

Hutchinson-Gilford Progeria Syndrome with Severe Calcific Aortic Valve Stenosis and Calcific Mitral Valve

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The case of a 12-year-old girl with clinical features of progeria with severe calcific valvar aortic stenosis is presented. The mitral valve showed the presence of calcium, and peripheral vascular disease was also present, though there was no family history of this. Aortic valve replacement was deferred because of insufficient data relating to this condition. The

genetics and phenotypic mechanisms of the disease are reviewed. In view of the association of progeria with valve disease, all patients should undergo electrocardiography and echocardiography as part of their routine work-up.

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Progeria - premature aging - is a rare disease of which approximately 40 cases are currently recognized worldwide. As cardiovascular changes are the major cause of death in this condition, all patients should undergo electrocardiography and echocardiography as part of their routine work-up, especially in view of the association of progeria with aortic valve disease.

Case report

A 12-year-old girl, who was the elder of two siblings of a non-consanguineous marriage, and who had a normal perinatal history, was evaluated for a cardiac murmur. The patient's complaints were dyspnea on exertion and atypical effort angina over a three-month period. The girl had not attained menarche, and physical examination revealed a short stature, shrunken facies, sparse hair, sparse eyebrows, micrognathia, thin lips, a 'beaked' nose and absent secondary sexual characteristics suggestive of a premature aging syndrome (Fig. 1). Her finger-nails were thin and brittle, but there were no signs of cataract. The girl's parents revealed that she had started to develop this appearance after the age of one year.

There were no features of mongolism, and intelligence was normal. There was bilateral carotid shudder, and the right radial and brachial pulses and



Figure 1: The clinical features of progeria.

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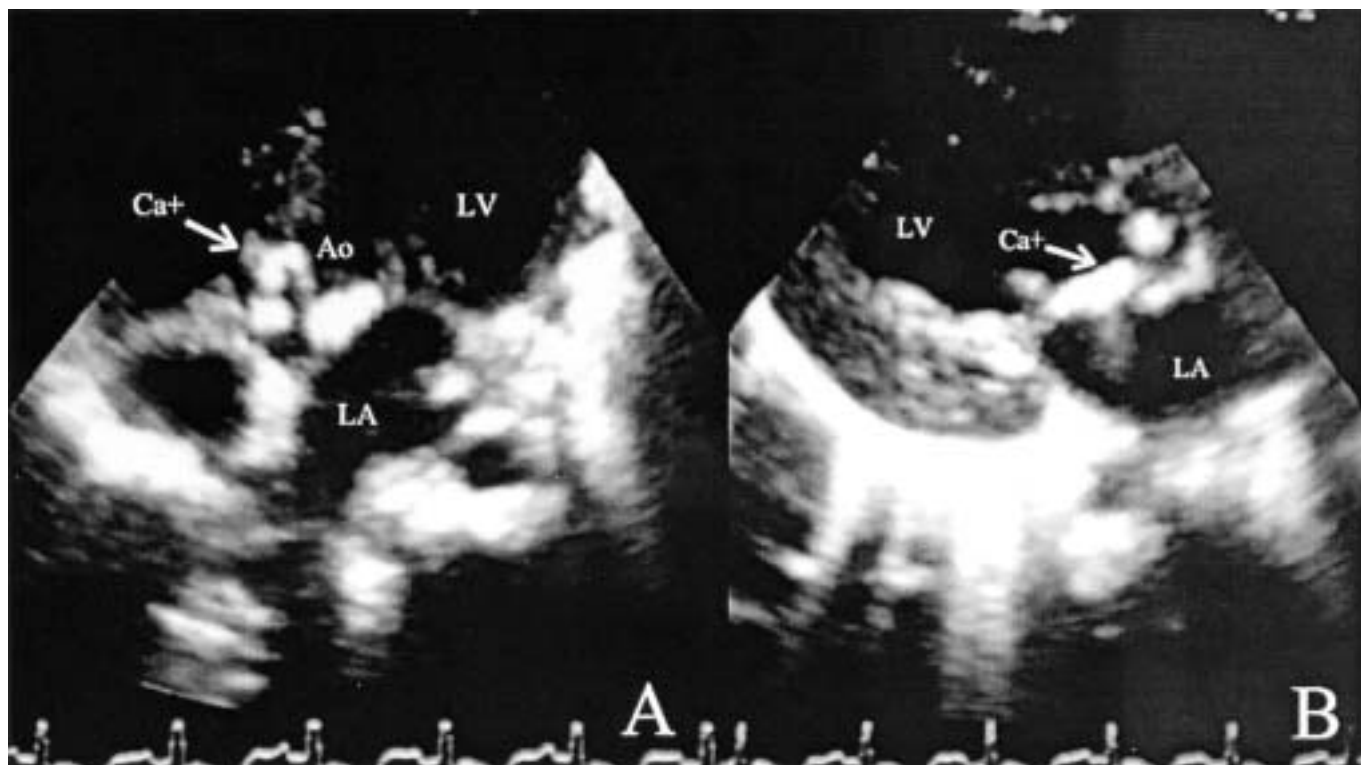


Figure 2: A) Four-chamber echocardiographic view showing calcific deposits (Ca+, arrow) over the aortic valve. B) Parasternal echocardiographic view showing calcium (Ca+, arrow) on the mitral valve. Ao: Aorta; LA: Left atrium; LV: Left ventricle.

bilateral pulses below the popliteal artery were non-palpable. The blood pressure in the left upper limb was 124/86 mmHg. There was no brachiofemoral delay, and clinical findings of severe aortic stenosis and mild aortic regurgitation were present.

Electrocardiography revealed left ventricular hypertrophy with a strain pattern, while echocardiography showed calcific deposits over the anterior mitral leaflet and aortic cusps (Fig. 2). Severe aortic stenosis with a peak systolic gradient of 75 mmHg and mild aortic regurgitation, as well as trivial mitral regurgitation, were seen. There was concentric left ventricular hypertrophy, and good left ventricular function. The aortic annulus diameter was 12 mm.

The patient's lipid profile revealed the following: total serum cholesterol 184 mg/dl; triglycerides 80 mg/dl; high-density lipoprotein cholesterol 44 mg/dl; and low-density lipoprotein cholesterol 129 mg/dl. A family screening was not contributory. Aortic valve replacement was deferred as insufficient data were available on valve replacement in this lethal condition among young children.

Discussion

Premature aging is generally associated with several cutaneous signs (1). Classical inherited premature

aging syndromes include pangeria (adult premature aging or Werner's syndrome), in which the onset occurs between 15 and 30 years of age, in association with cataract and sclerodermatous skin changes, none of which was identified in the present patient. However, the patient showed distinct features of progeria, or Hutchinson-Gilford progeria syndrome (HGPS). In contrast, acrogeria refers to premature aging of the extremities, and manifests within the first six years of life, though this condition is differentiated by the eyes and hair being unaffected, and there being a normal life expectancy.

Photosensitivity, especially congenital, is also apparent in these patients. For example, poikiloderma congenitale (Rothmund-Thomson syndrome) has an onset of between the ages of three and six months, with signs of early cataract formation, poikilodermatous skin changes and premature graying of the hair with alopecia.

In Cockayne's syndrome, the onset of disease occurs by the second decade of life, with cutaneous photosensitivity, ocular defects, short stature, long limbs, large hands and feet, and a characteristic facies with protruding ears.

Other causative conditions of progeria include congenital progeroid syndromes (e.g. trisomy 21), excessive exposure to radiation (especially ultraviolet rays),

diseases causing elastolysis (e.g. cutis laxa), thickened immobile skin with joint symptoms (e.g. diabetic cheiroarthropathy), and a loss of subcutaneous fat (generalized lipodystrophy).

In progeria, the diagnosis rests on the clinical presentation (2), as in the present patient. This is a rare condition, with the Hutchinson-Gilford Progeria Syndrome Research Center estimating that HGPS affects between 1 in 4 million (estimated actual) and 1 in 8 million (reported) children. Indeed, the total reported incidence during the twentieth century, and since the condition was first identified, is marginally in excess of 100 cases (3). Currently, between 30 and 40 known cases of HGPS have been identified worldwide (4), and 97% of these have been among the white population (4). The presence of HGPS is usually recognized during the second year of life (2), with patients reaching their third decade rarely exceeding the body weight and height of a six-year-old child. Except for the external abnormalities, most of the signs and symptoms, as well as the cause of death, result from the complications of sclerosis (4).

Clinical features have been divided into characteristic groups. Those features which are always present include scalp alopecia, prominent scalp veins and eyes, micrognathia, delayed abnormal dentition, thin limbs, short stature, incomplete sexual maturation and decreased subcutaneous fat. The usually-present features include sclerodermatous skin, generalized alopecia, eyebrow/eyelash alopecia, protruding ears, thin lips, patent anterior fontanelle, high-pitched voice and dystrophic nails.

Cardiac involvement is a central problem of this syndrome, and manifests as coronary artery disease, valvular stenosis and hypertension (4). The present patient was not hypertensive, but had calcific aortic valve stenosis as well as calcium deposition in the mitral leaflets. There was no evidence of coronary artery disease, however.

Among the 32 typical cases of progeria reviewed by Makous et al. (4), specific mention of the cardiovascular system was made in 31 patients. The age range in this group ranged from 2 to 26 years (average 9 years). A highly accelerated calcific deposition was seen to occur in the coronary, aortic (5), cerebral, subclavian and axillary arteries, mitral annulus, and aortic valve cusps (2). The calcific sclerosis that affects the aortic valve represents a degenerative change, and exemplifies an exaggeration of normal aging (6).

Cardiac murmurs in patients with progeria are probably due to arteriosclerosis which involves principally the anterior cusp of the mitral valve and the proximal portions of the aortic valve cusps. Atherosclerotic involvement of the left ventricular outflow tract, with extension to the adjacent areas of the ascending aorta,

may also produce cardiac murmurs. Almost 40% of progeria patients usually develop cardiac murmurs, and these generally appear after the age of five years. The use of valve surgery has been discussed in adult progeria (Werner's syndrome), but in order to avoid the use of prosthetic material the mitral valve may be repaired and the aortic valve replaced with a homograft. Aggressive surgical treatment has been performed, with a low perioperative risk, in adult progeria (7).

Electrocardiographic evidence of myocardial infarction is not common in progeria. Coronary atherosclerosis is usually extensive, as is atherosclerotic involvement of the aorta, and occlusion of the right coronary ostium is especially common. Angina pectoris rarely appears before the patient is aged six years. Death usually occurs within four years after the onset of angina pectoris, as a result of acute coronary insufficiency either with or without myocardial infarction. Heart failure may precede death (4).

Systemic hypertension is common in progeria. It may appear before the patient reaches the age of five years, but the situation is often unclear until after the age of six years. Accompanying nephrosclerosis is not uniformly present (4). Arteriosclerosis elsewhere is neither necessarily extensive nor advanced, but is usually present. The present patient had significant associated peripheral occlusive vascular disease. The detection of significant asymptomatic arteriosclerosis in children with progeria is as difficult and unsatisfactory as it is in adults (4).

With regard to the genetic etiology and phenotypic manifestation of progeria, there is a sporadic autosomal dominant mutation in the majority of cases, while others have an autosomal recessive mode of inheritance (6). A strong association of rare lamin A (LMNA) coding sequence mutations with HGPS has been shown, which implicates this syndrome as a laminopathy (8). The HGPS gene was localized to chromosome 1q, and a de-novo single-base substitution of G608G (GGC→GGT) within exon 11 was implicated (9). A perturbation in the glycosylation of connective tissue in HGPS may be due to a defect in the UDP-galactose:beta-N-acetylglucosamine-beta-1,4-galactosyltransferase 3 gene that has been mapped to the interval 1q21-23 (10). There is a lack of binding of collagen in basement membranes and cartilage in HGPS, which suggests the involvement of proline/arginine-rich end leucine-rich repeat protein (PRELP), the deficiency of which accounts for many manifestations. Moreover, PRELP also accounts for the fact that, unlike many other collagen-related diseases, the symptoms of HGPS are not congenital. The appearance of PRELP after the third month of life coincides with the appearance of HGPS symptoms (11). Elastin and type IV col-

lagen production are elevated in fibroblasts derived from the skin of patients with HGPS, and are associated with accelerated aging (12).

Mechanisms differ between adult and childhood progeria. Neither serum nor urinary hyaluronan concentration is a reliable diagnostic or prognostic marker for HGPS, underlining the difference between the adult and childhood conditions (13).

The current prognosis for progeria is poor, and at present no effective therapy is available. The average life expectancy in progeria is 13 years (range: 7 to 27 years) (6), with death resulting from cardiovascular abnormalities - usually myocardial infarction or congestive cardiac failure - in 75% of cases (14).

In conclusion, progeria is a rare disease of which approximately 40 cases are currently recognized worldwide. As cardiovascular changes are the major cause of death in progeria, all patients should undergo electrocardiography and echocardiography as part of their routine work-up, especially in view of the association of progeria with aortic valve disease.

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