing fixators or the incorrect selection of their removal timing, and the therapy for stimulating connective tissue such as the development of connective tissue stimulat.

Significance of the study: To determine the association between whirlpool-like deformity of the chest wall in children and connective tissue dysplasia.

2. Methods

The study was conducted on 64 patients based on punch biopsy analyses. Of these, 49 were boys and 15 were girls. Of the total number of children (64), boys make up 49 (76.5%) and girls 15 (23.5%). By age, the patients were distributed as follows: 4–7 years – 12 (18.8%), 8–11 years – 21 (32.8%), and 12–18 years – 31 (48.4%). Grade II FCD was observed in 42 (65.6%) patients, and grade III FCD in 22 (34.4%) patients.

All patients underwent surgical procedures using the D. Nuss method. The thresholds for biochemical markers were determined for all patients using tandem mass spectrometry (TMS) and chromatomass spectrometry (CMS) to diagnose connective tissue dysplasia. Patients received prophylactic drug therapy to stimulate connective tissue, and their biochemical changes were examined.

3. Results and Discussion

ccording to the study results, the whirlpool-like deformity of the thoracic cage was found to be associated with connective tissue dysplasia based on the following examination findings.

The patients' medical history revealed that a whirlpool deformity was noted from an early age in 30 (58%) children, while in 12 (23%) patients, the disease manifested in the first year of life, In 10 (19%) children, the deformity appeared by the age of 3.

The T.I. Kadurina and L.N. Abakumova (2014) table was used to determine the degree of connective tissue dysplasia in children with FCD.

A scoring system based on skeletal-articular, ectodermal, muscular, and visceral signs was used to determine the degree of CTD in children with FCD.

Table 1

Preoperative indicators (scores) of CTD changes in the group with FCD

Groups		DCT (points)			
		Bone-joint	Ectodermal	Visceral	Total
4-7 years					
II- degree	B	15,3±1,15	2,8±0,28	1,3±0,2	P<0,05
n= 5	G	14,5±2,12	4,7±1,06	1,7±0,3	
III- degree	B	17,7±2,9	3,5±2,3	1,8±0,25	P<0,05
n=7	G	16,0±2,0	3,8±1,04	1,8±0,2	
8-11 years					
II- даража	B	12,1±2,9	2,5±1,2	1,5±0,6	P<0,05
n=11	G	15,0±1,4	5,7±3,8	2,7±1,06	
III- degree	B	15,3±1,7	3,6±1,7	1,5±1,05	P<0,05
n=10	G	20,5±3,5	5,2±0,3	2,7±1,06	
12-18 years					
II- degree	B	12,3±2,9	4,2±2,5	2,1±1,4	P<0,05
n=24	G	15,2±4,2	6,2±4,5	4,2±1,7	
III- degree	B	11,6±1,15	1,5±0,7	1,5±0,5	P<0,05
n=7	G	14,2±1,2	1,7±2,5	1,8±0,2	

According to the study protocol, prophylactic treatment to restore impaired bone turnover synthesis was administered to 39 (60.9%) patients with FCD before surgery. In 25 (39.1%) patients, the connective tissue–stimulating drug therapy was not completed in full.

One of the most noteworthy and important indicators for detecting changes in CTD is the blood proline level, which affects metabolic processes in connective tissue, a major component of the extracellular matrix. According to the data obtained from the preoperative period, the patients can be divided into groups with specific changes in blood proline composition and in those who received prophylactic CTD (see Table 2). Thus, in boys aged 4–7 years with grade II FCD, preoperative examinations revealed a decrease in blood proline levels, with an average reduction of 40.9% below the acceptable range. Proline plays a crucial role in the synthesis and breakdown of connective tissue, and this decrease is considered a factor associated with dysplastic changes in the context of impaired metabolic processes. Collagen synthesis in children of this age group is not sufficiently stable, which is why, for a number of reasons, CTD is more pronounced in patients of this age.

Table 2

Blood Proline Levels (M±m) in Children with CTD in the Presence or Absence of Preoperative Treatment for FCD

№	Indicators		Treated with BTD (n=19)		DCT is untreated (n=17)	
		Age	Boys (n=6)	Girls (n=0)	Boys (n=10)	Girls (n=1)
1	II degree FCD	4-7 years	152,4±23,26		82,3	
		8-11 years			109,5±17,6	
		12-18 years	349,4±43,36		151,5±28,9	
			(n=7)	(n=6)	(n=6)	(n=1)
2	III degree FCD	4-7 years	132,6±47,2	102	79,6±4,8	112
		8-11 years	160,03±42,2	166,1±3,53	97,6±10,3	
		12-18 years		325,8±45,5	-	-

As a result of prophylactic treatment in the preoperative period, the proline level in the blood of patients aged 12–18 decreased, with the mean value representing only 6.20%. Connective tissue formation and regeneration in this group are determined by age; connective tissue formation is completed and metabolic processes stabilize.

In children aged 4-7 with grade III FCD, a 15.91% decrease in blood proline levels was observed compared to the preoperative period after one year of treatment, in patients aged 8-11 years, a decrease was found compared to the normal value of 42.96%. In turn, for girls, this indicator was 18.28%, for patients aged 8-11, it was 44.5%, and for the 12-18 year old group, the result was 12.53% lower than the average age-specific indicators.

A separate group of children with grade III FCD, in whom no preventive measures were taken in the preoperative period, deserves special attention. In boys aged 4-7 with grade II FCD, the blood proline level decreased by 18.49 percent, and in those aged 8-11, by 43.04 percent, a decrease of 7.08% was found in boys aged 12-18, while for girls of the same age, the decrease was only 5.69%.

Thus, in addition to the clinical indicators for the development of kyphosis, it can be noted that the severity of the kyphosis, as determined by the blood proline level, has a specific value. It is necessary to significantly restore the homeostatic levels of proline in the blood before preparing patients for surgery and implementing preventive measures to treat their CTD. However, in a similar group of children without preventive measures, a low proline level was found. Apparently, these aspects must also be taken into account when preparing a patient for such an important surgical intervention.

One of the main stages of the study was to examine the excretion rate of oxyproline in the urine of children with urinary tract abnormalities in the postoperative period to detect structural changes in the bladder-trough-urethra complex (see Table 3). Considering grade III FCD in children aged 4–7 and prophylactic treatment of CTD, the

urinary oxyprolin level in boys decreased by 4.54%, and in the 12–18-year-old group, it decreased by 2.35%. The excretion of oxyproline was found to be 12.18% higher in boys with grade III FCD aged 4-7, and 13.62% higher in those aged 8-11. For girls, this indicator decreased by 15.2% in the 4-7 age group, by 16.37% in the 8-11 age group, and by an average of 0.51% in the 12-18 age group.

In children with grade III of urinary retention, significant changes were observed in the urinary indicator's fluctuation when urinary retention was not prophylactically treated (see Table 3). Thus, the highest average prevalence was found in the 4-7 year age group (53.46%), followed by 8-11 year-olds (21.35%), and the 12-18 year-old patient group. In turn, for girls with Grade III FCD aged 4-7, this indicator exceeded the average by 15.2%, at 8-11 years - by 16.37%, and at 12-18 years - by 0.51%.

In patients with grade II FCD, the urinary OP level (see Table 3) was observed to be higher in the untreated group compared to the treated group. This was particularly pronounced in boys aged 4-7 years, reaching 53.46%. In children aged 8-11, this decreased to 21.35%, and in those aged 12-18, to 3.54%. In girls, the excretion of OP was 12.31% higher than the average in the 12-18 age group only.

Table 3

Urinary Oxoproline Levels (M±m) in Patients Who Did Not Receive Preoperative Prophylactic Treatment in the FCD

№	Indicators		Treated with BTD (n=31)		BTD is untreated (n=28)	
		Age	Boys (n=10)	Girls (n=0)	Boys (n=14)	Girls (n=2)
1	II degree FCD	4-7 years	(n=5) 37,74±0,35		(n=3) 55,4±0,62	
		8-11 years			(n=6) 71,6±1,03	
		12-15 years	(n=5) 62,2±0,96		(n=5) 65,96±0,95	(n=2) 77,5±0,31
2	III degree FCD		(n=11	(n=10)	(n=7)	(n=5)
		4-7 years	(n=6) 40,5±1,18	(n=4) 53,8±1,2	(n=3) 57,3±0,36	(n=3) 57,6±0,96
		8-11 years	(n=5) 67,04±0,92	(n=3) 80,3±0,95	(n=4) 80,2±3,38	(n=2) 82,9±0,77
		12-15 years		(n=3) 77,4±0,7		

Untreated grade III FCD (see Table 3), In boys aged 4–7 years, urinary OP decreased by 53.46%, in those aged 8–11 years by 21.35%, and in those aged 12–18 years by an average of 3.54%. In girls aged 12-18 in the same group, a decrease in OP of 12.31% was noted.

In boys with untreated, severe stage III FCD (see Table 3), the excretion of oxypolin was significantly: 58.72% in the 4-7 age group, in boys aged 8-11 years - 35.93%. In girls aged 4-7 years, the studied indicator was 23.34%, while in those aged 8-11 years, it was 20.14% higher than the average indicator.

Thus, we can conclude that the urinary oxiproline index is an integral indicator of the connective tissue component, which determines the degree of changes in the metabolic processes of connective tissue.

The results of the urinary GAG test in grade II FCD (see Table 4) are as follows: in boys aged 4-7 years, an increase of 17.05% was detected, whereas after prophylactic treatment in grade III, In children aged 4-7, the level of GAG in the urine increased by 44.1%, and in the 8-11 year old group, by 31.8%. In turn, urinary GAG excretion was 64.4 per cent in girls aged 4-7, 32.6 per cent in the 8-11 year old group, and remained at an average level in children aged 12-18.

In boys with grade III FCD aged 4-7, taking into account the fluctuations in the urinary GAG concentration, an increase

of 44.1% was recorded, and in the 8-11 age group, an increase of 31.8% was noted. For girls, this indicator fluctuated around the average statistical level: 64.4% in the 4-7 age group, 32.6% in the 8-11 age group, and 12-18 years.

A key finding of the study was the investigation of urinary GAG levels in children with grade III chronic kidney disease, even in the untreated state (see Table 4). The distribution of the analysed indicator was higher in boys aged 4–7 years, at 64.7%, and in those aged 8–11 years, at 61.2%. In girls of the corresponding age group, the GAG content was found to be 2.17% higher in the 4-7 year age group compared to the 12-15 year age group.

Table 4

Glucosaminoglycan profiles in urine of patients with FCD who received prophylactic treatment before surgery (M±m)

№	Indicators		Treated with BTD(n=31)		BTD is untreated (n=28)	
		Age	Boys (n=10)	Girls (n=0)	Boys (n=14)	Girls (n=2)
1	II degree FCD	4-7 years	(n=5) 3,98±0,23		(n=3) 5,6±0,25	
		8-11 years			(n=6) 7,9±0,21	
		12-15 years	(n=5) 5,1±0,15		(n=5) 5,4±0,38	(n=2) 6,75±0,07
			n=11	n=10	n=7	n=5
2	III degree FCD	4-7 years	(n=6) 4,9±0,23	(n=4) 5,8±0,22	(n=3) 6,2±0,1	(n=3) 6,3±0,26
		8-11 years	(n=5) 6,46±0,33	(n=3) 6,9±0,2	(n=4) 7,8±0,17	(n=2) 7,75±0,6
		12-15 years		(n=3) 6,9±0,3		

Studies have shown that in children with grade III FCD, the level of urinary GAGs in the preoperative period is an indicator of readiness for surgical treatment. In boys aged 4–7 years, urinary GAG excretion was detected in up to 82.4%, and in those aged 8–11 years in up to 59.18%. In girls of the aforementioned group, urinary excretion of GAG was found to be 40% higher in 4-7 year-olds and 43.5% higher in 8-11 year-olds compared to the average.

Thus, the intensity of urinary excretion of OP and GAG in children with FCD can be regarded as an indicator of the severity of bladder dysfunction. The most characteristic feature is age-related fluctuations, with a high excretion in the early years in the FCD II and III groups, which gradually decreases as the child grows. The data obtained are similar to those reported by renowned authors on comparable changes, such as the gradual formation of connective tissue and the regulatory characteristics of its regeneration in terms of years.

Taking into account the effectiveness of comprehensive prophylactic treatment, 39 children achieved improved BT synthesis in the postoperative period (see Table 5). The results show that blood proline levels increased by an average of 67% in boys and 72% in girls. A similar positive effect of the prophylactic treatment was observed before the plate removal, which provided the basis for removing the plate without fear of recurrence.

Table 5

Analysis of changes in blood proline levels following prophylactic treatment (Mean ± m)

Patients Age	Gender	1 after the operation	Before taking the plate
4-7 years (n=7)	Boy	265,6±47,5	370,1±34,1
	Girl	287,3±77,1	345,2±59,1
8-11 years (n=13)	Boy	185,3±52,2	375,3±63,04
	Girl	173,9±113	-
12-18 years (n=19)	Boy	247,3±71,03	389,1±51,8
	Girl	321,7±33,7	433±59,6

The laboratory results showed that blood proline levels in the 25 individuals with DCT differed from those of the untreated patients (see Table 6).

Table 6

Analysis of changes in blood proline levels in the absence of prophylactic treatment (Mean ± SD)

Patientsr Age	Gender	1 after the operation	Before taking the plate
4-7 years (n=7)	Boy	180,4±54,06	311
	Girl	185	304
8-11 years (n=7)	Boy	163,5±10,6	301,5±0,7
	Girl	-	-
12-18 years (n=11)	Boy	272,4±28,9	308,9±21,7
	Girl		

Taking the data obtained into account, it can be emphasised that restoring the synthesis of BT metabolic processes is sufficiently stringent, thereby preventing the risk of recurrence in patients in this group.

Table 7

Analysis of changes in urinary OP and GAG levels following complex prophylactic treatment (Mean ± SD)

Age	Sex	1 after the operation (n=30)	Before taking the plate (n=32)
4-7 years (n=6)	Boy OP	40,0±4,3	59,0±5,7
	GAG	4,03±0,5	5,1±0,3
	Girl OP	53,6±6,3	61,5±0,6
	GAG	5,8±1,2	4,8±0,4
8-11 years (n=12)	Boy OP	61,2±0,2	54,06±2,9
	GAG	6,1±1,2	4,4±0,17
	Girl OP	76,7±1,3	70
	GAG	6,6±0,6	5,4
12-18 years (n=15)	Boy OP	67,5±9,2	62,4±4,3
	GAG	5,9±1,2	4,8±0,4
	Girl OP	80,02±7,2	75,3±5,04
	GAG	7,6±1,1	6,8±0,4

In the preoperative period, 25 patients did not complete the treatment regimen to correct DCT. Two of them experienced a recurrent form of FCD. Their laboratory parameters were found to be low: blood proline (75 mmol), urinary OP (89 mmol/day) and high urinary GAG excretion – 9.2 mmol/day.

Table 8

Analysis of changes in urinary OP and GAG levels in patients not receiving complex prophylactic treatment (Mean ± m)

Patients Age	Gender	1 after the operation (n=11)	Before taking the plate (n=9)
4-7 years (n=5)	Boy	42,4±3,6 6,4±0,8	51,1 4,1
	Girl	54,1 6,1	- -
8-11 years (n=6)	Boy	67,3±5,5 6,7±0,5	55,2 4,4
	Girl	- -	65,3 6
12-18 years (n=9)	Boy	75,1±5,5 6,9±0,2	65,6±5,1 5,7±0,6
	Girl	-	-

In the postoperative period, prophylactic treatments were fully implemented to prevent the recurrence of FCD. Six months later, at the follow-up examination, blood proline had significantly recovered to 28.21% (see Table 8), whereas urinary levels of OP and GAG were significantly lower (32% and 46%, respectively). Prior to the removal of the D. Nass plate, the above indicators showed a tendency towards recovery, but remained significantly lower than those in the fully prophylactically treated group.

Thus, it can be noted that in children with FCD, prophylactic treatment of DCT has a high positive characteristic associated with the restoration of CT synthesis processes. The quantitative characteristics of the BT components and their recovery after prophylactic treatment were exemplified by a reduction in recurrence in all patient groups, particularly in cases where the drug therapy was administered pre-operatively.

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