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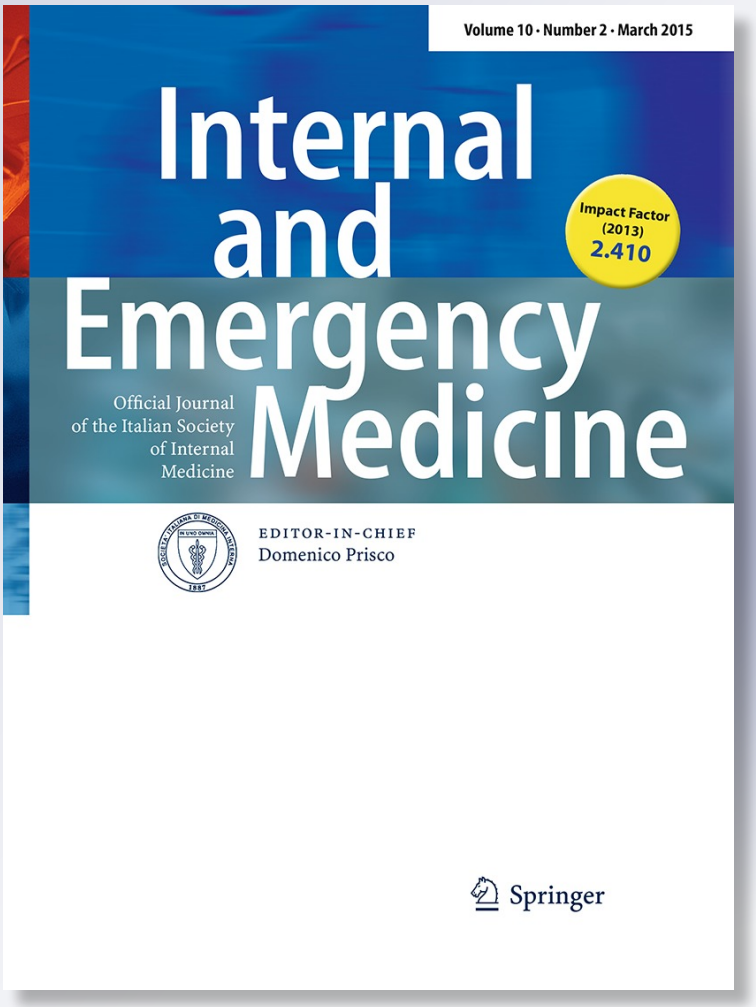

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IM - CASE RECORD

Aortic dissection and stroke in a 37-year-old woman: discovering an emerging heritable connective tissue disorder

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Introduction

Alessio Pieroni, Danilo Toni

Aortic dissection is an uncommon cause of stroke in young patients, and can lead to a severe prognosis, especially if not promptly diagnosed and adequately treated. Among the etiologies that can underlie an arterial dissection in the young, there are heritable connective tissue disorders (HCTDs) with increased vascular fragility [1]. Among them, the Loeys–Dietz syndrome (LDS) is a recently defined aortic aneurysm syndrome, inherited as an autosomal-dominant disease, and caused by heterozygous mutations in various proteins of the transforming growth factor beta (TGF-β) pathway [2]. We report a case of a young woman with LDS, which had been unrecognized until the patient presented to the emergency department (ED) with focal neurological symptoms due to an acute ischemic stroke secondary to aortic dissection. The diagnosis of LDS type 2, confirmed at the molecular level, offered the opportunity to describe and discuss several causes of arterial dissection in the young, and focus on the underlying diseases, particularly focusing on this recently described HCTD.

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Case record

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A 37-year-old woman was admitted to our ED about 5 h after the sudden onset of right hemiplegia and aphasia. A few days prior to the index event, she had been admitted to a peripheral ED for headache and vertigo. She had been studied with a head computed tomography (CT scan), reported as normal, and had been discharged home after improvement of symptomatology. In the following 2 days, she had suffered again from headache, and had complained of new-onset right-hand paresthesia. Except for tobacco smoking, the patient's past and family histories were unremarkable for relevant diseases, and she did not take any medicine. At our ED, neurological examination showed a complete right hemiplegia and mixed aphasia with a National Institutes of Health Stroke Scale (NHISS) score of 14. She was studied with a magnetic resonance imaging (MRI) of the brain that showed a large left frontal–parietal acute ischemic lesion (Fig. 1). The magnetic resonance angiography (MRA) showed the absence of a flow signal in the left internal carotid artery (ICA). Acute thrombolytic treatment was ruled out due to the delay from symptom onset to hospital admission. A carotid Doppler ultrasound examination showed a complete occlusion of the left common carotid artery (CCA) extended to the ICA, and occlusion of the right CCA with a low flow signal at the carotid bifurcation. The left vertebral artery (VA)

showed a high flow velocity. The patient was immediately submitted to a total body computed tomography angiography (CTA) that showed an aortic artery dissection extending from the aortic bulb to the beginning of the descending tract and involving the supra-aortic vessels (Fig. 2). From the brachiocephalic artery, the dissection extended to the right CCA, leading to the vessel occlusion up to the carotid bifurcation. The left carotid tree was occluded from its beginning to its supraclinoid portion. Both VAs and the circle of Willis presented a regular flow. Moreover, the CTA showed a possible right kidney infarction and a superior mesenteric artery fusiform ectasia and ectasia of the celiac trunk (Fig. 3). Emergency surgical intervention was ruled out, due to the high risks of worsening the neurological condition, and the patient was admitted to our Stroke Unit. The patient underwent a strict blood pressure (BP) monitoring to avoid both hypertension and hypotension; to obtain a mean BP of 100/60 mmHg, she was treated initially with continuous i.v. nitrate infusion, and later with lercanidipine 5 mg/day orally. The electrocardiogram showed nonspecific repolarization abnormalities, and the transthoracic echocardiography revealed a high-grade aortic insufficiency with a dilatation of the aortic bulb (44 mm). Blood cell count and biochemical analysis, thyroid assessment, lipid profile, inflammatory markers and protein electrophoresis were normal. Investigation for syphilis infection was negative. A brain MRI repeated at day 7 confirmed the presence of the left frontal–parietal infarct without hemorrhagic infarction, and showed a new left frontal ischemic lesion. The MRA was unchanged since the previous examination. At day 18, a new CTA was obtained revealing the persistence of aortic dissection without modifications from the previous study.

Marco Castori, Marco Ritelli, Marina Colombi

A physical examination revealed bifid uvula, jaw hypermobility with signs of temporomandibular joint dysfunction, as well as two postsurgical atrophic scars on the left leg. The patient did not show generalized joint hypermobility or instability nor any facial dysmorphism. A provisional diagnosis of LDS type 2 was proposed. A mutational screening of *TGFBR1* and *TGFBR2* genes demonstrated the presence of the known heterozygous c.1460G > A mutation in exon 9 of *TGFBR1*. This mutation causes the arginine to glutamine amino acid change in position 487 (p.Arg487Gln). The arginine residue in position 487 is also reported to be substituted by other amino acids, therefore representing a mutational hot spot [3]. Parents and relatives were unavailable. Hence, the de novo or inherited nature of the identified mutation was not able to be tested.

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After 1 month, the patient was discharged to a rehabilitation clinic with mild right inferior facial musculature palsy, right hemiparesis and mild right limb hypoesthesia (NIHSS score 8). Therapy at discharge was losartan 50 mg/day and low molecular weight heparin for deep vein thrombosis prophylaxis. Four months after the stroke, the patient underwent aortic root surgical reconstruction with St. Jude composite-graft replacement by the Bentall method. The therapy after surgical operation was warfarin and acetylsalicylic acid 100 mg/day. A year later, neurological examination showed right inferior facial musculature palsy, no motor disturbances except for severe distal paresis of right leg with mild spastic hypertonia, and mild right limb

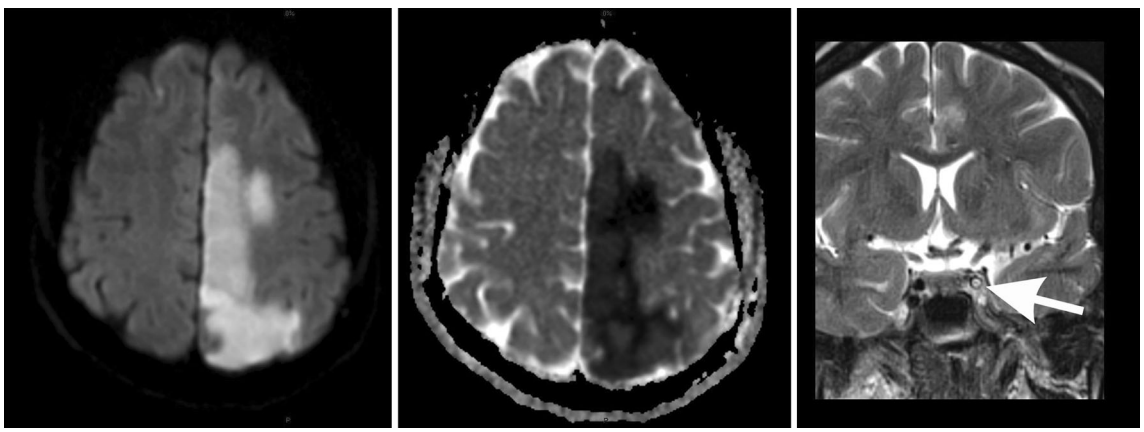

Fig. 1 Acute left frontal–parietal ischemic lesion on diffusion-weighted image (*left*) and apparent diffusion coefficient (*center*) on magnetic resonance imaging of the brain. On the right side, is a thrombus inside the left internal carotid artery (*arrow*) on T2-weighted scan

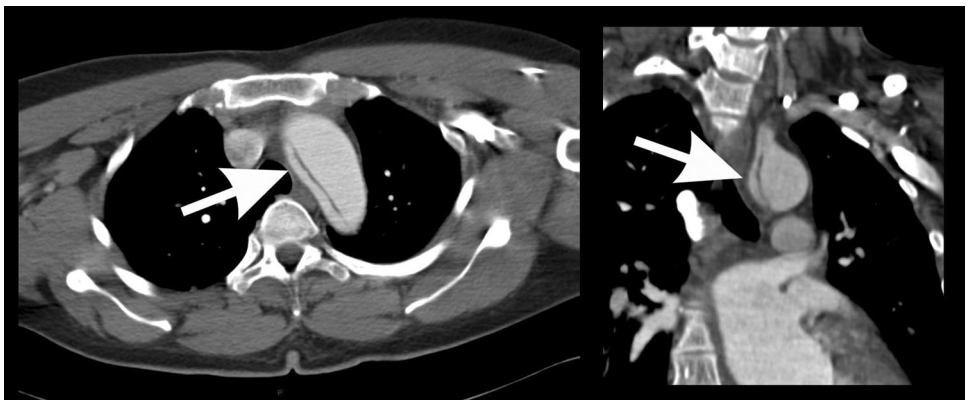

Fig. 2 Aortic arch dissection (*arrows*) on computed tomography angiography

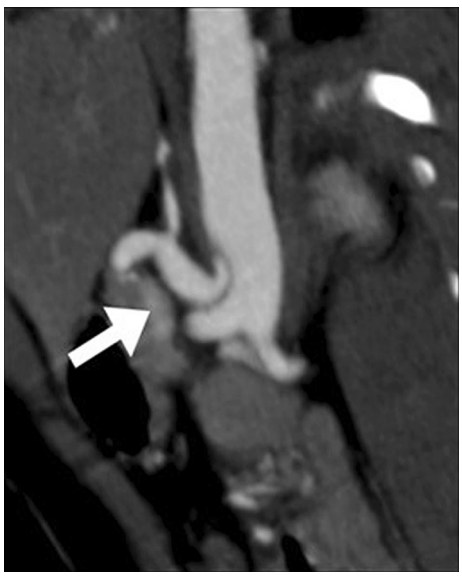

Fig. 3 Superior mesenteric artery fusiform ectasia, and ectasia of the celiac trunk (*arrow*) on computed tomography angiography

hypoesthesia (NIHSS score 4). A control brain MRI did not reveal any additional ischemic lesion, and a new CTA showed the correctly placed vascular graft and the persistence of aortic dissection with initial epiaortic vessels' involvement. The whole carotid tree was patent without sign of dissection except for the left ICA where a progressive reduction of the lumen occurred up to its intracranial tract, ending with a subocclusive stenosis.

Discussion

Acute management

Alessio Pieroni, Danilo Toni

Recognizing arterial dissection as a cause of acute stroke may be a challenge for physicians operating in acute settings. Such a diagnosis should be sought in the presence of focal neurological signs of abrupt onset and severe, sharp, chest or back pain, sometimes migrating along the chest, back or neck. If dissection extends to the coronary ostia, it can cause a cardiac ischemia with elevated cardiac biomarkers and dynamic electrocardiographic changes, and sometimes a pericardial tamponade. Moreover, life-threatening complications are aortic rupture or extension of the dissection into branch vessels that might compromise perfusion of multiple distal organs. Physical examination is crucial in making the diagnosis, which is guided by a diastolic murmur of aortic insufficiency and asymmetrical, decreased or absent peripheral pulses [4]. Moreover, as in the case reported, the history of transient neurological signs during the few days before the stroke onset could suggest an ongoing vascular dissection. In the clinical suggestion of an HCTD, a baseline screening of the entire arterial tree is mandatory, and requires a CTA or MRA. Echocardiography and carotid Doppler ultrasound examinations should also be performed. When presenting with focal neurological symptoms, a rapid diagnosis is crucial to avoid any thrombolytic or antiplatelet/anticoagulant therapy. Moreover, the decision to perform an emergency surgical correction of dissection would be challenging in the presence of cerebral hypoperfusion, and treatment should be focused on extremely careful BP, heart rate and cardiac rhythm control, to find a balance between an acceptable cerebral perfusion and minimal distention of the artery wall. Continuous hemodynamic monitoring should be arranged by placement of the patient in a highly monitored setting [14].

Differential diagnosis

Marco Castori, Marina Colombi, Alessio Pieroni

The diagnosis of aortic dissection in the young or young–adult patients lacking any other predisposing factors, including traumatic injury, cocaine use, syphilis, bicuspid aortic valve or pregnancy, should lead to consideration of

an HCTD. Accurate physical examination and family and personal history reconstruction are the milestones for diagnosis formulation and further molecular investigations. In particular, in LDS, the diagnosis is usually established after the identification of the causative mutation, which, in turn, could be used as a pre-symptomatic tool for the index patient's relatives at risk.

LDS was first described in 2005, when Loeys et al. [5] presented ten families with a phenotype characterized by marked propensity to arterial tortuosity and widespread vascular aneurysms and dissections with joint hypermobility, other skeletal manifestations, craniofacial dysmorphism (i.e., craniosynostosis and hypertelorism, and bifid uvula, and cleft palate), variable intellectual impairment, and minor skin changes. To date, the exact prevalence of LDS is unknown, since many patients may remain undiagnosed or misdiagnosed as a result of the clinical overlap with other better defined genetic syndromes or normal somatic variability. LDS can be stratified into two different phenotypic groups: LDS type 1 characterized by the abovementioned craniofacial features, and LDS type 2 that refers to patients without or with subtle craniofacial involvement, except for isolated bifid uvula, but with possible cutaneous signs, visceral rupture and joint hypermobility [6]. Both LDS types associate with overlapping mutational spectra [7] and exhibit broad phenotype variability, testifying for the same nosologic entity [8, 9]. LDS is caused by heterozygous mutations in various proteins of TGF-β pathway, including TGF-β receptors type 1 and 2 (*TGFBR1* and *TGFBR2*), TGF-β type 2 (*TGFB2*), and the dominant-negative inhibitor of the TGF-β response SMAD3 [2]. Two-thirds of the patients exhibit *TGFBR2* mutations, whereas in about one-third, *TGFBR1* is the causal gene without any strong genotype–phenotype correlations. Very few patients actually show mutations in *TGFB2* and *SMAD3* (the so-called aneurysms-osteoarthritis syndrome) [2]. TGF-β belongs to a family of multifunctional cytokines that control proliferation, differentiation, migration, and death of many cell types, influencing several processes including maintenance of the extracellular matrix and morphogenesis of many tissues such as cartilage, bone, and vasculature [5, 10].

The natural history of both types of LDS is characterized by widespread aggressive arterial aneurysms with the aortic root most commonly involved (98 %). Arterial aneurysms of the head and neck or abdomen are found in ~20 % of patients, while tortuosity is commonly observed in the epiaortic and intracranial arteries. Mean age at death has been originally fixed at 26 years, with thoracic aortic dissection as the most common cause (67 %) [5, 6]. Notably, arterial pathology is known to be more aggressive and widespread in LDS than other aneurysm syndromes, with dissections occurring at younger ages and at smaller diameters [5, 6, 11]. In a series of 25 LDS type 1 patients, Rodrigues et al. [12] find a 32 % incidence of carotid or vertebral vessel aneurysms, almost all intracranial, and a 12 % incidence of dissections or pseudoaneurysms of either intra- or extracranial vessels in patients submitted to head and neck CTA and MRA. Intracranial vessels' tortuosity, particularly of the vertebral artery, is recognized in all patients In a series of 56 patients with spontaneous carotid artery dissection, *TGFBR2* gene mutations were identified in two patients, one with an LDS type 2 presentation and the other without connective tissue signs [13].

LDS shows significant overlap with Marfan syndrome (MFS), another autosomal-dominant HCTD, caused by mutations in the extracellular matrix protein fibrillin-1 gene. The similarities of LDS and MFS mirror molecular interactions, since recent evidence suggests that fibrillin-1 deficiency leads to dysregulation of the TGF-β signaling cascade [1]. MFS is a well-known HCTD characterized by propensity to proximal aortic aneurysms, dissection and rupture, lens dislocation, and a peculiar habitus with disproportionately long limbs (dolichostenomelia), and digits (arachnodactyly), severe scoliosis, pectus carinatum and micrognathia. In contrast to LDS, dislocation of the lens is common in MFS, but exceptional in the former. In addition, vertebral artery tortuosity occurs at a significantly lesser frequency in MFS than in LDS [1].

LDS also show some similarities to Ehlers–Danlos syndromes (EDSs), a heterogeneous group of HCTDs caused by mutations in genes encoding fibrillar collagens or collagen-modifying enzymes. They are variably characterized by skin hyperextensibility, delayed wound healing with atrophic scarring, joint hypermobility, easy bruising, and generalized tissue fragility. The most remarkable overlap is that with vascular EDS, caused by heterozygous mutations in the type III collagen gene (COL3A1), and dominated by thin and translucent skin, characteristic facial appearance and marked propensity to vascular and internal organ ruptures. At variance with LDS, vascular EDS patients lack marfanoid habitus and aneurysms of the thoracic aorta [1].

A predisposition to progressive dilatation of the ascending aorta, and multiple thoracic aneurysms and dissection in the absence of other syndromic features exists as well. Unlike LDS, in such conditions, mainly inherited as an autosomal-dominant disease, and caused by mutations in various genes including some involved in the TGFB pathway, cardiovascular involvement is typically isolated [14, 15].

Other genetic syndromes associating with ascending aortic aneurysms include arterial tortuosity syndrome, various hereditary cutis laxa, Shprintzen–Goldberg syndrome, Turner syndrome and Noonan syndrome. Unlike

MFS and vascular EDS, in these conditions, the constellation of additional anomalies often makes clear-cut the differential without significant concerns in the emergency setting.

Follow-up

Alessio Pieroni, Marco castori

An accurate imaging surveillance is crucial in the outpatient setting, and should include echocardiography, performed at least yearly, and MRA/CTA, with a frequency depending on the clinical/radiological condition [7]. It is noteworthy that in LSD, aneurysms distant from the aortic root would be overlooked by echocardiography [2]. Carotid Doppler ultrasound examination should also be performed, as well as skeletal investigations, with special focus for cervical spine instability.

Due to the low rates of intraoperative mortality as compared with other HCTDs with pronounced vascular friability registered in experienced centers, valve-sparing aortic root replacement is actually considered the intervention of choice in LSD patients with aortic dissection [2, 16]. The decision to perform this procedure should be based on the absolute dimension of the aorta, rate of progression, valve function, severity of noncardiac features, family history, and information about genotype [2, 7]. Nevertheless, choosing the timing of intervention will be challenging in the case of cerebral hypoperfusion, as in the case reported here. The severity of craniofacial malformations in LDS, estimated with a craniofacial severity index, seems to correlate with cardiovascular outcomes, and may be useful in determining the thresholds for surgery [6].

Besides prophylactic surgical repair and imaging follow-up, an additional prevention strategy is represented by the use of blood pressure-lowering medication such as β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, to reduce hemodynamic stress on the vasculature. Moreover, moderate aerobic physical activity discarding any contact sport or isometric exercise, and avoidance of any cardiovascular-stimulating drugs including routine use of nasal decongestants, should be recommended [2].

Conclusion

Alessio Pieroni, Danilo Toni

Stroke due to aortic dissection is a medical emergency, requiring prompt diagnosis and treatment. Similarly, a correct underlying etiological diagnosis is mandatory, especially in the case of an underlying HCTD, for both the index patient and the relatives at risk. Recently described, LDS is emerging as a condition with a more severe prognosis than other HCTDs, and may be more prevalent than previously thought. To date, cerebrovascular diseases have only been described as iatrogenic complication of cardiovascular surgical or endovascular interventions in LDS patients. In the case presented, cardiovascular and systemic features of LDS had developed without complication, and, consequently, were unnoticed until the onset of an acute stroke secondary to aortic dissection. The knowledge of such emerging HCTD will probably increase in neurologists and physicians who deal with cerebrovascular disease although it might remain underdiagnosed, particularly in patients with minimal or no dysmorphic features.

Conflict of interest None.

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