KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
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ISSN 0022–9032 e-ISSN 1897–4279

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**Article type:** Editorial

**Received:** November 7, 2023

**Accepted:** November 7, 2023

**Early publication date:** November 8, 2023

# 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 which are in differential diagnosis with Marfan syndrome (MFS) and other heritable rare connective tissue diseases (CTDs). LDS hallmarks are represented by vascular disease extended beyond the aortic root, arterial tortuosity, hypertelorism, cleft palate and bifid uvula [1, 2]. The genes associated with LDS types, all belonging to the TGFbeta signalling, are the following: LDS1/TGFBR1, LDS2/TGFBR2, the most severe, LDS3/SMAD3, LDS4/TGFB2 the most clinically similar to MFS, LDS5/TGFB3 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 paper 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 patients with LDS detecting their presence in 100% and 68% patients, respectively. Their results underline and support [6, 7] the importance of quantitative

tortuosity analysis of cervical and aortic arteries in LDS with the aim of investigate the potential of these clinical markers in early detection of LDSs and in their differential diagnosis with other CTDs. Indeed, increased carotid tortuosity is a known marker of disease severity associated to earlier aortic root replacement [6]. Moreover, the quantitative tortuosity index of intracranial (carotid and vertebral) arteries is higher in LDS compared to MFS allowing also a vascular differential diagnostic marker between the two diseases [7].

Aortic involvement was prevalent in this study as assessed by two different methods at aortic root and 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] incurred in a first aortic event (9 A-type AD, 6 elective thoracic aortic surgeries, and one sudden death) at median age of 35 years. Noteworthy, second and third aortic event occurred in 9 and 4 patients, respectively, underscoring the need of a lifelong surveillance in patients after thoracic aortic surgery, particularly if linked to 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 the sex, age and aortic diameters of these 2 patients to understand if the absence of aortic and cardiovascular events is justified.

In the Results section, the Authors report that 6 LDS reach the diagnostic criteria for Marfan syndrome also because they have 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 is a lack of detailed descriptions of all the systemic manifestations of each patient and of the exact localization of the ectasia or aneurysm of the aorta with a precise size of diameters in each of the patients necessary for clinical diagnosis

The Authors underline in Discussion the marked variability of the intrafamilial clinical features. It is important to clarify that this correct observation is actually common to hereditary pathologies. In syndromic aneurysms it is certainly easier to notice it because of the pleiotropism of these pathologies. Instead, 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 missing in one generation and reappear in the next one of a pedigree. Moreover, through generations of a family patients may display isolated BAV and/or thoracic aneurysm or associated BAV/thoracic aneurysm.

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

**Article information**

**Conflict of interest:** None declared.

**Funding:** None.



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