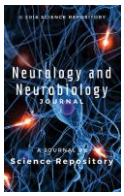

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Research Article

Spontaneous cervical artery dissection and prevalence of right-to-left shunt

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ABSTRACT

The pathogenesis of a spontaneous cervical artery dissection (sCAD) remains unknown. It has been hypothesized that most sCAD cases result from of a connective tissue disorder with a vascular phenotype. Collagen is the main component of some cardiac structures (such as the mitral, tricuspid and interatrial valves and interventricular septa). Therefore, assuming that anomalies of the connective tissue are involved in sCAD, we would expect to observe cardiac defects in patients with sCAD. The authors evaluated the prevalence of right-to-left shunt (RLS), due to a patent foramen ovale (PFO) in 52 patients with sCAD compared to 60 healthy subjects. RLS was assessed with transcranial Doppler contrast (TCDc) monitoring of the middle cerebral arteries. 42.3% of sCAD patients were positive to TCDc, whilst RLS was present in only 18.3% ($p<0.05$) of the control subjects, thus confirming that RLS is more prevalent in sCAD than in the general population. Our data might be the result of a common genetic substratum (involving alterations of connective tissue) that could lead on one hand to a predisposition for sCAD and, on the other, to endotelial/endocardiac alterations with persistence of the foramen ovale.

Introduction

Although the pathogenesis of spontaneous cervical artery dissection (sCAD) still has to be fully clarified, it is known to be a frequent cause of stroke in young and middle-aged patients, making early diagnosis and management mandatory. Indeed, numerous genetic and environmental risk factors have been postulated [1]. Connective tissue disorders with structural abnormality in the extracellular matrix, potentially caused by basic molecular defects, can predispose to sCAD [2]. In fact, a high number of spontaneous arterial dissections and cardiovascular anomalies have been observed in hereditary pathologies of the connective tissue [3-5]. Collagen is the main component of some cardiac structures (such as the mitral, tricuspid and interatrial valves and the interventricular septa). If the hypothesis that connective tissue aberrations are involved in sCAD is valid, then cardiac defects should be observed in patients with sCAD as well. To our knowledge, the prevalence of a right-to-left shunt (RLS), due to a patent foramen ovale (PFO), has never been addressed in patients affected by sCAD. Therefore, this study was set up to evaluate

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the prevalence of RLS in subjects with sCAD compared to that of a control group.

Material and Methods

A total of 52 patients with a diagnosis of sCAD were enrolled at the Stroke Unit of the Neurosciences Department, University of Pisa along with 60 healthy subjects matched for age and gender. After obtaining written informed consent. Exclusion criteria were: migraine with aura, obstructive sleep apnea and cluster headache being RLS a frequent finding in such diseases [6-9].

sCAD has been defined as a dissection which occurs in healthy individuals without known risk factors for stroke and developing spontaneously without relevant trauma 4. All subjects enrolled in the study were examined for the presence of signs referable to disorders of connective tissue, such as marfanoid habitus, facial dysmorphism, thin translucent skin, palpebral teleangectasias or joint hypermobility and therefore excluded on the basis of their clinical data. The diagnosis of dissection was made by a duplex-sonography, brain magnetic resonance imaging and magnetic resonance angiography of the intra and extra cranial vessels.

RLS was assessed by bilateral TCDc (DWL Multigate system X4-TCD 7, FRG) monitoring of both middle cerebral arteries during normal ventilation and after Valsalva manoeuvres, according to the Consensus Meeting of the European Society of Neurosonology [10]. An agitated saline solution (9 ml) mixed with 1 ml of air was injected into an antecubital vein and RLS was diagnosed if at least one microbubble (MB) was recorded within 15 seconds after the injection. RLS was classified as latent if the MB was documented only during the Valsalva manoeuvre and as permanent if the MB was also detected during normal ventilation. The RLS was graded as follows: low (1–10 MBs), medium (11–20 MBs) or high (>20 MBs or curtain effect). Transoesophageal echocardiography was then performed to confirm the presence of PFO in all subjects enrolled (sCAD and control group) if RLS was discoved. Statistical analysis was performed by the c2 test and a P value of < 0.05 was considered statistically significant

Results

The subjects with sCAD had an average age (± SD) of 45.2 ± 10.1 years and a male/female ratio of 38/14. Controls had an average age of 42.8 ± 7.4 years (male female ratio 3:1). All subjects had sufficient temporal windows. A cervical artery dissection involved one artery in 45 out of 52 sCAD patients (86.5%): the extracranial carotid artery in 25 cases (55.6%), the intracranial carotid artery in 9 (20%) and the vertebral artery in 11 (24.4%). Multivessel dissections reported in 7 patients (13.5%).

The presence of RLS was documented in 22/52 (42.3%) sCAD patients and transoesophageal echocardiography confirmed the presence of PFO in all of these cases. RLS was also found in 11 out of 60 (18.3%) of the control subjects. The sCAD patients were divided into two groups according to the presence of latent or permanent RLS. A total of 18 (81.8%) patients with latent RLS were placed into the first group graded as follows: 8/18 (44%) had low-grade RLS, 6/18 (33.3%) had medium-grade and 4/18 (22.2%) had a high-grade shunt. The second group included those with a high-grade shunt (4/22 patients, 18.2%) and one of these patients had a curtain effect. There was a statistically significant difference between the prevalence of RLS in sCAD patients and controls ($p<0.027$). whilst there was no significant difference in the characteristics of the shunt between the two groups.

Discussion

To the best of our knowledge, the current study represents the first investigation aimed at assessing the prevalence of RLS in sCAD, revealed by the number of MBs detected during TCDc monitoring. Our data showed that RLS was present in 42.3% of sCAD patients: a much higher prevalence than that observed in the healthy population group (18.3%). The aetiology of spontaneous cervical artery dissection (sCAD) is largely unknown although it has been associated with ultrastructural connective tissue abnormalities, mostly without other clinical manifestations of a connective tissue disease [11]. Indeed, it has been suggested that the presence of a structural defect in the extracellular matrix of the arterial wall might lead to a genetic predisposition [4].

The hypothesis that a structural aberration of the connective tissue might be a causal factor in arterial dissection is supported by the high incidence of dissections and cerebral aneurysm in subjects affected by hereditary pathologies of the connective tissue, such as IV Ehlers-Danlos syndrome (EDS), Marfan syndrome, fibromuscular dysplasia, osteogenesis imperfecta type I or autosomal dominant polycystic kidney disease [2, 4]. The presence of cardiovascular abnormalities in subjects affected by hereditary pathologies of the connective tissue have been widely observed.

Literature data have shown an association between connective tissue diseases, persistence of ductus arteriosus and defects of the interventricular and inter-artrial septum, such as an aneurysm of interatrial septum [12-15]. It has been reported that patients affected by sCAD show mild ultrastructural connective tissue alterations in almost half of the cases. Marked aberrations include numerous composite fibrils within mid-dermal collagen bundles and large-diameter composite fibrils, resembling those found in patients with EDS. Elastic fibre abnormalities were also present, with focal, electron-dense deposits which were microcalcification and pronounced fragmentation similar to the moth-eaten, porous appearance observed in marfanoid hypermobility syndrome [16, 17].

However, studies aimed at the detection of mutations or genetic polymorphisms that might be responsible for structural (collagen) or functional vessel defects (metalproteinasis, elastasis, and alpha-antitrypsin) have given negative results, with the exception of those concerning the dissections in patients with known risk factors 10 (vascular Ehlers-Danlos sindrome, mostly mutations in the pro-a1(V) and pro-a2 (V) encoding genes) [18-20]. It has thus been hypothesized that most sCAD cases are a manifestation of a connective tissue disorder with a vascular phenotype [21].

The morphology of connective tissue elements has been documented to be aberrant in the majority of skin biopsies in sCAD patients without clinical stigmata of known connective tissue disorders, indicating a molecular defect in the biosynthesis of the extracellular matrix. This finding suggests that patients with sCAD may be affected by some kind of unknown connective tissue disorder which predisposes predisposing

to a structural weakness of the vessel wall and therefore increasing their risk for dissection [22].

Sarnowski et. al reported that PFO was less prevalent in patients with sCAD compared to the large population with newly diagnosed cerebrovascular disease [23]. These data, however, are not comparable with ours for the diversity of the study population so that no conclusive consideration may be stated.

The high prevalence of RLS in patients affected by sCAD showed in our study could represent the result of a common genetic substratum (alterations of connective tissue), which might lead to a predisposition for sCAD and, on the other hand, to endotelial/endocardiac alterations with persistence of PFO. However, whether both disorders (sCAD and RLS) really do share common mechanisms still requires further investigation with larger studies on a wider population.

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