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Systemic connective tissue abnormalities in patients with saccular intracranial aneurysms

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Objectives – Our purpose was to identify the incidence and significance of markers of systemic connective tissue abnormalities (CTA) in patients with saccular intracranial aneurysms (SIA). *Materials and methods* – This prospective case–control study included 199 consecutive patients with SIA (103 women and 96 men, mean age – 43.2 years) and 194 control patients – blood donors (108 – men, 86 – women, mean age – 38.4 years). Aneurysms were verified by conventional cerebral angiography. All patients were examined by the first author using a specially designed questionnaire and a standardized physical examination with special emphasis on systemic CTA. *Results* – Twelve markers of systemic CTA were significantly higher in patients with SIA than in controls: visible vessels on face and chest (59.8%), scoliosis (44.7%), varicose veins in legs (39.7%), flatfoot (34.6%), hyperextensibility of the skin (33.6%), spontaneous epistaxis (25.6%), easy bruising (20.6%), abdominal hernia (13.6%), periodontal disease (10.5%), chest deformations (7.5%), abdominal striae (3.5%), joint hypermobility (2.5%). A blinded validation study in a subset of 43 patients showed similar results. Among patients with SIA, 125 of 199 patients (62.8%) had at least three markers of systemic CTA compared with 23 (11.8%) of the controls ($P < 0.0001$, OR = 12.5, 95% CI 7.45–21.1). The mean number of markers of systemic CTA in patients with SIA was 3.07 and 1.17 in controls. *Conclusion* – Patients with SIA have multiple markers of systemic connective tissue abnormalities. Systemic weakness of connective tissue represents a risk factor for development of SIA. Identification of these markers may help in detection of high-risk patients.

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Key words: connective tissue; intracranial aneurysms; markers; risk factors

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Introduction

Saccular intracranial aneurysms (SIA) are dilatations of intracranial arteries most often located at a branch point of major arteries on the circle of Willis. Despite modern therapy, many patients die or are left disabled as a direct result of a severe initial hemorrhage. The development of effective screening programs depends on understanding the pathogenesis of SIA. The pathogenesis of aneurysm formation and rupture is not clearly understood but is undoubtedly multifactorial. It is generally accepted that SIA arise from an interaction between structural weakness of the arterial wall and hemodynamic factors. Any disturbances of connective tissue elements in the vascular wall can weaken its strength. This may be caused by hereditary and acquired factors. Acquired factors may include smoking, arterial hypertension, infection, and alcohol abuse. Genetic factors may include inheritable connective tissue diseases (1–3). In some cases, patients with SIA may have multiple congenital anomalies or signs of hereditary connective tissue diseases (4, 5). However, the role of systemic connective tissue abnormalities (CTA) in patients with SIA is not well established. Therefore, the purpose of this study was to evaluate the frequency of signs

of systemic CTA in a large group of patients with SIA compared with healthy controls.

Methods

This prospective case–control study included 199 patients with saccular intracranial aneurysms (SIA) (103 women and 96 men, mean age – 43.2 years) and 194 control patients – blood donors at the regional blood transfusion center (108 – men, 86 – women, mean age – 38.4 years). We consecutively recruited patients with SIA admitted to our regional neurosurgical center from 2003 to 2006. Aneurysms were verified by conventional cerebral angiography. 36 (18.1%) patients had multiple aneurysms. Twenty two patients (11%) had unruptured aneurysms. One hundred and ninety patients were operated of whom 177 had clipping and 13 coiling. In nine patients, surgery was not performed.

Selection of patients with aneurysms for the study was carried out on the following criteria.

Inclusion criteria for patients with SIA

1. The patient had at least one saccular intracranial aneurysm, confirmed by cerebral angiography.
2. The patient lived in Yekaterinburg or in the Urals region.
3. The patient agreed to conduct additional examinations.

Exclusion criteria

1. The patient had fusiform, traumatic, or mycotic aneurysm.
2. The patient had contraindications to additional methods of investigation.
3. The patient refused further examination.

The control patients were examined in the regional blood transfusion center during 2003–2006.

Inclusion criteria for the control group

1. The patient had no history of stroke, intracranial hemorrhage and other serious neurological and somatic disease, and hereditary connective tissue diseases.
2. The patient had no relatives with intracranial aneurysms and inherited connective tissue diseases.
3. The patient's age and sex were matched to patients with SIA.
4. The patient agreed to additional methods of examination.

We did not perform MR-angiography in control patients because the frequency of aneurysms for an average adult without specific risk factors is only 2–3% (6).

The Medical Ethics Committee of the Urals State Medical Academy approved this study. Informed consent was obtained from all participants.

All patients were examined using a specially designed questionnaire which included detailed information about the present and past history of diseases, the history of their pedigree, about smoking and alcohol consumption, results of physical and neurological examinations, physician consultations, and treatment. Arterial hypertension was defined as a history of blood pressure (diastolic pressure $\geq$90 mm Hg and/or systolic values $\geq$140 mm Hg) or if physician observed blood pressure of 140/90 mmHg or above on three consecutive measurements at least six hours apart. In the process of data collection, patients were asked in details about previous diseases that can be due, at least partly, to connective tissue pathology: periodontal disease, myopia, bronchiectasis, spontaneous pneumothorax, esophageal diverticula, intestinal perforation, the expansion of the esophagus, hernias, varicose veins, ptosis and cysts of various organs, scoliosis, flatfoot, easy bruising, spontaneous nose bleeds, bleedings from the gastrointestinal tract, hereditary disease of connective tissue (polycystic kidney disease, Ehlers–Danlos syndrome, Marfan syndrome, neurofibromatosis, pseudoxanthoma elasticum). All these disorders can be features of different inherited connective tissue disorders, and sometimes these disorders can be isolated (7).

To identify signs of connective tissue disease in patients with SIA and controls, the physical examination was conducted by a special procedure. Examination was carried out with the patient standing in good light. It included height, weight, body mass index, extensibility of skin over the middle of the clavicle. Extensibility of the skin was considered as high if the magnitude of the skin fold over the external end of the clavicle was at least 4.0 cm. This size was measured using a ruler. We also detected the presence of visible small blood vessels (red or blue thin venules) on the face (cheeks and/or around nose), on chest, and other parts of the body, including telangiectasia and angiomas. Varicose veins on legs were also estimated (8). The presence of longitudinal flatfoot was determined using a pressure-sensitive film (9). Scoliosis was detected using scoliometer measurement (10). Chest deformities (pectus excavatum, pectus carinatum) were

described. Arachnodactyly was determined in the presence of disproportionately long fingers and feet such as spider fingers, positive wrist, or thumb signs: Walker–Murdoch sign (increased finger length relative to wrist circumference) and Steinberg sign (a long thumb relative to palm width) (7). We also conducted tests for detection of joint hypermobility at distal phalangeal, metacarpophalangeal joints, wrist, elbow, knee, and ankle by the active range of joint motion measurements and goniometer (11, 12). This test was positive if joint hypermobility was detected at least in one of these joints. Some patients with SIA had a history of easy bruising and frequent (at least three times per year) spontaneous nasal hemorrhages. Therefore, we asked all patients about this too. Easy bruising was determined as the frequent appearance of purple, brown, or red discoloration on the skin of legs or arms, more rare – on the trunk. Often, it was not related to trauma or patients told that it seemed disproportionate to injury or trauma. Cutaneous striae detected on the abdomen, over the upper thighs, forearms, and deltoids without history of corticosteroid therapy. Diagnosis of hernias was determined on the basis of history of hernia (inguinal/femoralis/umbilical/postoperative) or visible hernia during physical examination.

This study was prospective and case controlled but not blinded as all patients were examined by the present author (ERL). However, to validate our results, we performed a smaller blinded study of markers of CTA. Forty three patients with operated SIA (15 male and 28 female, mean age 39.9 years) and 43 sex- and age-matched controls (blood donors) were examined in 2004 and 2008 (mean interval 4.2 years). These patients were part of the present study of 199 patients with SIA and 194 patients of controls. They were examined by two examiners, one of them did not know to which group (patients with SIA or controls) patient belonged. Patients with SIA and controls were disguised by caps because some patients with SIA had visible suture in the place of craniotomy. Both examiners detected the same external markers of CTA.

Statistical analysis

The differences in mean values or frequencies between patients with SIA and controls were statistically examined by an unpaired *t*-test and chi-square test. The odds ratio (OR) and its 95% confidence interval (CI) were estimated using multiple conditional logistic regression models. The relation between connective tissue abnormality and arterial hypertension was analyzed with logistic regression analysis.

Results

We identified frequent signs of systemic connective tissue abnormalities (CTA) in patients with SIA (Table 1). All these signs of CTA in patients with SIA, except for two features (myopia and arachnodactyly), were statistically significant. Therefore, we detected 12 statistically significant signs of CTA. Some of them are presented in Fig. 1.

The patients with SIA had different combinations of these markers. To quantify the degree of connective tissue disturbances, we determined the number of markers of systemic CTA in each patient with SIA and in the control group (Table 2). The mean number of markers of systemic CTA in patients with SIA was 3.07 and 1.17 in controls. This difference was statistically significant; therefore, systemic connective tissue abnormalities can be assumed in patients with at least three markers of CTA.

Among patients with SIA, 125 of 199 patients (62.8%) had at least three markers of systemic CTA compared with 23 (11.9%) of the controls ($P < 0.0001$, OR = 12.6 95% CI 7.5–21.2). We assessed and recorded also other risk factors for SIA including arterial hypertension, smoking, and alcohol consumption. Frequency of smoking and alcohol consumption did not differ significantly in the two study groups. The frequency of arterial hypertension was significantly higher in patients with SIA than in controls: 115 patients (57.8%) and 18 (9.3%), respectively ($P < 0.001$, OR 13.4, 95% CI 7.6–23.5). We then tested the association of SIA with 3 or more markers of CTD adjusted for arterial hypertension. The adjusted OR was 8.9 (95% CI 7.6–23.5, $P < 0.001$).

We estimated clinical manifestations of aneurysms in patients with SIA who had three and more markers of CTA compared with patients who had less than three markers (Table 3).The most important clinical feature in patients with SIA who had three or more external markers of CTA were multiple aneurysms which were five times more frequent than in patients who had less than three markers. This was statistically significant ($P = 0.005$). 30 of 36 patients with multiple aneurysms (83.3%) had three or more markers, and 20 of these 30 patients were women. The size of aneurysms did not differ according to numbers of CTA. All three

Table 1 Markers of systemic connective tissue abnormalities (CTA) in patients with saccular intracranial aneurysms (SIA) and in controls

Markers of systemic CTA	Patients with SIA (n = 199)	Patients of controls (n = 194)	P	OR	95% CI
Visible small vessels on face	119 (59.8%)	53 (27.3%)	0.0000	3.95	2.59–6.04
Scoliosis	89 (44.7%)	55 (28.3%)	0.0012	2.04	1.34–3.10
Varicose veins on legs	79 (39.7%)	43 (22.2%)	0.0004	2.31	1.48–3.59
Flatfoot	69 (34.6%)	32 (16.5%)	0.0001	2.68	1.66–4.33
Hyperextensibility of the skin	67 (33.6%)	24 (12.4%)	0.0000	3.59	2.14–6.03
Myopia	52 (26.1%)	66 (34.0%)	0.1536	0.68	0.44–1.06
Spontaneous nasal hemorrhages	51 (25.6%)	11 (5.6%)	0.0000	5.73	2.88–11.39
Easy bruising	41 (20.6%)	11 (5.6%)	0.0001	4.31	2.14–8.68
Abdominal hernia	27 (13.6%)	7 (3.6%)	0.0015	4.19	1.78–9.87
Periodontal disease	21 (10.5%)	0	0.0000	0	–
Chest deformities	15 (7.5%)	0	0.0001	0	–
Joint hypermobility	5 (2.5%)	0	0.0269	0	–
Striae	7 (3.5%)	0	0.0087	0	–
Arachnodactyly	2 (1.0%)	0	0.1623	0	–

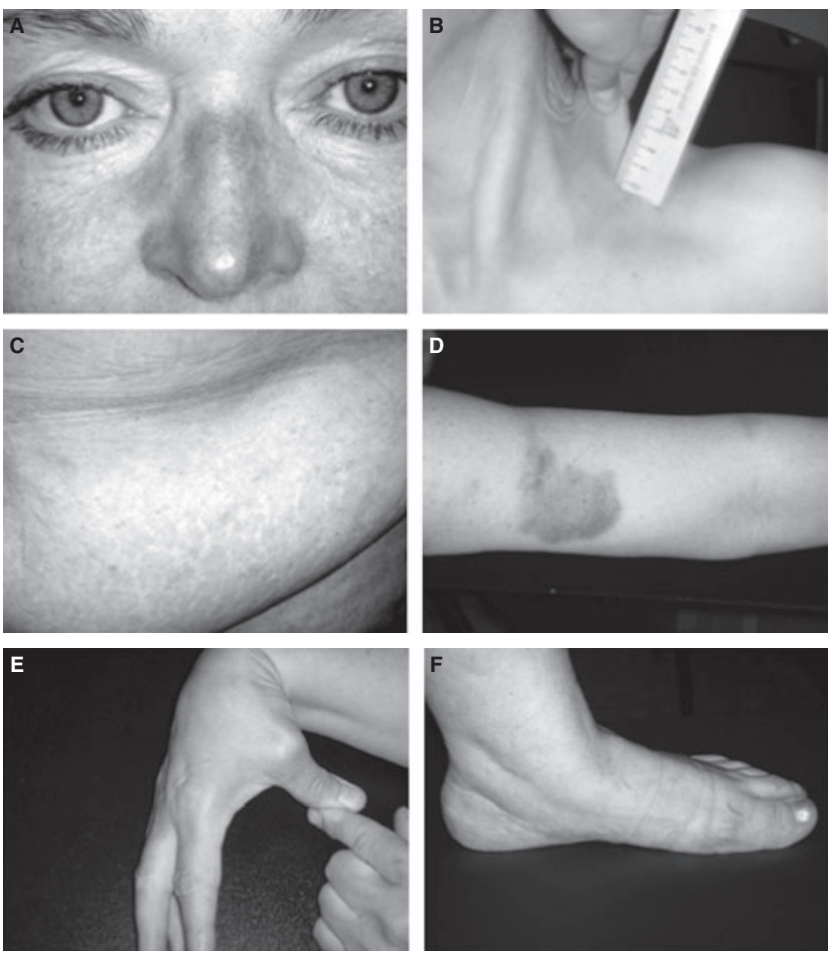

Figure 1. (A) This is severe vascular network of visible blood vessels on cheeks and nose; many patients had less pronounced network. (B) This is hyperextensibility of the skin over the middle of the clavicle; the magnitude of the skin fold over the external end of the clavicle is 4.0 cm. This size was measured using a ruler. (C) Cutaneous striae on the abdomen without history of corticosteroid therapy. (D) Easy bruising: purple and brown discoloration on the skin of one arm not related to trauma. (E) Joint hypermobility at distal phalangeal joint. (F) This is longitudinal flatfoot which exists since childhood.

patients with SIA and hereditary connective tissue diseases had more than three external markers of CTD. Among these patients, two patients had inherited autosomal dominant polycystic kidney disease and one patient had Marfan syndrome.

Table 2 The number of markers of systemic connective tissue abnormalities (CTA) in patients with saccular intracranial aneurysms (SIA) and in controls

Number of markers of systemic CTA	Patients with SIA (n = 199)	Controls (n = 194)	P	OR	95% CI
1	24 (12.1%)	79 (40.7%)	<0.0001	0.19	0.11–0.33
2	39 (19.6%)	38 (19.6%)	0.997	1.0	0.61–1.65
3	48 (24.1%)	20 (10.3%)	0.0003	2.76	1.57–4.86
4	37 (18.6%)	3 (1.5%)	<0.0001	14.5	4.4–48.03
5	24 (12.1%)	0	<0.0001	–	–
6	11 (5.5%)	0	0.0009	–	–
7	4 (2.0%)	0	0.047	–	–
8	1 (0.5%)	0	0.323	–	–
Markers are absent	11 (5.5%)	54 (27.8%)	<0.0001	0.15	0.07–0.30

Table 3 Clinical characteristics of patients and manifestation of saccular intracranial aneurysms (SIA) depending of number of markers of systemic connective tissue abnormalities (CTA)

Characteristics	Three and more markers of CTA (N = 125)	Less than three markers of CTA (N = 74)	P
Men	56 (44.8%)	40 (54.0%)	0.208
Women	69 (55.2%)	34 (45.9%)	0.208
Age range	21 – 73	14 – 64	
Mean age	44.2	41.8	0.129
Arterial hypertension	74	41	0.600
Smoking	68	34	0.250
Alcohol consumption	45	24	0.609
Multiple aneurysms	30 (24.0%)	6 (8.1%)	0.005
Unruptured SIA	12 (9.6%)	10 (13.5%)	0.395
Subarachnoid hemorrhage	113 (90.4%)	64 (86.5%)	0.395
Intracranial hematoma	29 (23.2%)	22 (29.7%)	0.309
Recurrent hemorrhages	24 (19.2%)	13 (17.6%)	0.775
Family history of SIA	8 (6.4%)	2 (2.7%)	0.249
Family history of intracranial hemorrhages	26 (20.8%)	8 (10.8%)	0.07
Hereditary connective tissue diseases	3 (2.4%)	0	0.18

Discussion

In the present study, we found that patients with saccular intracranial aneurysms (SIA) have more typical markers of connective tissue abnormalities than a sex- and age-matched control group, suggesting that systemic connective tissue abnormalities play a role in the pathogenesis of SIA. Arterial hypertension was the only acquired risk factor, which was significantly associated with SIA. Adjustment for arterial hypertension showed that the risk of having SIA was still significantly increased by the presence of at least three markers of CTA. However, the slightly reduced risk suggested that arterial hypertension may explain a minor part of the association seen between SIA and multiple CTA.

Wolswijk et al. (13) compared joint mobility, bone quantity and stiffness, and skin extensibility at the ventral part of both forearms and at the medial part of the upper leg in 59 patients with ruptured SIA and sex- and age-matched controls. Patients with ruptured intracranial aneurysms had a higher degree of joint mobility than healthy controls; all other signs were not significant. Assessor at this study was not blinded for patients and controls. Yurt et al. (14) examined 62 patients with SIA. They found that patients with SIA had a higher incidence of biomarkers of systemic connective tissue disease than controls. Dittrich et al. (15) investigated 43 consecutive patients with cervical artery dissections and 43 consecutive patients of similar age with ischemic stroke of other etiology. The clinical investigation contained 25 items characteristic for connective tissue diseases such as hyperextensible skin, articular hypermobility, capillary fragility, and facial stigmata. The investigator was blinded for the diagnosis. There was no difference between patients with spontaneous cervical artery dissection and control subjects with ischemic stroke of other etiology.

Our present study had several strong methodological features. It included a very large group of patients and a closely matched control group of equal size, all subjects were examined by the first author of this article, and it was prospective and used predesigned questionnaires and examination schedules. It was not blinded, however, because such a study would be very resource demanding in a large cohort of patients. To evaluate the influence of bias, we subsequently did a double-blind validation study 4 years later in a subset of the original cohort. It revealed an even bigger difference between patients and controls, probably because of development of new markers of connective tissue abnormalities in the intervening years.

It should be noted that common mechanisms can be involved in the development of each of the identified markers of systemic CTA (16–21). Some of these markers are very similar to those seen in Marfan syndrome and Ehlers–Danlos syndrome type IV, but they are often less severe. This suggests that SIA is a multisystem disorder with features that overlap with some inherited

connective tissue disorders. Patients with three or more markers of systemic CTA have more severe abnormalities of connective tissue. It would be interesting to follow a large cohort of patients with more than three markers of CTA prospectively in order to see the frequency of aneurysms in these patients compared with the normal population. Such a study would provide data relevant to the early detection and prevention of SIA. However, it would have to be long-lasting, very large, and very resource demanding.

Patients who have three or more markers of CTA may be predisposed to develop multiple SIA and De Novo SIA. MR-angiography or CT-angiography may, therefore, be indicated for patients with multiple external markers of CTA after surgery of SIA, for example, every 5–10 years to identify De Novo aneurysms.

Conclusion

Patients with SIA have multiple markers of systemic connective tissue abnormalities. Systemic weakness of connective tissue represents a risk factor for development of SIA. Identification of these markers may help in detection of high-risk patients.

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Conflict of interest

No conflict of interest.

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