Commentary: Calcific aortic stenosis in progeria: A personalized approach to a difficult problem

Alexey Zubritskiy, MD, PhD,a,b,c and Igor E. Konstantinov, MD, PhD, FRACS,a,b,c,d

Although the mechanism of atherosclerosis was described more than 100 years ago,1 the molecular mechanisms of dramatic progression of atherosclerosis in rare patients with Hutchinson–Gilford progeria syndrome (HGPS) became somewhat clearer only recently. HGPS is an extremely rare condition (1 in 18-20 million new births).2,3 Because of its rarity, limited information is available regarding the natural history of cardiac and vascular abnormalities in this syndrome. HGPS is characterized by accelerated cardiovascular disease, which leads to significant morbidity and mortality from myocardial infarction or stroke at an average age of 13 years.4

The disorder is associated with aberrations in the LMNA gene (chromosome 1). This gene normally encodes lamin A and lamin C—major components of the nuclear lamina. Point mutation in the LMNA (p.G608G) results in the synthesis of progerin (truncated prelamin A), which lacks the cleavage site needed to remove the farnesylated and carboxymethylated C-terminus. The accumulation of mutant lamin A (ie, progerin) causes nuclear instability and changes in chromatin and gene expression and is thought to be responsible for HGPS. It is believed cardiovascular dysfunction can be caused by progerin-induced alteration of multiple mechanotransduction pathways in the vessel wall, leading to dedifferentiation, calcification, DNA damage, and vascular smooth muscular cell death (Figure 1). Secondary to this, endothelial dysfunction occurs with the reduction in the production of endothelial nitric oxide, which also contributes to vascular smooth muscular cell damage, and, therefore, establishes the vicious cycle of vascular damage. Cardiovascular phenotype in HGPS may be defined as generalized atherosclerosis with increased vascular stiffness, calcification and fibrosis, left ventricular diastolic dysfunction, and heart valve disease.2-5

Treatment for HGPS is predominantly supportive; however, recent studies of farnesyltransferase inhibitor lonafarnib by Gordon and colleagues6,7 have shown a survival benefit of 2.5 years in patients treated with this drug compared with untreated patients with HGPS. In 2023, lonafarnib was approved by Food and Drug Administration as the first treatment of HGPS.8

Structural heart disease in patients with progeria usually requires a personalized approach that considers the severity of the primary disease, comorbidity, and individual risks. Different treatment options for calcific aortic stenosis in patients with progeroid syndromes have been described. Vukovic and colleagues,9 successfully performed aortic valve replacement using transaortic interrupted sutures with concomitant coronary bypass grafting in a 33-year-old woman with progeria. Musumeci and colleagues10 opted for transapical aortic valve implantation in a 23-year-old man with HGPS and severe aortic stenosis with excellent early- and mid-term outcome.
The report by Hoganson and colleagues, published in this issue of the Journal, describes a thoughtful, personalized approach to this rare subset of patients. The use of custom-made left ventricular apical to aortic conduits may be beneficial in patients with progeria and extremely narrow aortic annulus with extended aortic and mitral valve calcification, especially considering the potential risks of Ross–Konno procedure or aorto-annuloplasty with aortic valve replacement.

References

FIGURE 1. Mechanism of cardiovascular damage in patients with Hutchinson–Gilford progeria syndrome. Normal endothelial cells produce nitric oxide (NO) and, thus, maintain normal vascular tone of the vascular smooth muscle cells. Impaired vascular wall permeability allows infiltration of the lipid-rich particle into the extracellular matrix, which is followed by migration of macrophages, engulfment of lipids, formation of foam cells, and accelerated atherosclerosis and calcifications.