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Comorbidities in young adults with vertebrogenic pathology and dysplastic phenotype

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Pathological changes in the spine are often accompanied by pain syndrome at a young age. However, the significance of comorbid disorders in the formation and course of vertebrogenic pain syndrome has not been studied enough.The objective of the article to clarify the role of comorbid disorders in young adults with unclassified dysplastic phenotype in the formation of vertebrogenic pain syndrome. 61 male patients from 18 to 26 years old with pain syndrome in the spine were examined. Depending on the presence of signs of a dysplastic phenotype the patients were divided into two groups. The first group included 28 patients (median age 22 (21; 23) years), the second group consisted of 33 people (median age 23 (19; 24) years). All patients underwent a comprehensive examination, including neurological and somatic examination, neuroradiological, ultrasound and psychological methods of investigation, also took into account clinical and anamnestic data. Pain syndrome, the state of the autonomic nervous system and the presence of signs of a dysplastic phenotype were assessed using scales and indices. Statistical data processing was performed using the STATISTICA 10.0 program. Differences were considered statistically significant when $p < 0.05$. According to neuroimaging data, signs of widespread dysplastic and more pronounced scoliotic and kyphoscoliotic changes of the spine, vertebral anomalies, segmental instability were authentically more frequent in patients with the unclassified connective tissue dysplasia phenotype ($p<0,05$). They had more severe vertebrogenic pain syndrome, which was more intense and long-lasting and was on the background of a greater neurological deficit with autonomic lability and psychopathological disorders, headaches, somatic dysfunction with a prevalence of diseases of the bronchopulmonary system and ENT organs in the control group ($p<0.05$). Research findings allow us to consider the prevalence of pathological changes in the spine, depressive disorders, somatic and cerebral burden as factors contributing to the formation of pain syndrome in patients with vertebrogenic pathology and connective tissue insufficiency.

Keywords: young age, pain syndrome, comorbid diseases, connective tissue dysplasia, spine.

Introduction

Spinal pain is the second most frequent medical condition in the world and represents a serious socioeconomic problem, as it is most common among the working-age population [1]. Recently, there has been an increase in the prevalence of spinal diseases among young people [2; 3]. At the same time, they often have signs of connective tissue dysplasia with multiple organ involvement, which may influence the course of pain syndrome [4; 5]. The most widespread are undifferentiated forms of connective tissue dysplasia (UCTD). Young people with increased dysplastic stigmatization according to UCTD make up from 20 % to 80 % among young people [6–8]. Dysplastic-associated diseases usually have a progressive course, and the spinal column undergoes regular degenerative changes [9; 10]. Investigating the role of comorbid diseases in the course of pain syndrome in young adults with vertebrogenic pathology will provide a systematic approach to the treatment of this category of patients. This has both practical and theoretical significance [11; 12]. The study aimed to clarify the role of comorbid disorders in young people with an unclassified dysplastic phenotype in the formation of vertebrogenic pain syndrome.

Materials and methods

The study involved 61 male patients with pain in the cervical, thoracic and/or lumbar spine. The main (1) group included 28 patients with signs of a dysplastic phenotype (median age 22 (21; 23) years). The control (2) group consisted of 33 people (median age 23 (19; 24) years). All patients underwent a comprehensive examination, including clinical and anamnestic diagnostic methods, including the collection of anamnesis about already identified functional disorders, morphological features, diseases that could be markers of CTD; neurological and physical examination; neuroradiological (X-ray, MRI, CT of different parts of the spine, head); ultrasound (echocardiographic and doppler evaluation of brachiocephalic vessels — according to indications), consultations of specialists — orthopedist, therapist, ophthalmologist, psychologist — according to indications and psychological research methods. The pain intensity was assessed using the Visual Analogue Scale (VAS) and psychological testing for the presence and severity of depression was performed using the Beck Scale. To assess the involvement of connective tissue in the pathological process, the sum of the diagnostic coefficients of the signs of connective tissue dysplasia was calculated based on Wald's sequential analysis as modified by Genkin A. A. (2018) [13]. Statistical data processing was performed using the STATISTICA 10.0 program (TIBCO Software Inc.). Methods of nonparametric and parametric statistics were used (Mann — Whitney U-test, Fisher's exact test, Pearson's $\chi 2$ test, $\chi 2$ test with Yates' correction, Pearson correlation test).

Data in the text and tables are presented as median, upper and lower quartiles (Me [LQ; UQ]). Differences were considered statistically significant at $p < 0.05$.

Results

According to the data of neuroradiological examination, it was revealed that degenerative-dystrophic changes in the spine dominated in patients of both groups. In group 1 patients signs of a widespread dysplastic and degenerative-dystrophic process, more

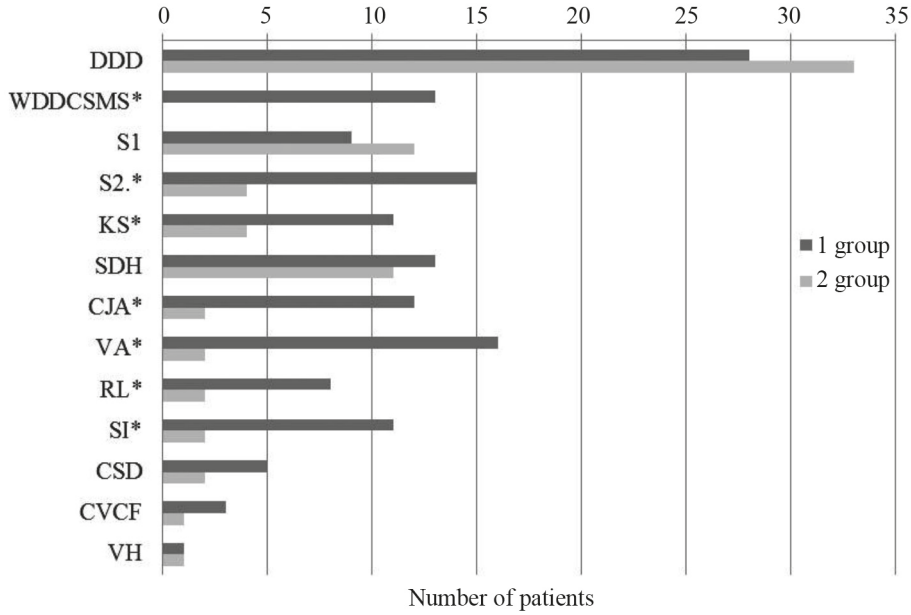

Fig. 1. Distribution of patients depending on the frequency of structural pathology of the spine according to neuroradiological research

Note: * — significance of differences between groups when $p < 0.05$; DDD — Degenerative disc disease; WDDCSMS — widespread (in 3 regions of spine) dysplastic and degenerative changes in spinal motion segments; S1 — first degree of scoliosis according to the Chaklin's classification (Cobb angle is 1°–10°); S2 — second degree of scoliosis according to the Chaklin's classification (Cobb angle is 11°–25°); KS — kyphoscoliosis; SDH — Spinal disc herniation; CJA — Craniovertebral junction anomalies; VA — Vertebral anomalies; RL — Retrolisthesis; SI — Segmental instability; CShD — the consequences of Scheuermann's disease; CVCF — consequences of vertebral compression fracture; VH — Vertebral hemangiomas.

pronounced scoliotic and kyphoscoliotic changes in the spine, anomalies, segmental instability and retrolisthesis were significantly more frequent ($p < 0.05$) (Fig. 1).

The main group was dominated by widespread pain in 3 parts of the spine; in the control group, pain localized in one part of the spine was more common ($p<0.05$), Table 1.

Table 1. **Patient distribution depending on pain prevalence**

Pain	1 group (n = 28)	2 group (n = 33)	p (1–2)
in 1 part of the spine	2 (7,1 %)	19 (57,6 %)	p<0,05
in 2 part of the spine	12 (42,9 %)	10 (30,3 %)	p>0,05
in 3 part of the spine	14 (50 %)	4 (12,1 %)	p<0,05

Note: p — significance of differences between groups; Group 1 — patients with connective tissue dysplasia phenotype; 2 — control group.

Pain syndrome in patients with connective tissue insufficiency phenotype lasted for a longer time than in patients of the control group (medians are 4.5 (4.0; 5.0) and 2.0 (2.0; 3.0) years), and was more intense (medians are 5.0 (4.0; 5.0) and 4.0 (3.0; 4.0) points),

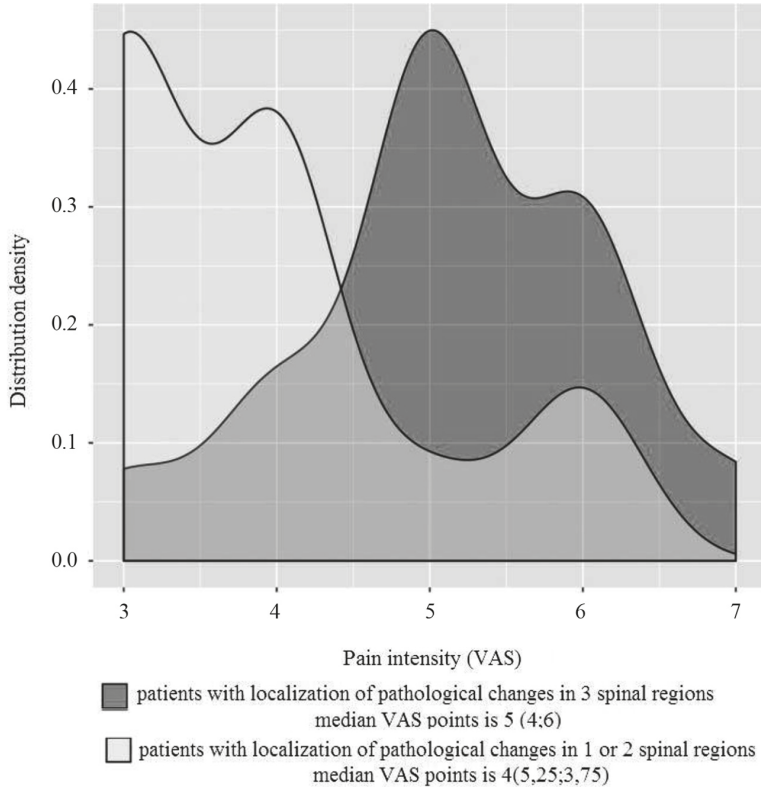

Fig. 2. Distribution density of patients with connective tissue dysplasia phenotype depending on the prevalence of pathological changes in the spine and indicators of pain severity in the spine

$p < 0.05$. At the same time, in patients of the main group with widespread lesions of the spine (within 3 parts of the spine), higher pain indices were determined according to the VAS than in patients with pathological changes within one or two parts of the spinal column ($p < 0.05$) (Fig. 2).

Pain syndromes were accompanied by changes in the psychoemotional sphere. Psychopathological disorders in patients occurred mainly in the form of neurotic disorders — asthenic syndrome, anxiety-phobic and obsessive-compulsive disorders. Depressive disorders assessed on the Beck Scale were encountered in varying degrees of severity. In patients of group 1 signs of depression were detected significantly more often than in group 2. At the same time, moderate depression prevailed in them ($p < 0.05$) (Table 2).

Correlation analysis of the Beck Depression Scale and VAS Scale indicators revealed a moderately strong relationship ($r = 0.66$, $p < 0.05$), indicating a direct relationship between the severity of pain syndrome and the severity of depression (Fig. 3).

The studies also showed that patients of group 1 were significantly more likely to have cephalgia syndrome than in the control group (Table 3). Despite the predominance of tension headache in patients of group 1, significant differences with the control group were obtained in terms of the proportion of patients with hypertensive headache (Table 3).

Table 2. **Psychopathological disorders in the examined patients**

	1 group (n=28)	2 group (n=33)	P 1–2
Psychopathological disorders (total)	28 (100 %)	21 (63.6 %)	p < 0.05
Of them:			
Asthenic syndrome	24 (85.7 %)	16 (76.2 %)	p > 0.05
Obsessive-compulsive disorder	6 (21.4 %)	2 (9.5 %)	p > 0.05
Anxiety-phobic disorder	15 (53.6 %)	8 (38.1 %)	p > 0.05
Moderate depression	6 (21.4 %)	1 (4.8 %)	p > 0.05
Mild depression	11 (39.3 %)	2 (9.5 %)	p < 0.05
Minimal depression	6 (21.4 %)	11 (52.4 %)	p < 0.05

Note: p — significance of differences between groups; Group 1 — patients with connective tissue dysplasia phenotype; 2 — control group

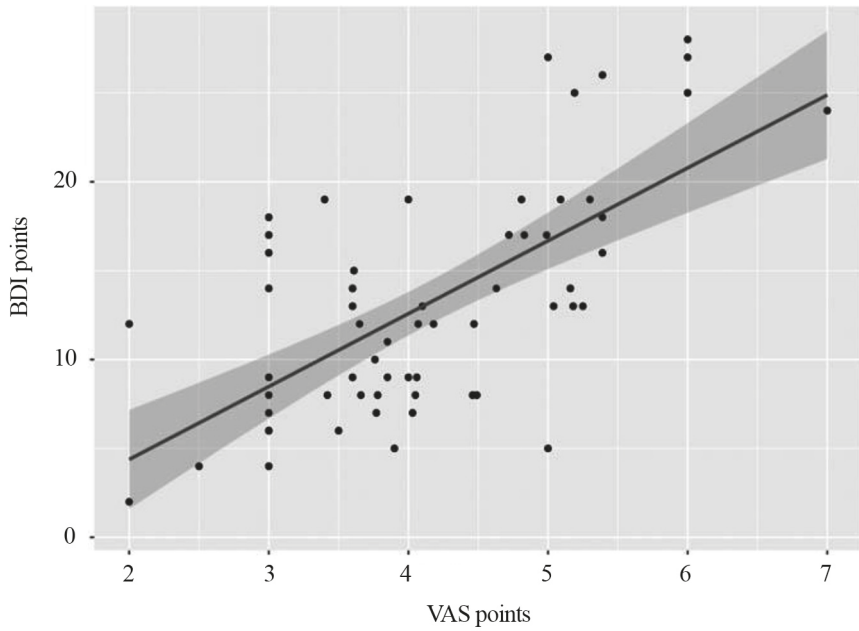

Fig. 3. Graph of the correlation between the VAS scores and the Becks Depression Scale

Note: BDI — Beck Depression Inventory; VAS — Visual Analogue Scale.

Table 3. **Distribution of patients depending on the presence and signs of cephalgia syndrome**

Signs		1 group (n = 28)	2 group (n = 33)	P 1–2
Presence of cephalgia syndrome		21 (75 %)	8 (24.2 %)	p<0.05
Of them:				
Localization (area)	Frontotemporal	10 (47.6 %)	0 (0 %)	-
	Parieto-occipital	2 (9.5 %)	2 (25 %)	p<0.05
	Diffuse	9 (42.8 %)	6 (75 %)	p>0.05
Type	Tension headache	11 (52.3 %)	6 (75 %)	p>0.05
	Migraine	3 (14.3 %)	1 (12.5 %)	p>0.05
	Hypertensive	7 (33.3 %)	1 (12.5 %)	p<0.05

Note: p — significance of differences between groups; 1 group — patients with connective tissue dysplasia phenotype; 2 group — control group

Cephalgia syndrome was more often observed in patients with mild CNS pathology detected during neuroimaging. According to MRI / CT of the head, changes in the central nervous system in group 1 were represented by arachnoid cysts, external-internal and external hydrocephalus, foci of gliosis in 85.7 % of cases. The openness of the circle of Willis was found in 42.8 %. In the same part of the patients of the main group, according to the data of ultrasound diagnostics, signs of venous dysgemia were determined.

In 18 (64.3 %) patients of group 1, according to anamnesis, perinatal pathology of the central nervous system was found, in group 2 it was detected only in 2 (6.1 %) patients ($p < 0.05$).

Neurological deficit due to organic CNS pathology was manifested by signs of pyramidal insufficiency, cranial nerve dysfunction, vestibulocerebellar insufficiency, and cognitive disorders predominantly in group 1 patients. Peripheral nervous system disorders were characterized by radicular syndromes ($p < 0.05$) (Fig. 4).

Almost obligate manifestations of CNS lesions were autonomic disorders, which were more often detected in patients of the main group (24 / 85.7 % and 6 / 18.1 %, $p < 0.05$). Disorders of the autonomic nervous system (ANS) were presented in the form of lipotimia, accompanied by a feeling of lightheadedness, nausea, weakness, sweating; orthostatic disorders that arose when the body position changed from horizontal to vertical with darkening in the eyes and tachycardia; hyperhidrosis; panic attacks. In patients with CTD, orthostatic disorders (15 / 62.5 %) and lipotimia (9 / 37.5 %) dominated. Panic attacks occurred in 12.5 % of cases.

Analysis of the Kerdo index indices, which makes it possible to assess the direction of autonomic shifts mainly in cardiovascular system revealed the presence of sympathicotonia and parasympathicotonia in both groups. The comparison of Kerdo index in subgroups with sympathicotonia and parasympathicotonia in the 1st and 2nd groups revealed statistically significant differences between them ($p<0.05$), Table 4. In group 1, both sympathicotonia and parasympathicotonia indexes had more pronounced values than in group 2 (Table 4).

Table 4. **Values of the Kerdo index in the examined patients**

Group	Positive Kerdo index (predominance of sympathetic reactions)	Negative Kerdo index (predominance of sympathetic reactions)
1 group N = 28	13 (46.4 %) median Kerdo index: 22.0 (6.5; 22.4)	15 (53.6 %) median Kerdo index: –24.0 (–24.6; –15.0)
2 group N = 33	14 (42.4 %) median Kerdo index: 4.7 (2.5; 6.0)	19 (57.6 %) median Kerdo index: –4.1 (–8.7; –1.6)
P 1–2	<0.05	<0.05

Note: p — significance of differences between groups; Group 1 — patients with connective tissue dysplasia phenotype; 2 — control group

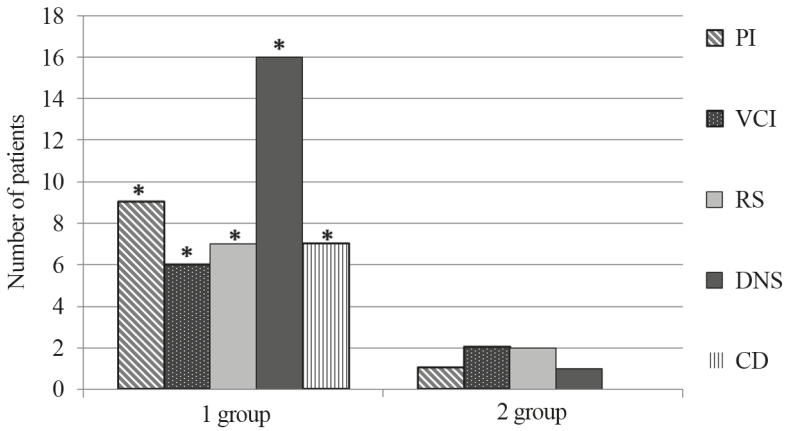

Fig. 4. Neurological status of group 1 and 2 patients

Note: * — significance of differences between groups when p < 0.05; PI — pyramidal insufficiency; VCI — vestibulocerebellar insufficiency; RS — radicular syndromes; DCN — dysfunction of cranial nerves; CD — cognitive disorders.

In the structure of somatic disorders in patients with a dysplastic phenotype, inflammatory diseases of the ENT organs and the bronchopulmonary system (67.8 %), pathology of the heart and cardiac activity (57.1 %) as well as dysfunction of the digestive system (42.8 %).

Patients of the main group who had a history of diseases of the ENT organs and the bronchopulmonary system rated the severity of pain syndrome higher on the VAS scale than patients without them ($p < 0.05$) (Fig. 5).

Discussion

Our investigation showed that patients with vertebrogenic syndrome and CTD phenotype revealed scoliotic, kyphoscoliotic spinal deformities, functional instability, and vertebral retrolisthesis due to connective tissue insufficiency significantly more frequently than the control group according to clinical data and neuroimaging. This is consistent with the data of numerous researches [6; 9; 14–16]. These patients were characterized by a

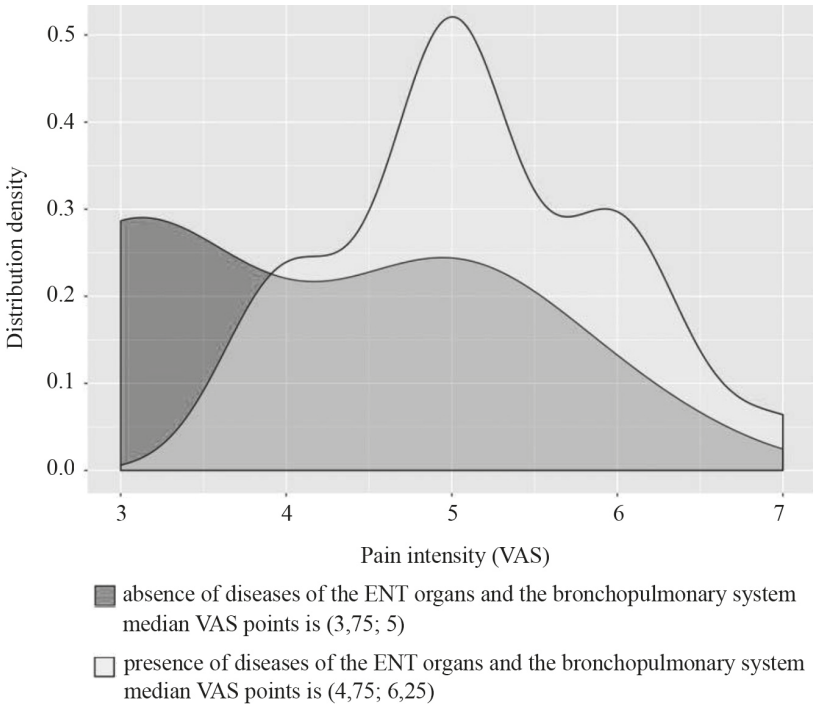

Fig. 5. Distribution density of patients with the phenotype of connective tissue dysplasia, depending on the presence of diseases of the ENT organs and the bronchopulmonary system in the anamnesis and indicators of the severity of pain in the spine.

more intense pain syndrome associated with the involvement of more spinal structures in the pathological process. The duration of pain syndrome in them was significantly longer than in the control group. Prolonged or frequently repeated pain impulses due to peripheral irritation of nociceptors of the osteoarticular system can lead to increased activation of central neurons in the dorsal horns of the spinal cord — central sensitization. On the other hand, impaired neurotransmitter transmission, for example, in depression, which occurred in the structure of psychopathological disorders in patients with CTD, can be a predisposing factor in the development of dysfunction of the antinociceptive system — central desensitization. Central sensitization and disinhibition lead to the development of hypersensitivity in relation to pain stimuli and, as a consequence, to a higher assessment of pain syndrome intensity [17; 18], which we observed in patients with CTD. In addition, impaired magnesium-calcium or serotonin metabolism, which affects the functioning of the antinociceptive system, is quite common in these patients [6].

It is known that chronic pain syndromes can be accompanied by the formation of pathological integrations in the CNS, such as generators of pathologically increased excitation and pathological algic system involving different structures of the brain and spinal cord [19]. Pathological system formation is possible when the nervous system is damaged and CNS integrative control is impaired [19]. Pathological systems are not only the basis of developing neuropathological syndromes but can also suppress physiological systems and their antisystems, contributing to the development of pathological processes. In this connection, it can be supposed that the formation of pathological inte-

grations occurs faster and they are more stable on the background of structural changes in the brain tissue. In 85.7 % of the examined patients of the main group, mild structural changes of the brain tissue were detected, which could be one of the risk factors for the development of neuropathological syndromes — cephalgia, autonomic dysfunction, psychopathological and somatic disorders. Patients with CTD had significantly more frequent neurological deficit in the form of pyramidal, cerebellar, mild extrapyramidal insufficiency and cognitive disorders, disorders of oculomotor and trigeminal facial nerve functions. They were significantly more likely to have a history of perinatal CNS pathology (PPCNS) compared to the control group ($p<0.05$). Therefore, we cannot exclude the influence of epigenetic factors and deny the hypothesis that PPCNS may be a risk factor for connective tissue dysplasia, and the latter may lead to decompensation of neurological pathology [20; 21].

Cephalgia syndrome in patients with CTD manifested predominantly tension headache (52.3 %) and hypertensive cephalgia (33.3 %), in contrast to that indicated in the literature as the most frequent migrainous headache [6]. Migrainous type of headache was determined in 14.3 % of cases. Among the factors responsible for cephalgia syndrome, a significant role belongs to vertebrogenic pathology (including craniovertebral anomalies), angiodystonia of cerebral vessels, often with the phenomena of venous insufficiency and hydrocephaly.

Autonomic disorders are almost obligatory disorders in patients with the CTD phenotype, occurring in the undifferentiated form of CTD in 78 % of cases [6]. In our studies, they were found in 85.7 % of patients. Among autonomic symptoms, orthostatic disturbances dominated (62.5 %), accompanied by darkening of eyes, tachycardia, and light dizziness when moving from horizontal to vertical position. Analysis of the data obtained by Kerdo index calculation in the patients revealed significant shifts towards sympathicotonia (46.4 %), and vagotonia (53.6 %). They were significantly higher in patients with CTD phenotype, indicating more pronounced tension of different parts of autonomic nervous system in patients of this group. Patients with CTD are considered to be more susceptible to the development of psychoemotional disorders [6; 22; 23]. In our study, we showed that Beck Depression Scale signs of depression in patients with the dysplastic phenotype were revealed more frequently than in the control group. Moderate depression was predominant (39.3 %). Correlation analysis revealed a moderate reliable relationship between the severity of vertebrogenic pain syndrome and the level of depression, which suggests the role of the psychoemotional factor in the formation of pain in vertebrogenic pathology in this group of patients.

Somatic diseases detected in patients of the main group correspond to the structure of pathologies associated with connective tissue dysplasia [4; 6]. Polyorganic lesions in CTD are caused by a wide representation of its components in the body [24]. In our study, a large proportion were inflammatory diseases of ENT organs and bronchopulmonary system (67.8 %), heart and cardiac pathology (57.1 %), and digestive system diseases (42.8 %). Diseases of ENT organs and bronchopulmonary system with a tendency to chronization are associated with immune system disorders. However, the mechanisms of immune disorders in CTD are still almost unstudied, and the available data are contradictory. The presence of immune disorders accompanying bronchopulmonary and visceral CTD syndromes increases the risk of associated pathology of the corresponding organs and systems [6]. This makes it necessary to do more research in this direction.

Conclusion

The studies allowed us to specify that vertebrogenic pain syndrome in young patients with the phenotype of undifferentiated CTD occurs on the background of structural changes of the spinal column and comorbid pathologies — neurological deficit with vegetative lability and psychopathological disorders, cephalgia, somatic dysfunction with the predominance of disorders of the bronchopulmonary system and ENT organs. The correlation between the severity of pain syndrome and depressive disorders as well as its dependence on the prevalence of pathological changes in the spine, its prevalence in persons with greater somatic and cerebral aggravation allows taking these factors into account when we speak about the formation of pain syndrome mechanisms in patients with vertebrogenic pathology and connective tissue dysplasia.

A comprehensive investigation of the signs of connective tissue dysplasia in young adults with vertebrogenic pathology will allow predicting the progression of pain syndrome and determines the necessity of a multidisciplinary approach to minimize the influence of comorbid disorders on the course of pain syndrome.

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