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Phenotypic Markers of Connective Tissue Dysplasia in the Diagnosis of Intracranial Aneurysms

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Abstract
A frequent manifestation of connective tissue dysplasia (CTD) is the development of muscular-elastic vessels pathology, in particular, intracranial arteries. In some cases, patients with intracranial aneurysms (IA) may have congenital anomalies or certain signs of hereditary CTD.
To assess external phenotypic symptoms of CTD in patients with established IA, we examined 60 patients. The main group consisted of 30 people with verified IA, a control group of 30 people without aneurysms.
Anamnesis, therapeutic examination, anthropometry, analysis of results of MR/CT angiography of patients with IA were carried out. CTD was determined according to the Recommendations of the Russian scientific medical society therapists in 2016.
As a result, the most frequent CTD fen: wide gap between the first and second toes, fused earlobe, short 5th fingers, telangiectasia, scoliosis, short 1 toe, Walker-Murdoch sign, blue sclera, varicose veins, hallux valgus, syndactyly of 2-3toes, hyperextensible skin, Skin striae distensae, dental crowding, flatfoot, multiple moles, hyperextensibility of thumbs, dolichostenomelia, flat back, thin skin, clinodactyly, protruding ears, arachnodactyly.
In the main group, almost all the main signs of CTD were found more often than in the control. Authentically often patients with IA have: telangiectasia, short 5th fingers, syndactyly of 2-3toes, hyperextensible skin, Skin striae distensae, dental crowding, multiple moles i, blue sclera, hallux valgus, hyperextensibility of thumbs, walker-murdoch sign, short 1toe, scoliosis, wide gap between the first and second toes, fused earlobe, varicose veins, thin skin, clinodactyly, thumb (Steinberg) signs.
The conclusion that the determination of phenotypic CTD signs, which are authentically more common among patients with cerebral aneurysms, can be used for early diagnosis and screening of intracranial aneurysms.

Keywords: intracranial aneurysms (IA), connective tissue dysplasia (CTD), phenotypic signs.

1. Introduction

Connective tissue dysplasia (CTD) is a genetically determined disorder of connective tissue development in the embryonic and postnatal periods characterized by defects in fibrous structures and the basic substance of connective tissue, leading to homeostasis disorder at all levels body [1].
The Committee Experts of Russian scientific society of cardiologists adopted the definition CTD as a violation of connective tissue polygenic-multifactor nature, combined into syndromes and phenotypes based on the commonality of external and/or visceral signs [2, 3].
Phenotypic manifestations of CTD are diverse; their clinical and prognostic value is determined not only by the degree of severity clinical sign, but also by the nature of the combinations of dysplastic-dependent changes. The expressed distribution of connective tissue in the body determines the damage of many organ systems [4, 5].
The frequent manifestation of CTD is the development of cardiovascular syndrome, with a predominance pathology of muscular-elastic vessels (70.67%), in particular, intracranial arteries (56.47%) [6]. The main group of cerebral vessels pathology consists of ruptures aneurysms of the Willis' circle [7].

Currently, many researchers agree that aneurysms occur primarily in bifurcations of the brain arteries, where there is a weakness of the "ligamentous apparatus". Degeneration of the internal elastic membrane is of great importance in the occurrence of aneurysms. Since there in the cerebral arteries no external elastic membrane, any changes in the internal membrane significantly weaken vascular wall [8].
Family intracranial aneurysms occur in 7-20% of patients with aneurysmal subarachnoid haemorrhage (ASH) and are not associated with any of the inherited connective tissue diseases. Family members with first-degree relative with patients ASH have a risk of intracranial aneurysms rupture four times higher compared to the General population [1, 9]. In some cases, patients with IA may have multiple congenital anomalies or some signs of hereditary connective tissue diseases [10].
The aim of the study was to evaluate external phenotypic signs of connective tissue dysplasia and morphoanatomical features of cerebral vascular lesions among patients with verified intracranial aneurysms.

2. Methods

The study included 60 patients, 32 women and 28 men aged 18 to 69 years, the average age of 47.2 years. The main group consisted of 30 people (16 women and 14 men) with verified intracranial aneurysms, who were treated in the neurosurgical department of municipal clinical hospital №40 of Ekaterinburg for 2017-2018. Control group – 30 people (16 women and 14 men), who are treated in the municipal clinical hospital №40, who do not have any aneurysms. Aneurysms were verified by MRI and CT angiography.
Anamnesis, therapeutic examination, anthropometry, analysis of results of MR/CT angiography of patients with IA were carried out. CTD was determined according to the National recommendations of the Russian Scientific Society of Internal Medicine 2016. Determined relationship of the arm span/palm length/feet length to growth, stretch the skin, skinfold thickness, visible small blood vessels on the face, chest and other body areas, telangiectasia, striae, multiple moles, areas of depigmentation, varicose veins, chest deformities, scoliosis, flat feet, arachnodactyly (signs of the wrist and thumb), diastase of the rectus abdominis muscles and hernia anterior abdominal wall, signs of joint hypermobility and other.The results of MRI/CT angiography of 60 examined patients were analyzed.
Statistical processing of results was performed using the program Primer of biostatistics version 4.03. Each phenotypic sign of CTD was subject to analysis. Statistical significance was estimated using the $\chi 2$ criterion. The differences are significant at $p < 0.05$.

3. Results

As a result, the most frequent CTD fen: wide gap between the first and second toes, fused earlobe, short 5th fingers, telangiectasia, scoliosis, short 1 toe, Walker-Murdoch sign, blue sclera, varicose veins, hallux valgus, syndactyly of 2-3toes, hyperextensible skin, skin striae distensae, dental crowding, flatfoot, multiple moles, hyperextensibility of thumbs, dolichostenomelia, flat back, thin skin, clinodactyly, protruding ears, arachnodactyly. In the main group, almost all the main signs of CTD were found more often than in the control.
The defined external features of CTD and their detection frequency are shown in table 1.

Table 1. Phenotypic signs of connective tissue dysplasia in patients with verified intracranial aneurysms

Phenotypes	Frequency (n=60)	Aneurysms group (n=30)	Control group (n=30)	χ^2	P
Wide gap between the 1st and 2nd toes	24 (40%)	17	7	5,625	0,018
Fused earlobe	24 (40%)	17	7	5,625	0,018
Telangiectasias	22 (36,67%)	18	4	12,129	0,000
Short 5th finger	22 (36,67%)	18	4	12,129	0,000
Scoliosis	20 (33,33%)	15	5	6,075	0,014
Short 1 toe	19 (31,67%)	15	4	7,702	0,006
Walker-Murdoch sign	19 (31,67%)	15	4	7,702	0,006
Blue sclera	17 (28,33%)	14	3	8,208	0,004
Varicose veins	17 (28,33%)	13	4	5,253	0,022
Hallux valgus	17 (28,33%)	12	5	8,203	0,004
Syndactyly of 2-3 toe	16 (26,67%)	12	4	9,961	0,002
Hyperextensible skin	16 (26,67%)	12	4	9,961	0,002
Skin striae distensae	16 (26,67%)	12	4	9,961	0,002
Abnormal bite	16 (26,67%)	12	4	9,961	0,002
Flat foot	16 (26,67%)	11	5	2,131	0,144
Multiple moles	16 (26,67%)	12	4	9,961	0,002
Dental crowding	15 (25%)	10	5	1,422	0,233
Hypermobility of the first finger	14 (23,33%)	12	2	7,547	0,006
Thumb (Steinberg) Signs	14 (23,33%)	11	3	4,565	0,033
Flat back	12 (20%)	6	6	0,104	0,747
Thin skin	12 (20%)	10	2	5,104	0,024
Clinodactyly of 5th finger	12 (20%)	10	2	5,104	0,024
Protruding ears	12 (20%)	9	3	2,604	0,107
Dolichostenomelia	11 (18,33%)	7	4	0,455	0,505
Genus valgus	10 (16,67%)	8	2	3,000	0,083
Arachnodactyly	10 (16,67%)	8	2	3,000	0,083

Authentically often patients with IA have: telangiectasia (p=0), short 5th fingers (p=0), syndactyly (p=0,002), hyperextensible skin (p=0,002), striae (p=0,002), dental crowding (p=0,002), multiple moles (p=0,002), blue sclera (p=0,004), hallux valgus (p=0,004), hyperextensibility of thumbs (p=0,006), Walker-Murdoch sign (p=0,006), short 1toe (p=0,006), scoliosis (p=0,014), wide gap between the first and second toes (p=0,018), fused earlobe (p=0,018), varicose veins (p=0,022), thin skin (p=0,024), clinodactyly (p=0,024), thumb (Steinberg) signs (p=0,033).

The conclusion that the determination of phenotypic signs CTD, which are authentically more common among patients with cerebral aneurysms, can be used for early diagnosis and screening of intracranial aneurysms. These phenotypic signs we designated as external markers of dysplasia and presented in Diagram 1.

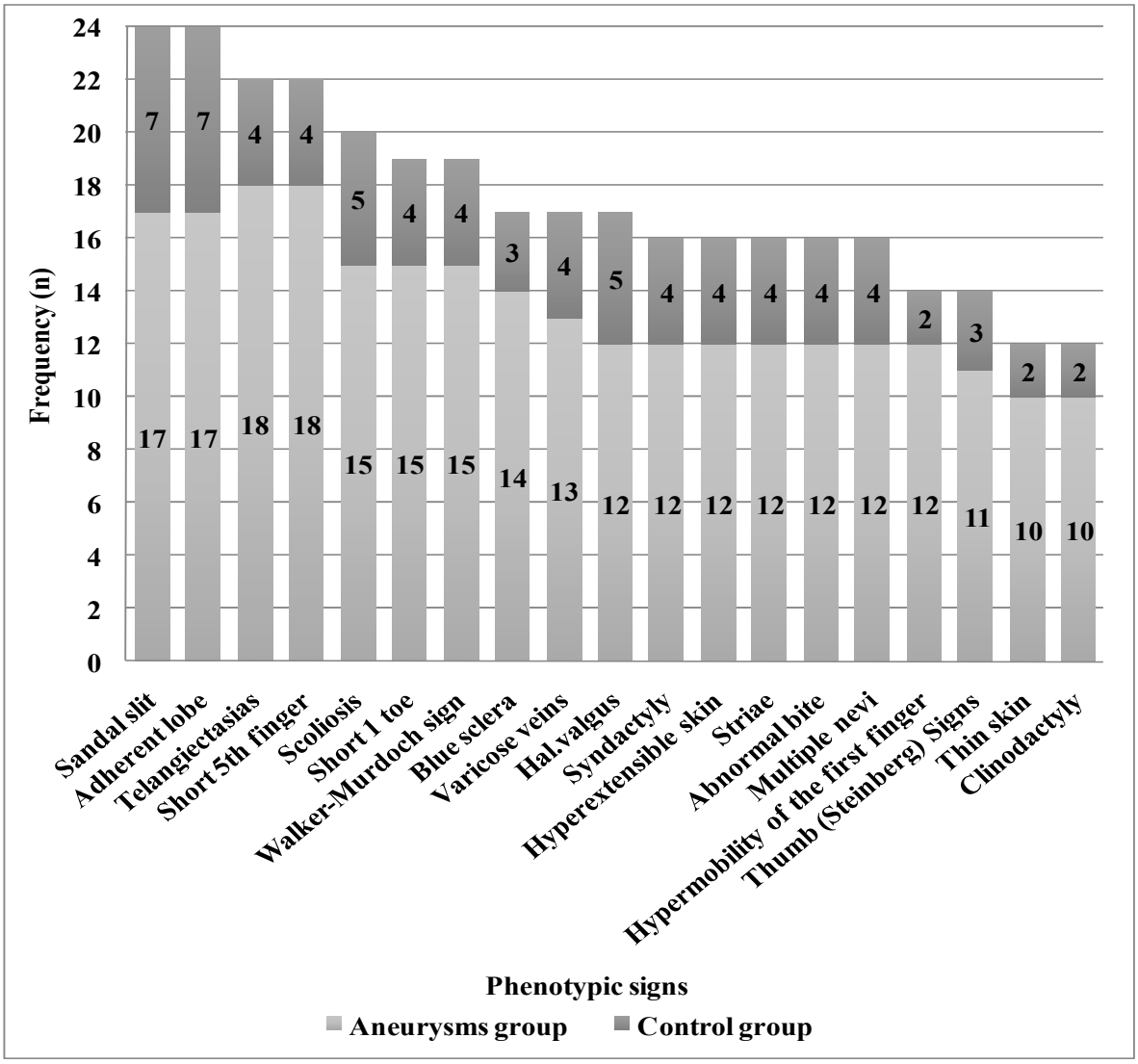

Diagram 1. The frequency of external signs connective tissue dysplasia in comparison groups

In addition, in this study, we found that the pathology of the muscle-elastic vessels was represented by damage to the coronary and cerebral arteries. Of the 40 revealed aneurysms (21 patients with 1 aneurysm, 8 patients with 2 aneurysms, 1 patient with 3 aneurysms) most often aneurysms were located in the anterior cerebral artery – 40%, in the internal carotid artery was 25%, in the middle cerebral artery was 22.5%, in the upper cerebellar and anterior connective artery was 5%, less frequently there were spinal artery aneurysms – 2.5%.

Aneurysms were accompanied by thinning, tortuosity and a decrease in the diameter of the other cerebral vessels. Among the patients with IA (30 people), the following abnormalities of cerebral arteries were revealed: aplasia/hypoplasia in 11 patients, stenosis in 10 patients, kinking in 4 patients, in 5 patients no pathology of cerebral arteries was detected.

4. Conclusions

Intracranial aneurysms were most often registered in the anterior cerebral artery – 40%, in the internal carotid artery – 25% and in the middle cerebral artery – 22.5%.

In 83.3% of patients with aneurysms of cerebral vessels were related to abnormal development of the arteries of the brain, of which the most common aplasia/hypoplasia, stenosis and kinking.

The conclusion that the determination of phenotypic signs CTD, which are authentically more common among patients with cerebral aneurysms such as telangiectasia, short 5th fingers, syndactyly, hyperextensible skin, striae, dental crowding, multiple moles, blue sclera, hallux valgus, hyperextensibility of thumbs, Walker-Murdoch sign, short 1toe, scoliosis, wide gap between the first and second toes, fused earlobe, varicose veins, thin skin, clinodactyly, Thumb (Steinberg) Signs, can be used for early diagnosis and screening of intracranial aneurysms.

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