Arterial tortuosity index, a promising imaging marker for early detection of Loeys-Dietz syndrome

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Loeys-Dietz syndrome (LDS) displays 5 types that should be considered in differential diagnosis from Marfan syndrome (MFS) and other heritable rare connective tissue diseases (CTDs). The hallmarks of LDS are vascular disease extended beyond the aortic root, arterial tortuosity, hypertelorism, cleft palate, and bifid uvula [1, 2]. The genes associated with LDS types, all of which belong to the TGFbeta signaling, are as follows: LDS1/TGFBR1, LDS2/TGFBR2 are the most severe, LDS3/SMAD3, LDS4/TGFB2 are the most clinically similar to MFS, and LDS5/TGFB3 are the mildest [3, 4]. Since untreated Heritable Thoracic Aortic Diseases (HTAD) present a poor prognosis, early diagnosis and appropriate treatment are crucial. The article by Chmielewski et al. [5], reports on 34 patients with LDS (15 index cases, 19 relatives) undergoing clinical and molecular characterization [5]. This article raises multiple interesting considerations.

Importantly, the authors performed, for the first time, a quantitative analysis of the tortuosity of both cervical vessels and thoracic aorta in LDS patients detecting its presence in 100% and 68% of patients, respectively. These results underline and support [6, 7] the importance of quantitative tortuosity analysis of cervical and aortic arteries in LDS to investigate the potential of these clinical markers in early detection of LDSs and in their differential diagnosis from other CTDs. Indeed, increased carotid tortuosity is a known marker of disease severity associated with earlier aortic root replacement [6]. Moreover, the quantitative tortuosity index of intracranial (carotid and vertebral) arteries is higher in LDS compared to MFS, which may become another vascular differential diagnostic marker between the two diseases [7].

Aortic involvement was prevalent in this study as assessed by two different methods at the aortic root and the proximal ascending aorta. Two calculators are available now to detect aortic dilatation at each aortic level on a very wide age range. Campens et al. [8] provide upper limits of normal thoracic aorta and Z-score equations, while Frasconi et al. [9] provide a novel tool built by a machine learning technique. This novel Q-score can also capture the joint distribution of these variables with all four diameters simultaneously, thus accounting for the overall aortic shape. Sixteen (47%) patients in the study by Chmielewski et al. [5] suffered from their first aortic event (9 A-type AD, 6 elective thoracic aortic surgeries, and one sudden death) at a median age of 35 years. Notably, second and third aortic events occurred in 9 and 4 patients, respectively, underscoring the need for lifelong surveillance in patients after thoracic aortic surgery, particularly in cases of dissection and genetic conditions [10].

In Table S3, the authors report the absence of aortic or cardiovascular events in 5 TGFB2 patients while only 2 patients turned out to carry pathogenic mutations in the gene (Table S1 & Results). It would be useful to know these 2 patients' sex, age, and aortic diameters to understand if the absence of aortic and cardiovascular events is justified.

In the Results section, the authors report that 6 LDS cases met the diagnostic criteria for MFS also because they had a score of 7/>7 for systemic features. If these patients have mutations in one of the 4 reported genes (TGFB2, TGFBR1&2, SMAD3), they have LDS. There are not enough details about all the systemic manifestations in each patient and the exact localization of the ectasia or aneurysm of the aorta. A precise size of diameters in each of the patients is necessary for clinical diagnosis.

The authors underline in Discussion considerable variability in the intrafamilial clinical features. It is important to clarify that this correct observation is common among hereditary pathologies. In syndromic aneurysms, it is certainly easier to notice it because of the pleiotropism of these pathologies. Rather, the bicuspid aortic valve (BAV) is a hereditary pathology with autosomal dominant transmission but with incomplete penetrance [11]; for this reason, it can even be absent in one generation and reappear in the next one. Moreover, through generations, patients may display isolated BAV and/or thoracic aneurysm or associated BAV/thoracic aneurysm.

In conclusion, the results of the study by Chmielewski and colleagues underline the importance of quantitative tortuosity analysis of cervical and aortic arteries in LDSs and the potential use of these clinical markers in early detection of LDSs and differential diagnosis from other CTDs. At this point, if quantitative tortuosity is a marker that can refine the working diagnosis and accelerate the differential diagnosis process, subsequent studies will have to confirm this but also elucidate whether the absence of tortuosity has a negative predictive value.

Article information

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