Loeys–Dietz syndrome: We have come a (Fur)long way

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Central Message

LDS: intermediate-term outcomes of medically and surgically managed patients.

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In 1987, Judith Furlong and colleagues¹ first reported a case of an 18-year-old man exhibiting “marfanoid” features (high palate, craniosynostosis, scoliosis, *pes planus*, pectus carinatum, mitral insufficiency, and a dilated aortic root) who eventually developed acute type A aortic dissection and died. Since her original report describing “Furlong Syndrome,” others have reported similar clinical associations, with varying degrees of severity but without a cause.² It was not until B. Loeys and H. Dietz, approximately 20 years later, identified the underlying genetic mutation in the transforming growth factor beta receptor complex.³ Their seminal work eventually identified a clinical triad of arterial tortuosity and aneurysm, hypertelorism, and bifid uvula or cleft palate, which led to what we now refer to as “Loeys–Dietz syndrome” (LDS). Their work, as well as others, recognized the very aggressive aortopathy leading to early mortality associated with this syndrome. Ultimately, this led to a lower threshold (4.2 cm) for surgical intervention by consensus guidelines.⁴

Aftab and colleagues⁵ examined a relatively large series of 53 patients with genetically confirmed LDS to determine both early and intermediate outcomes. The authors divided patients into those who underwent a cardiovascular repair (33) and those who had been medically managed (20). Outcomes of intervention were commendable, with early mortality and stroke of approximately 6% and 6%, respectively. Although there are difficulties from deriving natural history outcomes from retrospective data derived from the primary referring center (the patients’ historical data obtained before the index admission may often be incomplete), the authors clearly provided informative and comprehensive clinical data of each of these patients.

Several important inferences may be derived from this study. First, surgery can be performed safely in the patient population with LDS. An aggressive approach should be adopted with the goal to replace the entire proximal aorta with aortic valve-sparing techniques in patients with aneurysms; these patients are younger (mean age of 39 years in

this study). In patients with acute or chronic dissection, consideration for total arch replacement (with elephant trunk, traditional or frozen) should be made, because many of the patients with dissection will require distal thoracic aortic reoperations.

Second, patients with LDS with aortic dissection required more late aortic reoperations. Although the intermediate survival was not reported as different between those with and without dissection, longer follow-up may reveal a higher late mortality with dissection. It then becomes imperative to consider early surgical intervention (in experienced hands) to prevent aortic dissection. In this series, the 22 patients who underwent a proximal operation (valve-sparing aortic root replacement) did not develop proximal thoracic aortic dissection and did not require late distal reoperations (Figure 1).

Third, patients with LDS may die as the result of cardiovascular catastrophes, but other noncardiovascular conditions must be recognized. Twenty-two orthopedic procedures, 24 hernias, and 7 bowel resections were performed in this series of 53 patients. The cardiomyopathy associated with LDS is recognized—but poorly understood—and should be studied further.

Last, the authors’ indication for intervention was in concordance with the American Heart Association recommended guidelines of 4.2 cm. In this study, the median diameter was 4.3 cm in the surgical group and 3.4 cm in the nonsurgical group. However, this diameter was not indexed, thus, raising the question of whether indexing should be applied. Such indexing (eg, Z score), has led to a lower diameter threshold for intervention with Turner’s

syndrome.⁶ Even without indexing, there is strong evidence that LDS is a very aggressive disease and without prophylactic proximal aortic repair may lead to early mortality.⁷ Considering this, is it time to recommend even a lower threshold for intervention in LDS that may be based on indexing? Because the obvious goal in managing the patients with LDS is to prevent death from rupture or dissection, it would seem intuitive to intervene sooner, but how much sooner? This is also contingent on the native valve being spared, and the overall mortality and morbidity is low. Although we have come a long way in our understanding of LDS since the time of Judith Furlong and colleagues,¹ there is still much more to learn.

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