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RESEARCH

Diagnostic importance of phenotypic features of undifferentiated connective tissue dysplasia in spondylogenic vertebro-basilar insufficiency

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Background: The circulatory insufficiency in the vertebrobasilar system is significantly influenced by the spondylogenic mechanism. To understand the degenerative-dystrophic changes in the cervical spine, an assessment of the connective tissue's condition is required. The primary contributor to pathological conditions of connective tissue is undifferentiated connective tissue dysplasia (UCTD).
Aim: To assess the predictive importance of constitutional-biological markers (CBM) of UCTD in patients with spondylogenic vertebro-basilar insufficiency.
Materials and Methods: The research was carried out using the results of a comprehensive clinical and anamnestic examination of young patients with vertebrobasilar insufficiency. The study focused on investigating the main characteristics of CBM by comparing two groups of patients: one group with vertebrobasilar insufficiency (n = 136) and a control group without vertebrobasilar insufficiency (n = 136). The distribution of individual factors was analyzed using evidence-based medicine, modern clinical-statistical analysis methods such as variance and correlation analysis, as well as prognosis methods like serial analysis of Wald in modification of E.V Gubler to determine the diagnostic (I2, bit) and predictive value and impact factors of the different markers.
Results: The most significant CBM for UCTD were found to be presence of structural imbalance, scoliosis or kyphosis of the cervical spine, flatfoot, and vision impairments.
Conclusion: This study suggests that the diagnostic and prognostic value of CBM for UCTD is crucial in establishing a system of diagnostic and prognostic algorithms for evaluating the risk of developing vertebrobasilar insufficiency (SVBI).

Keywords: spondylogenic vertebro-basilar insufficiency, phenotypic markers, undifferentiated connective tissue dysplasia

Introduction

Vertebrobasilar is a common condition encountered in medical practice. Almost one-fourth of the transient ischemic attacks (TIA) and ischemic strokes involve the vertebrobasilar circulation. A vertebrobasilar TIA is associated with a 30–35% stroke risk over a period of 5 years (1, 2). In addition, there is a 5–11% risk of stroke or death within 1 year of medically refractory disease of the vertebrobasilar system. Therefore, a posterior circulation stroke has a high mortality rate ranging from 20–30%, which is a significant proportion (3–6).

Abbreviations: VBI: Vertebrobasilar insufficiency; TIA: Transient ischemic attack; DDSD: Degenerative-dystrophic spinal diseases; CT: Connective tissue; UCTD: Undifferentiated connective tissue dysplasia; SVBI: Vertebrobasilar insufficiency of spondylogenic origin; MRI: Magnetic Resonance Imaging; CBM: Constitutional and Biological Markers;

Atherosclerosis is one of the most common vascular conditions affecting the vertebrobasilar system due to the narrowing and occlusion of the vessels by plaques (7). The small vessels (50–200 μm in diameter) get occluded by a process known as lipohyalinosis, which has a frequent association with hypertension. This leads to small, round infarcts called lacunae, which may present as single lesions or as a distribution of multiple lesions scattered widely throughout the subcortex and the brainstem (8). In hypertensive individuals, weakening of vessel wall occurs due to lipohyalinosis, which may result in artery rupture and therefore in a focal hemorrhage. Most of the intracerebral hemorrhages result from the damage of these small vessels (2).

Chiropractic manipulation or neck rotation may traumatize the vertebral arteries due to their close anatomical relationship with the cervical spine. Moreover, some cervical spine impairments may lead to VBI. These discirculatory disorders in the vertebrobasilar system arise due to degenerative-dystrophic changes in the cervical spine and are referred to as spondylogenic (9–12).

Hemodynamic disturbances in the vertebrobasilar system on the background of degenerative lesions of the cervical spine have become an actual medical problem in Ukraine. In view of the young patients seeking medical care due to spondylogenic disorders, the increase in the incidence of degenerative-dystrophic spinal diseases (DDSD) among the population, especially of the dysplastic phenotype, is of concern. The study of the DDSD is also based on the condition of the connective tissue (CT). Among the pathological states of CT, the leading role belongs to CT dysplasia (5, 13–15).

Dysplasia of the CT manifests by reduction of the amount of certain types of collagen or by creating a disbalance in their ratio, which results in a decreased strength of CT of various organs and therefore a disturbance in their function. CT dysplasia can be easily found during physical examination in the detailed assessment of phenotypic (external and visceral) markers (14, 16).

The frequency of undifferentiated connective tissue dysplasia (UCTD) in the post-Soviet European states ranges from 9% to 80% depending on demographic factors like age, sex, ethnicity, and also on clinical groups of the study (17); therefore, the need to study the leading phenotypic markers of UCTD with the purpose of further predicting the risk of developing a pathology in this category of patients becomes vital.

The purpose of this study is to evaluate the most diagnostically important and prognostically notable constitutional and biological markers (CBM) in young patients with UCTD in VBI of spondylogenic origin (SVBI).

CS: Cervical Spine; PC: Prognostic Coefficients; I: Informativity; RG: Rehabilitation Group.

The objective and methods of research: The analysis of the frequency of the individual constitutional and biological markers (CBM) of UCTD with SVBI was performed by comparing two groups: the first group of patients with SVBI (n = 136) and the control group (n_0 = 136)—practically healthy individuals, selected by the «copied-pair» method based on age and sex. The diagnosis of SVBI by duplex vessels scanning, MRI of the cervical spine, and sonography of vertebral, basilar arteries in the rest and after functional probes was verified (10, 18–21).

All 272 patients in the clinic (patients with SVBI) and the ones undergoing comprehensive medical examinations (control group) were examined according to Glesby method (14), which provides an assessment of the presence/absence of CBM UCTD.

According to the results of filling phenotypic records, using the methods of variation statistics, the difference in the frequency of individual phenotype manifestations among patients in comparison groups was analyzed. Subsequently, on the basis of comparative analysis with the use of methods of non-parametric statistics (single-factor regression analysis and a sequential Wald analysis in the modification of Gubler) (22), the indicators of clinical informative value and predictive value of individual phenotype manifestations of SVBI were obtained. In the course of the research, such statistical methods were used as variation statistics, probability distribution with the estimation of the reliability of the obtained results, correlation and regression analysis (22). Such indicators as impact forces (η2;%) and their informativity (I; bit) were the basic criteria for estimating the predictive value of factors, which were calculated according to the standard method using the environmentally adapted «EXCEL» computer program.

Research results and their discussion

The constitutional and biological markers. On the base of conducted analysis it was revealed that, the most informative and significant CBM at the level of at least $p < 0.001$ were:

- the presence of structural imbalance in the cervical spine (CS) (the frequency of persons with a disproportional length of CS), which is defined more often in patients with SVBI (30.1 ± 3.9)%, whereas in the control group – (6.1 ± 2.1)% of patients ($p < 0.0001$);
- the presence of scoliosis or kyphosis of CS, which is defined more often in – patients with SVBI (33.8 ± 4.1)%, whereas in the control group – (10.3 ± 2.6)% of patients ($p < 0.0001$)
- the flatfoot was registered significantly more often in – patients with SVBI (19.9 ± 3.4)% and (3.7 ± 1.6)% patients in the control group ($p < 0.0001$);
- increased dental abrasion was registered significantly more often in – patients with SVBI (38.2 ± 4.2)%

TABLE 1 | Frequency, prognostic coefficients (PC), and informativity of the phenotypic features of undifferentiated connective tissue dysplasia in spondylogenic vertebrobasilar insufficiency development.

Phenotypic features of undifferentiated connective tissue dysplasia		Patients with SVBI (n = 136)		Control group (n = 136)		PC	I, bit
		abs.	P ± m,%	abs.	P ± m,%		
1		2	3	4	5	6	7
Structural imbalance in the cervical spine	Presence	41	30,1 ± 3,9	8	6,1 ± 2,1	+ 6,9	0,839
	Absence	95	69,9 ± 3,9	124	93,9 ± 2,1	−1,3	0,155
η^2 = 9,0%	p = 0,0001	136	100,0	136	100,0	–	**0,994**
Scoliosis or kyphosis	Presence	46	33,8 ± 4,1	14	10,3 ± 2,6	+ 5,2	0,608
	Absence	90	66,2 ± 4,1	122	89,7 ± 2,6	−1,2	0,155
η^2 = 8,0%	p = 0,001	136	100,0	136	100,0	–	**0,763**
Flatfoot	Presence	27	19,9 ± 3,4	5	3,7 ± 1,6	+ 7,3	0,592
	Absence	109	80,1 ± 3,4	131	96,3 ± 1,6	−0,9	0,065
η^2 = 6,0%	p = 0,0001	136	100,0	136	100,0	–	**0,657**
Dental abrasion	Presence	52	38,2 ± 4,2	19	14,0 ± 3,0	+ 4,4	0,530
	Absence	84	61,8 ± 4,2	117	86,0 ± 3,0	−1,4	0,175
η^2 = 7,0%	p = 0,0001	136	100,0	136	100,0	–	**0,705**
Myopia or other types of vision impairments	Presence	65	47,8 ± 4,3	34	25,0 ± 3,7	+ 2,8	0,321
	Absence	71	52,2 ± 4,3	102	75,0 ± 3,7	−1,6	0,179
η^2 = 5,0%	p = 0,001	136	100,0	136	100,0	–	**0,500**
Blue sclera	Presence	54	39,7 ± 4,2	27	19,9 ± 3,4	+ 3,0	0,299
	Absence	82	60,3 ± 4,2	109	80,1 ± 3,4	−1,2	0,123
η^2 = 4,0%	p = 0,001	136	100,0	136	100,0	–	**0,422**
Asthenic type of constitution	Presence	63	46,3 ± 4,3	37	27,2 ± 3,8	+ 2,3	0,221
	Absence	73	53,7 ± 4,3	99	72,8 ± 3,8	−1,3	0,126
η^2 = 4,0%	p = 0,002	136	100,0	136	100,0	–	**0,347**
Radial−lacunar iris	Presence	51	37,5 ± 4,2	27	19,9 ± 3,4	+ 2,7	0,244
	Absence	85	62,5 ± 4,2	109	80,1 ± 3,4	−1,0	0,095
η^2 = 3,0%	p = 0,010	136	100,0	136	100,0	–	**0,339**
Deformation of the breast	Presence	15	11,0 ± 2,7	3	2,2 ± 1,3	+ 7,0	0,308
	Absence	121	89,0 ± 2,7	133	97,8 ± 1,3	−0,4	0,018
η^2 = 3,0%	p = 0,004	136	100,0	136	100,0	–	**0,326**
Clinodactyly	Presence	67	49,3 ± 4,3	45	33,1 ± 4,0	+ 1,7	0,140
	Absence	69	50,7 ± 4,3	91	66,0 ± 4,0	−1,2	0,097
η^2 = 2,0%	p = 0,007	136	100,0	136	100,0	–	**0,237**
Curvature of the nasal membrane	Presence	11	8,1 ± 2,3	2	1,5 ± 1,0	+ 7,4	0,245
	Absence	125	91,9 ± 2,3	134	98,5 ± 1,0	−0,3	0,010
η^2 = 2,0%	p = 0,011	136	100,0	136	100,0	–	**0,225**
«Ability to roll the tongue into a tube»	Presence	41	30,1 ± 3,9	23	16,9 ± 3,2	+ 2,5	0,166
	Absence	95	69,9 ± 3,9	113	83,1 ± 3,2	−0,7	0,050
η^2 = 2,0%	p = 0,010	136	100,0	136	100,0	–	**0,216**
Increase in skin elasticity	Presence	16	11,8 ± 2,8	6	4,4 ± 1,8	+ 4,2	0,157
	Absence	120	88,2 ± 2,8	130	95,6 ± 1,8	−0,3	0,013
η^2 = 1,0%	p = 0,026	136	100,0	136	100,0	–	**0,169**
Angiectasia	Presence	12	8,8 ± 2,4	4	2,9 ± 1,4	+ 4,8	0,140
	Absence	124	91,2 ± 2,4	132	97,1 ± 1,4	−0,2	0,008
η^2 = 1,0%	p = 0,039	136	100,0	136	100,0	–	**0,148**
Anomalies of auricles	Presence	67	49,3 ± 4,3	52	38,2 ± 4,2	+ 1,1	0,061
	Absence	69	50,7 ± 4,3	84	61,8 ± 4,2	−0,8	0,047
η^2 = 1,0%	p = 0,067	136	100,0	136	100,0	–	**0,108**
Anomalies of bite	Presence	24	17,6 ± 3,3	15	11,0 ± 2,7	+ 2,0	0,068
	Absence	112	82,4 ± 3,3	121	89,0 ± 2,7	−0,3	0,011

(Continued)

TABLE 1 | (Continued)

Phenotypic features of undifferentiated connective tissue dysplasia		Patients with SVBI (n = 136)		Control group (n = 136)		PC	I, bit
		abs.	P ± m,%	abs.	P ± m,%		
η^2 = 0,0%	p = 0,119	136	100,0	136	100,0	–	**0,079**
High or gothic palate	Presence	6	4,4 ± 1,8	2	1,5 ± 1,0	+ 4,7	0,070
	Absence	130	95,6 ± 1,8	134	98,5 ± 1,0	−0,2	0,002
η^2 = 0,0%	p = 0,151	136	100,0	136	100,0	–	**0,072**
Length of IV finger bigger than II	Presence	42	30,9 ± 4,0	32	23,5 ± 3,6	+ 1,2	0,043
	Absence	94	69,1 ± 4,0	104	76,5 ± 3,6	−0,4	0,016
η^2 = 0,0%	p = 0,173	136	100,0	136	100,0	–	**0,060**
Sandal-like foot crack	Presence	44	32,4 ± 4,0	38	27,9 ± 3,8	+ 0,6	0,014
	Absence	92	67,6 ± 4,0	98	72,1 ± 3,8	−0,3	0,006
η^2 = 0,0%	p = 0,428	136	100,0	136	100,0	–	**0,020**

P – reliability of differences in the factor frequency between studying groups; PC – prognostic coefficients of the factor, I – informativity of the factor (bit), η2 – force influence of the factor (%).

and (14.0 ± 3.0)% patients in the control group ($p < 0.0001$);

- the presence of such signs as myopia or other types of vision impairments was registered more often in – patients with SVBI (47.8 ± 4.3)% and (25.0 ± 3.7)% patients in the control group ($p < 0.0001$).
- such a sign as blue sclera was seen in patients with SVBI in (39.7 ± 4.2)% and in (19.9 ± 3.4)% patients in the control group ($p < 0.0001$). Other markers are represented in **Table 1**.

One of the most significant CBM (first rank position, ρ = 1) is the presence of structural impairment of the cervical spine (CS) (short neck or long neck), the frequency of which in the group of patients with SVBI was significantly ($p < 0.0001$) higher [correspondingly—(30.1 ± 3.9)%, in the control group—(5.9 ± 2.0)%]. The informative character of this feature is the highest – I = 0.994 bits, which allows it to be used in the prognostication system: with PC = + 6.9 bits, without PC = −1.3 bits.

The curvature of the nasal membrane as the CBM of the dysplastic-dependent changes (ρ = 11) was reliably recorded in patients with SVBI ($p < 0.011$) more often (8.1 ± 2.3)% in contrast to the control group, where this feature was detected in (1.5 ± 1.0)% of cases; the informative value of this feature was −I = 0.225 bits, with PC = + 7.4 bits without PC = −0.3 bits, the relative risk of the presence of this marker is 24.6:1.

Dysplastic-dependent changes that lead to the symptom of «ability to roll the tongue into a tube» were diagnosed significantly more often ($p < 0.010$) in case of patients with SVBI (30.1 ± 3.9)% than in the control group (16.9 ± 3.2)%; the informative value of this feature was—I = 0.216 bits: with PC = + 2.5 bits, without PC = −0.7 bits, the relative risk of the presence of this marker is 3.5:1.

The increase in skin elasticity, as a marker of UCTD, was diagnosed 2.7 times more frequently (p = 0.026) in case of patients with SVBI than among patients in the control group (11.8 ± 2.8)% and (4.4 ± 1.8)% of people respectively); the clinical informative value of this feature was – I = 0.169 bits, with PC = + 4.2 bits, without PC = −0.3 bits, the

TABLE 2 | Screening algorithm of spondylogenic vertebrobasilar insufficiency development on the basis of phenotypic markers of undifferentiated connective tissue dysplasia assessment in young age.

Clinic value of phenotypic markers	Prognostic coefficients in the presence of different phenotypic markers	
	Yes	No
Structural imbalance in the cervical spine	+ 6,9	−1,3
Scoliosis or kyphosis	+ 5,2	−1,2
Flatfoot	+ 7,3	−0,9
Dental abrasion	+ 4,4	−1,4
Myopia or other types of vision impairments	+ 2,8	−1,6
Blue sclera	+ 3,0	−1,2
Asthenic type of constitution	+ 2,3	−1,3
Radial-lacunar iris	+ 8,5	−0,8
Deformation of the breast	+ 7,0	−0,4
Clinodactyly	+ 1,7	−1,2
Curvature of the nasal membrane	+ 7,4	−0,3
«Ability to roll the tongue into a tube»	+ 2,5	−0,7
Increase in skin elasticity	+ 4,2	−0,3
Angiectasia	+ 4,8	−0,2
Anomalies of auricles	+ 1,1	−0,8
Anomalies of bite	+ 2,0	−0,3
High or gothic palate	+ 4,7	−0,2
Length of IV finger greater than II	+ 1,2	−0,4
Sandal-like foot crack	+ 0,6	−0,3

TABLE 3 | The individual assessment scale for risk development of spondylogenic vertebrobasilar insufficiency.

Risk group (RG) of patients depending on the amount of prognostic coefficients				
RG – 1	**Results$_{min}$ ≤ - 13**	**RG – 2**	**Results$_{max}$ ≥ + 13**	**RG – 3**
Low risk level		Middle risk level		High risk level

relative risk of the presence of this marker is 14:1. The presence of such vascular signs of embryogenesis as a marker of UCTD as angiectasia was significantly (p = 0.039) more often recorded in case of patients with SVBI (3.0 times) than among patients in the control group, accounting for (8.8 ± 2.4)% and (2.9 ± 1.4)%, respectively; the clinical informative value of this feature was −I = 0.148 bits, with PC = + 4.8 bits: without PC = −0.2 bits, the relative risk of the presence of this marker is 24:1. Other CBM (anomalies of auricles, bite, high or gothic palate, length IV. bigger than II, sandal-like foot crack) also had their clinical informative value and corresponding prognostic factors (see **Table 1**).

Screening algorithm of spondylogenic vertebrobasilar insufficiency development.

Thus, our clinical and informational CBM analysis allowed us to get clinical and statistical characteristics for each of them (**Table 2**).

We could divide the patients into three rehabilitation groups depending on the risk of development of SVBI by clinically and informationally analyzing the CBM of UCTD in patients with SVBI (**Table 3**).

Conclusion

1. According to this study, the diagnostic and prognostic value of CBM of UCTD is necessary for substantiation of the risk level of SVBI development.
2. The indicated CBM integrate the effect of phenotypic peculiarities and the formation of the risk of vascular disorders. The structural imbalance of cervical spine and the presence of (kyphosis/scoliosis) are the most informative and prognostically significant CBM of UCTD in SVBI patients (23).

Author contributions

NN: Conceived and designed the trial: . NN, OT: Carried out the trial. NN: Analyzed the data. NN, RS: Prepared the manuscript. All authors contributed to the article and approved the submitted version.

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Informed Consent for participation

All necessary written informed consent was obtained prior to participation in the study.

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