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Editorial

Personalizing Aortic Surveillance in Paediatric Loeys-Dietz Syndrome

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In connective tissue disorders, such as Marfan syndrome and Loeys-Dietz syndrome (LDS), aortic root dimension has been the best predictor of adverse clinical outcomes to date and consequently is the usual basis for surgical indications for recommending prophylactic aortic root replacement. Other clinical features, including a family history of aortic dissection, rapid aortic growth, diffuse aortic root and ascending aortic dilation, and marked vertebral arterial tortuosity, have also been shown to be associated with increased risk of aortic complications.[1–5] Noninvasive measures of aortic stiffness may further identify patients with connective tissue disorders who are at higher risk of progressive aortic enlargement and adverse clinical outcomes, potentially allowing for closer monitoring and more aggressive therapy.[6,7]

LDS has been classified into 6 different subtypes caused by mutations in the following genes: *TGFBR1* (LDS1), *TGFBR2* (LDS2), *SMAD3* (LDS3), *TGFB2* (LDS4), *TGFB3* (LDS5), and *SMAD2* (LDS6). The 2 most common subtypes LDS1 and LDS2 have the more severe clinical phenotype, with more aggressive aortic disease having been identified in patients with *TGFBR2* mutations compared with *TGFBR1* mutations.[8–10]

In the current issue of the *CJC Pediatric and Congenital Heart Disease*, Khodabakhshian et al.[11] report a retrospective, single-centre cohort study comparing aortic dimensions, aortic biophysical properties, and left ventricular structural and functional parameters in 17 *TGFBR1* to 15 *TGFBR2* mutation positive patients with paediatric LDS. They collected data on clinical phenotype, including demographics, history of aortic surgery, current medications, family history, and clinical severity of LDS presentation. Using echocardiography, they measured aortic dimensions and cardiac chamber dimensions and systolic and diastolic function and calculated aortic *Z*-scores and aortic distensibility, strain, and stiffness index. They found that TGFBR2 patients were more likely to have undergone aortic surgery and to have used angiotensin receptor blockers, to have larger aortic *Z*-scores, and to have lower aortic distensibility and strain and higher aortic stiffness index at the level of the sinotubular junction and ascending aorta. They concluded from their results that paediatric LDS patients with *TGFBR2* mutations present with more severe cardiovascular phenotypes than with *TGFBR1* mutations, with larger aortic dimensions and increased aortic stiffness.

This study by Khodabakhshian et al.[11] raises the possibility of the need to routinely measure aortic stiffness in LDS, Marfan syndrome, and other connective tissue disorders and highlights the importance of personalizing aortic surveillance based on phenotype-genotype interactions.

In 2009, Tran-Fadulu et al.[8] first reported significant differences in clinical presentation and survival between adult and paediatric LDS patients with *TGFBR1* mutations compared with *TGFBR2* mutations.[8] Then in 2016, Jondeau et al.[9] reported that aortic root diameter before or at the time of type A aortic dissection tended to be smaller in adult and paediatric LDS patients carrying a *TGFBR2* mutation. Next most recently in 2022, Regalado et al.[10] reported that specific variants in *TGFBR2* in adults with LDS were associated with a substantially higher risk of aortic events with childhood onset. In this study, Khodabakhshian et al.[11] found that paediatric LDS patients with *TGFBR2* mutations were similarly more likely to have undergone aortic surgery and to have used angiotensin receptor blockers and to have higher *Z*-scores for proximal aortic dimensions at the level of the aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta.

Khodabakhshian et al.[11] also found differences in aortic distensibility, strain, and stiffness index at the level of the sinotubular junction and ascending aorta between paediatric LDS patients with *TGFBR1* mutations compared with *TGFBR2* mutations. The authors suggest that these changes in aortic mechanical properties may precede aortic remodelling and have independent predictive value for aortic disease progression. Despite recommended prophylactic aortic root replacement in patients with LDS at an aortic root diameter of $\geq$4.0 cm or 4.5 cm depending on the presence of other high-risk features, aortic dissections have been documented in patients with LDS with smaller aortic root dimensions.[1,12,13] So, the authors also suggest that risk stratification of patients with LDS should not be primarily size-dependent and encompass a complete evaluation from the root to the ascending aorta including the aortic biophysical properties.

As discussed by the authors, one of the limitations of the Khodabakhshian et al.[11] study was the small sample size of the

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TGFBR1 and *TGFBR2* mutation positive patient groups. In addition, this was a retrospective study without a standardized echocardiography protocol or data on measurement variability when measuring larger and/or effaced aortic structures. Further prospective work is therefore needed to determine if this approach will be informative and generalizable to the wider population with LDS.

In conclusion, Khodabakhshian et al.[11] have provided evidence that paediatric LDS patients with *TGFBR2* mutations exhibit a more severe aortic phenotype than those with *TGFBR1* mutations with larger proximal aortic dimensions, increased proximal aortic stiffness, and the increased need for pharmacological therapy with angiotensin receptor blockers and likelihood of needing aortic root replacement surgery. These findings provide further evidence on the importance of personalized aortic surveillance in paediatric LDS based on genotype, especially for TGFBR2 mutation positive patients.

Ethics Statement

The manuscript adhered to relevant ethical guidelines.

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Disclosures

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