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VARICOCELE AS A MANIFESTATION OF CONNECTIVE TISSUE DYSPLASIA

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Varicocele is spread in 35% of men with primary infertility and in 70-81% of men with secondary infertility, being common in 15% of the entire male population. The prevalence and recurrence of varicocele are relevant for investigating of the underlying etiological mechanisms of this disease. **Objective:** to evaluate the prevalence of connective tissue dysplasia in patients with varicocele. **Materials and methods.** A clinical study is conducted in 148 patients with varicocele. A generally accepted minor congenital anatomical abnormalities were discovered during the examination. Electrocardiography, intervalography and echocardiography were provided among all patients. **Results.** 129 people (87.2%) of the examined patients with varicocele had connective tissue dysplasia. The most frequent manifestations of connective tissue dysplasia are: malformation of ear pavilion (90.5%), asthenic body type (79.2%), disturbed occlusion and tooth growth (52.7%), arterial hypotension (47.3%). In the vast majority of cases (104 people, 70.2%) electrocardiograms of 148 patients with varicocele demonstrated different types of arrhythmia. In intervalography it was found that in half of the cases (83 patients, 56.1%) patients had disorders of the autonomic nervous system. During the regular echocardiography only 32 people (21.6%) didn't have any heart disease, on the other hand valvular and myocardial lesions were diagnosed in other patients. **Conclusions.** The deficiency of mesenchymal structures within the connective tissue dysplasia in varicocele is a systemic predisposing factor and requires a more in-depth examination of the cardiovascular system in such patients.

Keywords: varicocele; connective tissue dysplasia.

ВАРИКОЦЕЛЕ КАК ПРОЯВЛЕНИЕ СИНДРОМА ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ

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Актуальность. Варикоцеле выявляют у 35 % мужчин с первичным бесплодием и 70–81 % мужчин с вторичным бесплодием, обнаруживают у 15 % всех мужчин. Распространенность варикоцеле и его рецидивирование определяют актуальность поиска глубинных механизмов развития этого заболевания. **Цель исследования** — оценить распространенность дисплазии соединительной ткани у пациентов с варикоцеле. **Материал и методы.** Проведено клиническое обследование 148 пациентов с варикоцеле. При осмотре выявляли общепринятые малые анатомические аномалии развития. Всем пациентам выполняли электрокардиографию, интервалографию и эхокардиографию. **Результаты.** Дисплазия соединительной ткани была у 129 человек (87,2 %) из обследованных пациентов с варикоцеле. Наиболее частыми проявлениями дисплазии соединительной ткани были нарушение строение ушной раковины (90,5 %), астенический тип телосложения (79,2 %), нарушение прикуса и роста зубов (52,7 %), артериальная гипотония (47,3 %). При анализе электрокардиограмм 148 пациентов с варикоцеле в подавляющем большинстве случаев (104 человек, 70,2 %) наблюдали тот или иной тип нарушения ритма. По результатам интервалографии в половине случаев (83 пациента, 56,1 %) у больных отмечены нарушения деятельности вегетативной нервной системы. При проведении стандартной эхокардиографии лишь у 32 (21,6 %) человек патология сердца отсутствовала, а у остальных диагностированы те или иные поражения

клапанного аппарата и миокарда. **Заключение.** Неполноценность мезенхимальных структур в рамках синдрома дисплазии соединительной ткани при варикоцеле является системно предрасполагающим фактором и требует у таких пациентов более углубленного обследования сердечно-сосудистой системы.

Ключевые слова: варикоцеле; дисплазия соединительной ткани.

INTRODUCTION

Varicocele is detected in 35% of men with primary infertility, 70%–81% of men with secondary infertility, and 15% of all men. The prevalence of varicocele and its recurrence support the relevance of the search for the pathogenesis of this disease [1].

Changes in the gonadal veins are usually associated with increased pressure owing to anatomical changes (nutcracker syndrome and May–Thurner syndrome) [2, 3]. However, the condition of the walls of the testicular veins is mostly neglected in literature. The testicular veins are constantly exposed to static and dynamic factors, such as being fairly thin-walled structures that provide a vertically directed fluid flow (against gravity) to a height of 30–40 cm. The maximum pressure of the fluid column, which is known from hydrodynamics, is at the lowest point or at the level of the scrotum, and the vein walls are constantly experiencing the pressure described by Bernoulli's law [1, 4]. Thus, the traditionally cited factors for the development of varicocele (hypertension in the distal basins, upright posture, hormonal effects, and physical activity during the growth period) can only be of a permissive nature.

In the last decade, most research mainly focused on the connective tissue dysplasia syndrome (CTDS), which was identified as an above nosological entity. It is considered to be the cause of damage to internal organs, the musculoskeletal system in general, and the cardiovascular system in particular [5]. CTDS signifies a genetically determined embryonic and postnatal developmental condition of the connective tissue. It is characterized by defects in the fibrous structures and the main substance of the connective tissue that leads to a disorder of homeostasis at the tissue, organ, and organism levels in the form of various morphological and functional disorders of the visceral and locomotor organs. It has a progressive course, which determines the features of the associated pathology as well as the pharmacokinetics and pharmacodynamics of drugs [6].

Vascular syndrome in terms of venous system lesions manifests as pathological tortuosity of the vessels, varicose veins, and telangiectasias. Such changes lead to a decrease in venous tone and excessive deposition of blood in the peripheral veins. Morphologically, vascular syndrome is associated with a change in smooth muscle cells, endothelial dysplasia, increased growth of collagen fibers, and degradation of elastic fibers [7, 8]. Vascular syndrome usually manifests in adolescence and young adulthood and progresses as the patient ages [9, 10].

Diagnosis of CTDS is predominantly clinical. Important diagnostic features are minor anatomical developmental abnormalities. The presence of ≥3 minor anatomical developmental abnormalities indicates a high probability of morphogenesis disorders as congenital malformations [6].

The aim of this study was to assess the prevalence of connective tissue dysplasia in patients with varicocele.

MATERIALS AND METHODS

The study group included 148 patients aged 14–49 years (mean age, 17.9 ± 4.2 years) with varicocele. The control group consisted of 84 volunteers aged 14–29 years (mean age, 18.4 ± 3.7 years). The selection criterion for the control group was the absence of varicose syndrome at any localization (varicocele, varicose veins of the lower extremities, hemorrhoids, and phlebodysplasia). The two groups did not differ significantly in terms of age ($p = 0.44$).

During examination, generally accepted minor anatomic developmental abnormalities were revealed, and an integral assessment of the severity of CTDS was performed by assigning it in three degrees [11]. All patients underwent electrocardiography, intervalography, and echocardiography. The varicocele was diagnosed using the WHO classification.

Statistical data were analyzed using the statistics software package Statistica 10.0. Methods of descriptive statistics and nonparametric criteria (chi-square) were used.

RESULTS AND DISCUSSION

Clinical examination revealed signs of CTDS in 129 patients (87.2%) with varicocele. There were various lesions with different rates as presented in Table 1.

The most common symptoms of CTDS were as follows: auricular deformities (90.5%), asthenic body type

(79.2%), malocclusion and tooth growth impairment (52.7%), and arterial hypotension (47.3%).

A high level of external stigmatization was frequently observed in patients with varicocele (134 patients, 90.5%). Moreover, a combination of two stigmas of dysembryogenesis was recorded in 58 patients (39.2%), three stigmas in 37 patients (25.0%), four stigmas in 34 patients (23.0%), and five stigmas in 12 patients (8.1%).

An integral assessment of the CTDS severity in both groups revealed all degrees of CTDS. However, the rate of CTDS was two times higher in the study group: CTDS was absent in 44.0% (37 patients) of the control group versus 16.9% (25 patients) of the study group ($p < 0.001$) (Table 2).

Electrocardiography showed various rhythm abnormalities in the vast majority of patients with varicocele (104 patients (70.2%) versus 26 volunteers (31.0%) in the control group, $p = 0.0007$) (Table 3). The two groups differed significantly in terms of all types of abnormalities.

In the study group, sinus bradycardia (41.9%) and arrhythmia (28.4%) were prevalent. A significant rate of

Table 1

Clinical manifestations of connective tissue dysplasia in the main and control groups

Таблица 1

Клинические проявления дисплазии соединительной ткани в основной и контрольной группах

Clinical signs of connective tissue dysplasia	Study group ($n = 148$)		Control group ($n = 84$)		p
	n	%	n	%	
Asthenic body type	118	79.7	41	48.8	0.039
Postural disorders (scoliosis, kyphosis, and kyphoscoliosis)	58	39.2	18	21.4	0.044
Joint hypermobility	63	42.6	19	22.6	0.031
X- and O-shaped lower extremity deformities	18	12.2	3	3.6	0.043
Platypodia	37	25.0	9	10.7	0.029
Wrist deformity	28	18.9	6	7.1	0.033
Striae	9	6.1	–	–	–
Malocclusion and tooth growth impairment	78	52.7	22	26.2	0.011
Auricular deformities	134	90.5	41	48.8	0.006
Myopia	12	8.1	–	–	–
Cicatricial phimosis	17	11.5	1	1.2	0.009
Hernia of various sites	28	18.9	1	1.2	<0.001
Hemorrhoids	4	2.7	–	–	–
Varicose veins of the lower extremities	11	7.4	–	–	–
Arterial hypotension	70	47.3	16	19.0	0.003
Tendency to allergic reactions, catarrhal diseases of upper respiratory tract	31	20.9	6	7.1	0.017

Table 2

Comparative assessment of connective tissue dysplasia by the integral method in the main and control groups

Таблица 2

Сравнительная оценка дисплазии соединительной ткани интегральным методом в основной и контрольной группах

Severity of signs of connective tissue dysplasia	Study group (n = 148)		Control group (n = 84)		p
	n	%	n	%	
No signs	25	16.9	37	44.0	<0.001
Mild (total score <9)	60	40.5	24	28.6	0.207
Moderate (total score 9–16)	43	29.1	15	17.9	0.138
Severe (total score >17)	20	13.5	8	9.5	<0.450

Table 3

The results of electrocardiography in the main and control groups

Таблица 3

Результаты электрокардиографии в основной и контрольной группах

Results of electrocardiography	Study group (n = 148)		Control group (n = 84)		p
	n	%	n	%	
Normal sinus rhythm	44	29.7	58	69.1	0.0007
Sinus bradycardia	62	41.9	19	22.6	0.004
Sinus arrhythmia	42	28.4	7	8.3	0.003
Sinoatrial nodal block	17	11.5	2	2.4	0.024
Right bundle branch block	24	16.2	2	2.4	0.004
Left bundle branch block	23	15.5	3	3.6	0.012
Early repolarization syndrome	20	13.5	2	2.4	0.011

Table 4

The results of intervalography in the main and control groups

Таблица 4

Результаты интервалографии в основной и контрольной группах

Type of intervalogram	Study group (n = 148)		Control group (n = 84)		p
	n	%	n	%	
Eutonic	65	43.9	58	69.1	0.046
Sympathotonic	32	21.6	11	13.1	0.179
Vagotonic	51	34.5	15	17.8	0.041

different types of heart block (64 patients, 43.2%) was also observed.

Assessment of the specifics of the autonomic nervous system by intervalography showed functional abnormalities in over half of the cases (83 patients, 56.1%) in the study group (Table 4).

It is important to note that an increased parasympathetic tone was more prevalent in the study group (34.5% versus 17.8% in the control group, $p = 0.041$), which caused a decrease in venous tone that we consider essential in the development of the varicose process in patients with varicocele.

Echocardiography showed no cardiac pathology in only 32 patients (21.6%) with varicocele versus 52 volunteers (61.9%, $p < 0.001$) in the control group. Mitral and tricuspid valve prolapses were more common in the study group ($p < 0.001$ and $p = 0.008$, respectively). A tendency toward a higher frequency of ventricular chords pathology and dilated aortic annulus was noted in patients with varicocele (Table 5).

According to the data obtained, varicocele may be considered as a component of a general cardiovascular pathology.

Table 5

The results of echocardiography in the main and control groups

Таблица 5

Результаты эхокардиографии в основной и контрольной группах

Results of echocardiography	Study group (n = 148)		Control group (n = 84)		p
	n	%	n	%	
No abnormalities	32	21.6	52	61.9	<0.001
Mitral valve prolapse	45	30.4	4	4.8	<0.001
Tricuspid valve prolapse	21	14.2	2	2.4	0.008
Ventricular chord pathology	98	61.5	37	44.0	0.084
Aneurysm of interventricular septum	6	8.1	–	–	–
Dilated aortic annulus	32	21.6	9	10.7	0.076
Bicuspid aortic valve	4	5.4	–	–	–

Among 116 patients in the study group with heart pathology, only 29 (25.0%) had a previously diagnosed abnormality.

CONCLUSION

In our study, 129 (87.2%) of 148 patients with varicocele had various manifestations of CTDS, which cannot be an accident. However, the presence of CTDS could explain the frequent combination of various supposedly separate diseases and lesions (asthenic body type, myopia, malocclusion, tendency to colds, mitral valve prolapse, etc.), with varicocele as a particular manifestation of systemic connective tissue failure.

The logical question is whether varicocele is exclusively a manifestation of CTDS or if it is a consequence of the cardiovascular pathology. In this regard, we performed a comparative study where 148 patients underwent electrocardiography, intervalography, and echocardiography.

The prevalence of increased parasympathetic tone in patients with varicocele (34.5%) is of interest. Reduction in the tone of the venous vessels, which is a parasympathetic effect, allows us to understand the development of the varicose process in patients with varicocele.

The state of the cardiovascular system has been particularly studied. Thus, rhythm abnormalities (arrhythmias 28.4%, various blocks 43.2%) were present in 70.2% of the patients. At the same time, echocardiography showed lesions of the valves and the myocardium itself (valve prolapse 43.3%, chord pathology 61.5%) in 116 patients. Moreover, structural changes in the heart were diagnosed before enrollment in the study in only one-fourth of the patients.

The results indicate that the defects in mesenchymal structures associated with CTDS act as a systemic causative factor for varicocele.

Thus, a comprehensive study of the cardiovascular system, especially the heart, in all adolescents with varicocele and a high level of external stigmatization seems to be appropriate.

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