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Markers of Connective Tissue Dysplasia in Cervical Artery Dissection and Its Predisposing Factors[1]

M. V. Gubanova[a], *, L. A. Kalashnikova[a], L. A. Dobrynina[a], **, K. V. Shamtieva[a], and A. B. Berdalin[b]

[a] *Research Center of Neurology, Moscow, 125367 Russia*
[b] *Moscow State University, Moscow, Russia*
**e-mail: m.v.gubanova@yandex.ru*
***e-mail: dobrla@mail.ru*

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Abstract—Introduction: Cervical artery dissection (CeAD) is the most frequent cause of ischemic stroke in young adults. Dysplasia of arterial wall underlies its weakness and predisposes to dissection. **Objective:** To assess clinical signs of connective tissue dysplasia (CTD) in patients with CeAD using special criteria of CTD, and to evaluate predisposing factors for the CeAD development. **Materials and methods:** We examined 80 patients (mean age 38.5 ± 13.5; 49 females) with CeAD verified by MRI/MRA and 20 healthy volunteers. We estimated 48 signs of CTD included into the Villefranche diagnostic criteria for the vascular type of Ehlers–Danlos syndrome, the Ghent criteria for Marfan syndrome, the Beighton criteria of joint hypermobility and some others, as well as history of headache. Each sign was counted as present or absent, yielding the individual and mean CTD group scores. **Results:** Clinical CTD signs were more frequently detected in patients with CeAD than in controls (mean score 7.9 ± 3.6 vs. 4.6 ± 2.5; $p \le 0.05$. **Conclusions:** The presence of the 4 main and 2 additional diagnostic criteria of CTD has a high predictive value of CeAD and can be used as its diagnostic and prognostic criterion. Dissection of the arterial wall with signs of dysplasia is provoked by various additional factors.

Keywords: connective tissue dysplasia, cervical artery dissection, markers, provoking factors, prognosis
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INTRODUCTION

In recent years, there has been an increase in the frequency of diagnosis of cervical artery dissection (CeAD), which is the main cause (about 1/4 of all cases) of ischemic stroke (IS) at a young age, and also is one of relatively unknown causes of acute isolated cervico-cephalic pain syndrome [1–9]. The annual frequency of verified cases of CeAD dissection is 2–3 : 100000. According to the majority of researchers, this figure does not reflect the true frequency due to poor detection of this pathology, as evidenced by our clinical experience [1, 3, 6, 8–12].

It is assumed that the main reason for the development of dissection is the weakness of the arterial wall due to its dysplasia, which, according to our data, corresponds to fibromuscular dysplasia [1, 3, 13–16]. Detection of dysplasia not only in the dissected, but also in other arteries supplying blood to the brain, allowed researchers to designate it as a *generalized cerebral arteriopathy* [1, 13, 15–17]. The clinical confirmation of the above statement is the development of dissections of several major arteries in each fifth patient [3, 10, 12, 18–21]. Moreover, detection of changes in connective tissue, similar to those in the arterial wall, in 60% of patients with CeAD dissection during electron microscopy of the skin biopsysamples indicates the systemic nature of connective tissue dysplasia (CTD) [22]. Despite the rarity of well-known hereditary syndromes (Ehlers–Danlo type IV syndrome, Marfan, imperfect osteogenesis, fibromysilic dysplasia – up to 4%) [1, 6], and family cases (up to 1%) among the patients with CeAD dissection, the presence of systemic signs of CTD does not allow to exclude the hereditary nature of connective tissue pathology in the form of incomplete penetrance, de novo mutations, etc. [12, 23]. Earlier, we obtained data on the presence of mitochondrial pathology in patients with CeAD dissection, including cases with a detected mitochondrial DNA mutation [20, 24, 25]. The systemic nature of CTD implies the presence of clinical signs of tissue and organ damage with external manifestations, primarily in skin, bones, joints, and viscera.

In addition to the typical clinical manifestations of the dissection, the signs of CTD could be useful in determining the cause of IS, especially in absence of its verification with methods of neurovisualization,

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and in assessing the risk of dissection development in patients with headache, since the latter is present in almost half of patients with dissection.

Distinctive features of CTD, specific for the famous hereditary connective tissue diseases, are rarely found in patients with spontaneous dissection. This makes it difficult to directly use them for undifferentiated pathology of connective tissue (undifferentiated dysplasia), which is characteristic for the dissection of the arteries of the brain. There are very few foreign studies evaluating the frequency of undifferentiated dysplasia signs presence in patients with CeAD dissection [18, 19, 26, 27]. The application of criteria for diffuse connective tissue diseases developed for specific nosologies (hereditary syndromes, joint hypermobility, etc.) is also limited in assessing signs of CTD in patients with cerebral artery dissection [28–33]. Obviously, it is necessary to develop a diagnostic unified scale of CTD symptoms and to use it as a diagnostic tool for suspicion of cervical arteries dissection resulting in IS or acute isolated cervicocephalgic pain syndrome at a young age.

The fact that not all patients with CTD develop dissection suggests the action of additional provoking factors. Their combination with the already existing weakness of the arterial wall is of great importance. The provoking factors of dissection include usually light head and neck injuries, head turns, infections, alcohol, and estrogen-containing drugs [3, 6, 12, 34, 35].

The purpose of this study is to clarify the diagnostic features of CTD in the CeAD dissection, as well as the evaluation of provoking factors of its development.

MATERIALS AND METHODS

The study included 80 patients with spontaneous CeAD dissection, with 49 (61.25%) women (mean age 38.5 ± 13.5 years) among them. In all cases, the dissection of CeAD was verified by the signs of intramural (intravenous) hematoma in the MRI of the neck in the T1 fat-sat mode and the identification of characteristic angiographic signs in MRA, such as prolonged uniform or varying stenosis, cone-shaped pre-occlusive narrowing of the artery lumen, and dissective aneurysm or the formation of a double lumen of the artery. Dissection in 32 (40%) patients was located in the internal carotid artery (ICA), in 37 (46.25%) of them—in the vertebral artery (VA), and in 11 (13.75%)—simultaneously in the ICA and VA.

Clinical manifestations were represented by acute cerebrovascular accident (CVA)—in 46 (57.5%) patients, by acute isolated cervical-cephalgic pain syndrome—in 34 (42.5%), and by its combination with transitory ischemic attacks (TIA)—in 2 (2.5%) patients. Dissection of ICA was more frequent in men (61%, $p = 0.001$), and dissection of the VA—in women (59%, $p = 0.003$); the combined dissection of ICA and VA in men and women was registered with equal rate (13 and 14%, respectively).

All patients had a complete study of their history and underwent assessment of dissection development provoking factors, neurologic exam and evaluation for signs of CTD. The latter included 48 potential for dissection signs observed in the Ehlers–Danlo syndrome vascular type (Wulffranchian criteria), the Marfan syndrome (Ghent criteria), the hypermobility of the joints (the Bayton criteria), and other signs of CTD (All-Russian Scientific Society of Cardiologists, 2012; Smolnova, 2003) (Table 1). Each sign was counted as positive or negative (present or not), corresponding to one score (1 point if present, 0 points if not); on the given basis we calculated total CTD signs sum for each patient [28–33]. The presence and main features of the headache, which existed in a patient before the development of the dissection, were assessed separately. Body mass index was measured for all patients.

Control group consisted of 20 healthy volunteers. The experimental group and the control group did not differ significantly by sex and age.

The statistical processing of the results was carried out with IBM SPSS Statistics 23.0 software package (IBM, USA). The quantitative variables were the mean and standard deviation, the qualitative and ordinal variables—frequency and percentage share. The differences were considered statistically significant at $p \leq 0.05$. A comparison of the total CTD score in groups was carried out by the Student's t-test; the correlations between the individual quantitative variables were estimated by the Spearman method. To check the normal distribution of the quantitative trait, the Shapiro–Wilk test was used. Since some samples were not normal, the Mann–Whitney test was used to compare nonparametric data. For comparison of qualitative variables, the exact Fisher criterion was used. To estimate the predictive ability of individual signs of CTD in the development of dissection, binary logistic regression was used. The adequacy of the chosen logistic model was evaluated by ROC analysis.

RESULTS

In the group of patients with dissection, the total CTD symptoms score made up 7.9 ± 3.6 points and significantly differed from the control group—4.6 ± 2.5 points ($p = 0.0039$). Diagnostically significant signs (more than 8 points) were present in 53% of patients.

The body mass index (BMI) was 23 ± 3.9, which corresponds to the normal weight (19–25). The inverse relationship of BMI and CTD severity was revealed ($r = -0.245$, $p = 0.021$).

In dissection, the total CTD score was greater in women (8.7 ± 3 points) than in men (6.4 ± 2.5, $p = 0.054$). There was no significant difference in the comparison of CTD severity in patients with ICA dis-

Table 1. Estimated signs of CTD

Craniofacial features	• dolichocephaly; • down-slanting palpebral fissures: when the outer canthus is positioned lower than usual; • epicanthus: a fold of skin extending from the upper eyelid to or over the inner canthus of the eye; • malar hypoplasia (micrognathism); • retrognathia: abnormal posterior positioning of the mandible or, less frequently, the maxilla; • exophthalmos; • enophthalmos; • small chin; • thin lips; • soft, prominent ears, adherent lobe
Skeletal features	• Walker–Murdoch sign (wrist sign); • Steinberg sign (thumb sign); • high-arched palate; • reduced upper to lower segment ratio <0.86; • arm span to height ratio >1.03; • length of a foot to height ratio >15%; • length of palm to height ratio >11%; • reduced extension of the elbow (<170°); • scoliosis; • valgus deformities of the feet; • flatfoot longitudinal or transverse; • pectus excavatum; • pectus carinatum; • increased bone fragility
Articular features	• Beighton score ≥4; • small joints hypermobility; • dislocations, subluxations in more than one joint or repeated dislocations, subluxations in one joint
Cutaneous features	• thin, translucent skin (visible subcutaneous vessels); • easy bruising; • skin hyperextensibility, laxity (more than 3 cm); • striae atrophicae (not associated with marked weight loss or pregnancy); • acrogeria; • soft, velvety texture; • widened atrophic scars, papyraceous appearance or keloid scars; • skin pigmentation (dark spots); • molyuscoid pseudotumors and spheroid formations in the region of elbows and knees
Muscular features	• muscle weakness, poor tolerance of exercise; • tendon/muscle ruptures; • hernias and prolapses of organs, as well as postoperative hernia
Other features	• myopia, astigmatism; • blue sclera; • arterial, uterine, intestinal fragility or rupture; • early-onset varicose veins; • gingival recession; • dentinogenesis imperfecta (hypoplasia of teeth and disruption of their growth, diastema); • nasal bleeding; • propensity to constipation; • arterial hypotension

CTD—connective tissue dysplasia.

Table 2. Predisposing factors of cervical artery dissection

Predisposing factors	Patients
Minor trauma of head or extreme neck movements	63 (78.75%)
Alcohol	18 (22.5%)
Contraceptives (estrogen-containing)	13 (16.25%)
Infection	14 (17.5%)
Trophic factors (weight loss, protein-free diet, sports nutrition)	17 (21.25%)

Table 3. The frequency of CTD signs and history of headache in patients with CeAD and in the control group (binary logistic regression, $p < 0.05$)

CTD signs	Patients with CeAD ($n = 80$)	Control group ($n = 20$)	p	OR	95% CI	
					lower	upper
History of headache	48 (60%)	7 (35%)	0.022	4.07	1.169	14.183
Arterial hypotension (BP 110/70 mm Hg and below)	41 (51.25%)	4 (20%)	0.012	5.46	1.334	22.351
Extensive bruising	32 (40%)	2 (10%)	0.011	5.426	1.302	29.847
Widened atrophic scars	18 (22.5%)	0%	0.019	4.425	1.26	9.340
Translucent skin	23 (28.75%)	1 (5%)	0.034	7.27	1.077	80.113
Hight palate	16 (20%)	0%	0.034	3.201	1.07	8.85
Propersity to constipation	24 (30%)	2 (10%)	0.050	3.901	1.671	22.681
Nasal bleeding	27 (33.75%)	3 (15%)	0.043	5.012	1.042	24.114
Blue sclera	16 (20%)	1 (5%)	0.050	6.064	1.086	13.120

CTD—connective tissue dysplasia, CeAD—cervical artery dissection, p—value, OR—odds ratio, CI—confidence interval, BP—blood pressure.

section (6.9 ± 2.4 points) and VA dissection (8.4 ± 3.2); (6.9 ± 2.6) or isolated cervico-cephalgy pain syndrome (8.2 ± 3.8), as well as in patients younger than 45 years (7.8 ± 2.6 points) and over 45 years (6.4 ± 2.7).

Table 2 shows the incidence of dissection provoking factors. For the majority (63 patients, 78.75%) dissection development was preceded by neck movement or physical load with muscle tension of the neck or shoulder girdle. Practically all patients (78 patients, 97.5%) had provoking factors of dissection: one risk factor was present in 38 (47.5%) patients, and a combination of factors in 40 (50%).

Among the 48 evaluated signs of CTD, only 8 signs reliably differed from the control group. The groups also differed significantly in terms of history of headache. Table 3 shows the signs of CTD and their presence in patients with dissection in comparison with the control group, together with the results of binary logistic regression for these signs ($p \le 0.05$).

As it follows from the data of Table 3, a history of headache was noted in patients with dissection more often than in control group (60% vs. 35%, $p = 0.022$). Among patients with headache, there were more patients with VA dissection (58%) than ICA (33%) ($p = 0.006$). Headache, as a rule, was bilateral, had a pressing, squeezing, less often pulsing character, and was not accompanied by photo-, phonophobia, nausea, vomiting. The most frequent sign of CTD in patients with dissection, as compared with the control group, was arterial hypotension (BP 110/70 mm Hg and below) (51.25% vs. 20%, $p = 0.012$). It was more common with VA dissection (66%) than ICA dissection (41%) ($p = 0.022$), and was associated with a history of headache in 50% of cases.

Other characteristic signs of CTD were: a tendency to bruising, increased vulnerability (40% vs. 10%, $p = 0.011$); wide atrophic scars (22.5% vs. 0%, $p = 0.019$); thin, translucent skin (28.75% versus 5%, $p = 0.034$); high-arched palate (20% vs. 0%, $p = 0.034$); liability to constipation (30% vs. 10%, $p = 0.050$); nasal bleeding (33.75% versus 15%, $p = 0.043$); blue sclera (20% vs. 5%, $p = 0.050$). Based on the results of binary logistic regression, the detection of the above-described signs of CTD significantly increased the probability of dissection development in this category of patients—the odds ratio (OR) for these symptoms was from 3 to 7. In accordance with the statistical significance of the features under study, they were divided into basic (big) and additional (small) diagnostic and prognostic criteria (Table 4). Statistical significance from 0.01 to 0.02 corresponded to the main criteria; and statistical

significance from 0.03 to 0.05—to additional criteria. The introduction into the logistic regression model of established signs of CTD associated with dissection and IS, ensures the matching of the predicted and real distribution of patients in groups with and without dissection up to 75–77%.

In the presence of 4 basic and 2 additional diagnostic criteria, the maximum predictive power of the regression model is achieved simultaneously, which makes it possible to choose this combination of signs as a diagnostic and prognostic criterion for the development of dissection.

To determine the sensitivity and specificity of the obtained diagnostic scale, ROC analysis based on the results of a logistic model with 4 main and 2 additional diagnostic features was performed (Fig. 1). As the figure demonstrates, the ROC curve of the CTD signs is close to the ideal shape (the area under the curve is 0.90 (CI 0.84–0.96), the maximum sensitivity of the model is 86%, the specificity is 85%), that testifies effectiveness of application of the developed scale for the diagnosis of CeAD dissection or predisposition to it.

DISCUSSION

The study showed that signs of CTD are often found in patients with CeAD. This indicates the presence of widespread pathology of the connective tissue, and not just a local lesion of the extra- and intracranial arteries wall. The data obtained in this work is consistent with the results of our morphological studies showing the presence of dysplastic changes, which determine the weakness of the arterial wall and predispose to its dissection [1, 15, 16, 20]. Moreover, the study showed the widespread tissue involvement in CTD, which is not limited only to arteries that supply blood to the brain. In connection with this, the detection of CTD signs in young patients with IS of unknown origin, especially if neurovisual verification of dissection is unavailable for any reason, can serve as an additional argument in favor of this IS cause. This statement is indirectly confirmed by Giossi et al. (2014). The authors evaluated the signs of CTD in 84 young patients with impaired cerebral circulation due to dissection and in 84 patients with IS of another genesis and showed that CTD signs were more frequent in dissection (mean score 4.5 ± 3.5 versus 1.9 ± 2.3, $p < 0.001$). In addition, it was noted that patients with dissection often had an asthenic constitution, a lower cholesterol level, abused smoking less, less often suffered from high blood pressure and diabetes mellitus. Giossi et al. also noted that in patients with dissection bone anomalies (scoliosis and small funnel deformation of the chest) as well as hypermobility/weakness of the joints, increased skin extensibility, and characteristic facial features due to underdeveloped subcutaneous fat layer (hollow cheeks and wide open, forward eyes, stretched skin) were more common. A simultaneous extensive molecular genetic study did not reveal any patient with a specific type of hereditary connective tissue disease, which assumes the presence of an undifferentiated form of connective tissue pathology primarily involving the vascular wall. It is pertinent to note that back in 1998 Schievink et al. examined the hypothesis of subclinical disruption of connective tissue in many patients with CeAD dissection [18].

Table 4. Diagnostic and prognostic criteria of connective tissue dysplasia for cervical artery dissection

No.	Main diagnostic and prognostic criteria
1	History of headache
2	Arterial hypotension
3	Extensive bruising
4	Widened atrophic scars
Additional diagnostic and prognostic criteria	
1	Translucent skin
2	Nasal bleeding
3	Predisposition to constipation
4	Blue sclera
5	High-arched palate

Although other researchers noted the signs of CTD in patients with dissection, we were the first to identify the main and additional criteria of CTD on the basis of binary logistic regression, the use of which in

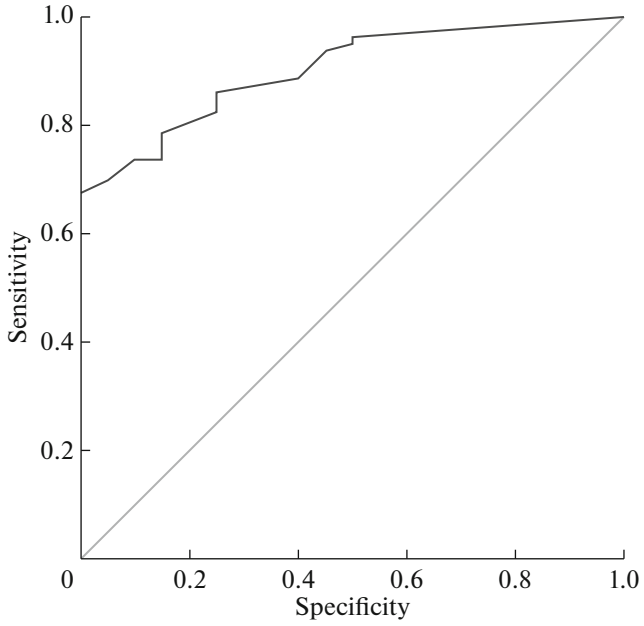

Fig. 1. ROC curve of diagnostic and prognostic criteria of connective tissue dysplasia for cervical artery dissection. Area under the curve 0.90 (CI, 0.84–0.96), model sensitivity 86%, model specificity 85%.

patients with IS of unspecified genesis makes it possible to diagnose the dissection of CeAD due to CTD with a high degree of probability. The main features included arterial hypotension, tendency to bruising, increased skin vulnerability, extensive atrophic scars (after cuts and surgical interventions), and a history of headache. Additional signs included thin, translucent skin, nasal bleeding, liability to constipation, blue sclera, and high-arched palate. Despite the heterogeneity of the selected CTD signs, their unifying feature is the common mesenchymal origin of their connective tissue base. Detection of the indicated signs in patients with IS, which clinical manifestation is characteristic for dissection not verified during neuroimaging, will serve an additional argument for dissection.

The morphological structure of the connective tissue includes various cells (fibroblasts and their subtypes, smooth muscle cells, macrophages, mast cells) and an intercellular matrix filled with the basic substance from the fibrous components (collagen, elastin), carbohydrate-protein complexes (proteoglycans and glycoproteins), and inorganic compounds. Differences in the connective tissue base of various anatomical structures have respect to micro- and macroarchitectonics, various quantitative correlations of structural and chemical elements that are detected with regularity in all types of connective tissue. This allows us to speak of a system united by a common mesenchymal origin, and the general principles of structural arrangement and functions.

Headache which was present in 60% of our patients with dissection, and which was one of the main diagnostic signs of CTD, also, in our opinion, is associated with CTD, and should not be considered a migraine, as it is seen by other authors [3, 6, 12, 26]. Such clinical features of anamnestic headache in patients with dissection, as rare photo- and phonophobia, nausea, and vomiting, indicate a lack of involvement of the central nociceptive structures of the brain, which play a key role in the genesis of migraine. The pathophysiological basis of the anamnestic headache during dissection seems to be the dystonic changes in the wall of the cranial arteries associated with their dysplasia [15, 16, 20].

CTD in patients with dissection is a stable and not a transient condition, which does not correspond to the rarity of dissection relapses [1]. Such dissociation presupposes the importance of the influence of additional external and internal factors that play the role of provocation. In majority of our patients (78.75%), dissection was provoked by neck movements, physical stress, and light head trauma that are accompanied by tension of the arteries and can cause an intimal tearing. According to foreign researchers, slight trauma plays a role in approximately 40.5% of cases of CeAD dissections [35]. A trivial recent infection that occurred 2–4 weeks preceding dissection, was noted in 14 (17.5%) of our subjects. According to the published data, the infection provokes the development of CeAD dissection in almost a third of cases that is statistically significantly more frequent than in strokes of a different genesis [34]. It is believed that the infection further "weakens" the extracellular matrix of the arterial wall, thereby provoking dissection. With the latter mechanism, obviously, the provocative role of contraceptives taken by 13 (16%) of the patients that we examined, is also significant. The provocative role of inadequate protein nutrition (fasting, vegetarian diet) and the use of drugs for weight loss as noted earlier [1, 7], is confirmed by the data obtained in this study on the inverse relationship of BMI and the degree of CTD ($p = 0.021$). Important role of provoking factors of dissection is shown in the study of A. Giossi et al.: various provoking factors were more often found in patients with IS due to dissection than in stroke of another genesis.

Thus, in the majority of patients with CeAD dissection there are signs of CTD, which indicates the widespread nature of arterial wall dysplasia as the main reason for dissection. The main and additional signs of CTD associated with dissection that we identified, can be used to specify the genesis of IS in cases when necessary instrumental studies are not available. In young people with headaches that do not meet the criteria for migraine, assessment of the main and additional signs of CTD can identify a risk group that threatens the development of dissection with the subsequent prescription of preventive treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement on the welfare of animals. This article does not contain any studies with animals performed by any of the authors.

Statement of compliance with standards of research involving humans as subjects. Each representative from the experimental and control groups signed an informed consent to participate in the study. The study protocol was approved by the local ethical committee of the Research Center of Neurology.

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