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A 13-Year-Old Boy from Thailand with Hutchinson-Gilford Progeria Syndrome with Coronary Artery and Aortic Calcification and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 13-year-old
Final Diagnosis: Hutchinson-Gilford progeria syndrome with coronary artery and aortic calcification and non-ST-segment elevation myocardial infarction
Symptoms: Chest discomfort
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare disease

Background: Hutchinson-Gilford progeria syndrome (HGPS), also known as progeria, is due to a mutation in the LMNA gene, resulting in a life expectancy of no more than 13 years, and a high mortality rate due to cardiovascular disease. We report the case of a 13-year-old boy from Thailand with Hutchinson-Gilford progeria syndrome with coronary artery and aortic calcification and non-ST-segment elevation myocardial infarction (NSTEMI).

Case Report: A 13-year-old Thai boy was diagnosed with progeria. His physical appearance included short stature and thin limbs with prominent joint stiffness. He had craniofacial disproportion, with the absence of earlobes and with micrognathia. His skin had a generalized scleroderma-like lesion and hair loss with prominent scalp veins. His mental and cognitive functions were normal. Unfortunately, the mutation status in the LMNA gene was not available for testing in Thailand. He was diagnosed as having NSTEMI based on clinical chest pain, 12-lead ECG, and elevated cardiac troponin level. The coronary calcium score reflected severe calcification of the aortic valve and coronary artery disease along the left main and left anterior descending arteries. The patient received treatment with medication and aggressive risk factor control. After 3 months of follow-up, the patient reported no recurrence of symptoms.

Conclusions: This case of Hutchinson-Gilford progeria syndrome is rare in that most patients do not live beyond 13 years of age. This patient presented with typical accelerated degenerative changes of the cardiovascular system, including NSTEMI.

MeSH Keywords: Aging, Premature • Coronary Artery Disease • Progeria • Myocardial Infarction • Lamin Type A • Vascular Calcification • Aortic Valve • Rare Diseases • Case Reports

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Background

Progeria, also known as Hutchinson-Gilford progeria syndrome (HGPS), is an extremely rare disease [1,2] caused by a sporadic autosomal-dominant mutation [3] or an autosomal-recessive inheritance [4,5]. The premature aging caused by this condition seems to affect boys and girls equally [6]. Progeria was first described in 1886 by Jonathan Hutchinson and by Hastings Gilford in 1897 [2]. The condition was later named Hutchinson-Gilford progeria syndrome [7]. The word progeria comes from the Greek words "Pro" meaning "before" or "premature" and "Geras" meaning "old age" [8]. The typical clinical appearance includes very short stature, underweight, skeletal dysplasia, and fragile bodies, like those of aging people. They also have baldness, widespread subcutaneous fat loss, sclerotic changes in the skin, and decreased joint mobility. The patients usually have normal mental and motor development [9–11]. Early death usually occurs in the second decade of life from myocardial infarction or cerebrovascular disease due to premature arteriosclerosis [12]. The average life expectancy for a child with progeria is about 13-14 years [13,14]. Some patients with this disease die younger and others live longer, even as old as 20 years [15]. Cardiovascular problems or cerebrovascular disease are the eventual cause of death in most children with progeria [14]. Postmortem cardiovascular findings include loss of vascular smooth-muscle cells in coronary vessels, with replacement by fibrous tissue [16,17]. In 2003, the cause of progeria was discovered to be a point mutation in position 1824 of the Lamin A gene [4,18]. A mutant of the Lamin A gene (LMNA) produces nuclear instability, cellular instability, and, finally, cellular disruption, leading to premature aging [19]. The prevalence rate is about 1 in 20 million [20]. According to the Progeria Research Foundation, as of September 1, 2020, there were 179 children living with progeria across 53 countries. All of these 179 children had a progerin-producing mutation in the LMNA gene, and 51 children with progeroid laminopathy had a mutation in the LMNA gene but were not producing progerin [21]. These children living with progeria tended to have heart attacks, strokes, and other aging-related conditions. In individuals with HGPS, progressive arteriosclerosis and associated cardiovascular abnormalities may result in potentially life-threatening complications during childhood, adolescence, or young adulthood [16].

Here, we report the case of a 13-year-old boy from Thailand with Hutchinson-Gilford progeria syndrome with coronary artery and aortic calcification and non-ST-segment elevation myocardial infarction (NSTEMI). To the best of our knowledge, this is the second case report of HGPS in Thailand since 1990 [22]. We describe the clinical characteristics and cardiovascular complications of this patient.

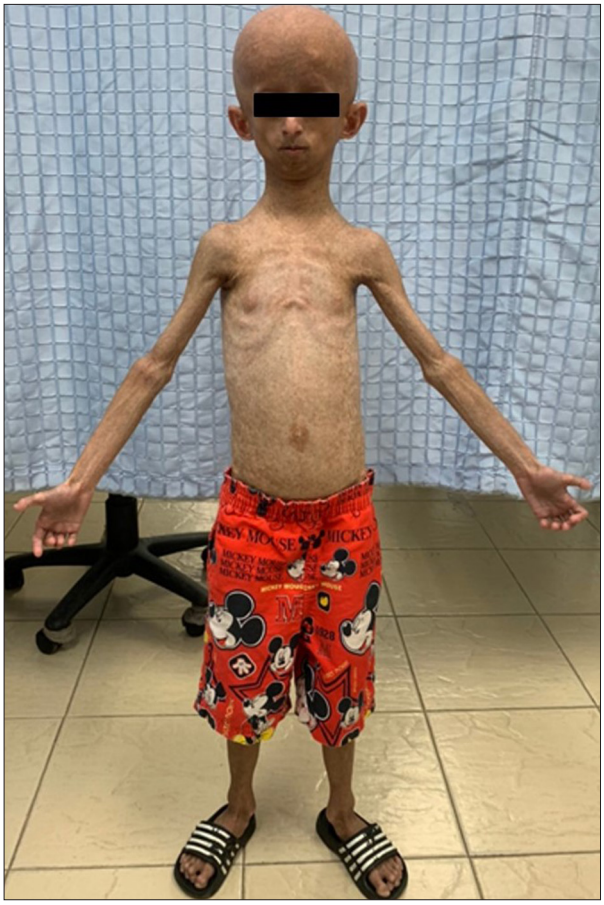

Figure 1. The patient was characteristically prematurely aged, with short stature, and prominent eyes, a small chin, total alopecia, and protruding ears. The cutaneous findings of this patient demonstrated scleroderma-like skin changes and a loss of subcutaneous fat.

Case Report

A 13-year-old Thai boy was sent to our cardiac clinic for evaluation of clinically progressive chest pain for 1 day prior to coming to the hospital. He reported a 3-month history of chest pain during exertion that was relieved at rest. He denied having fever, orthopnea, or paroxysmal nocturnal dyspnea. He was afebrile, had hypertension (148/64 mmHg) and tachycardia (heart rate 130/min), and had a normal respiratory rate and pattern. His body weight was 13 kg (<3rd percentile), height 117 cm (<3rd percentile), and the body mass index (BMI) 9.49 (kg/m^2). Dysmorphic features of the patient included short stature with premature aging changes (**Figure 1**). His distinctive appearance included alopecia with visible scalp veins, disproportionately large head, narrow face, prominent eyes, pterygium left eye, loss of eyelashes and eyebrows, thin lips, and small lower jaw. The cutaneous finding of this patient revealed thinning, wrinkling, and scleroderma-like skin changes. His hands had aged-looking skin, joint stiffness with decreased joint mobility, and

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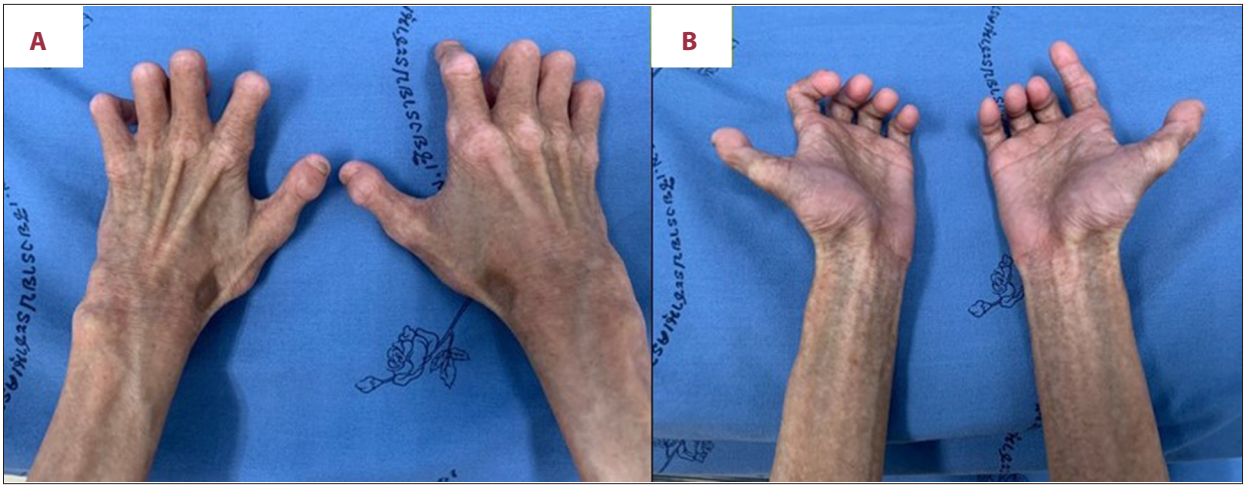

Figure 2. His hands demonstrated aged-looking skin, joint stiffness with decreased joint mobility, and a loss of subcutaneous fat (**A:** prone position) (**B:** supine position).

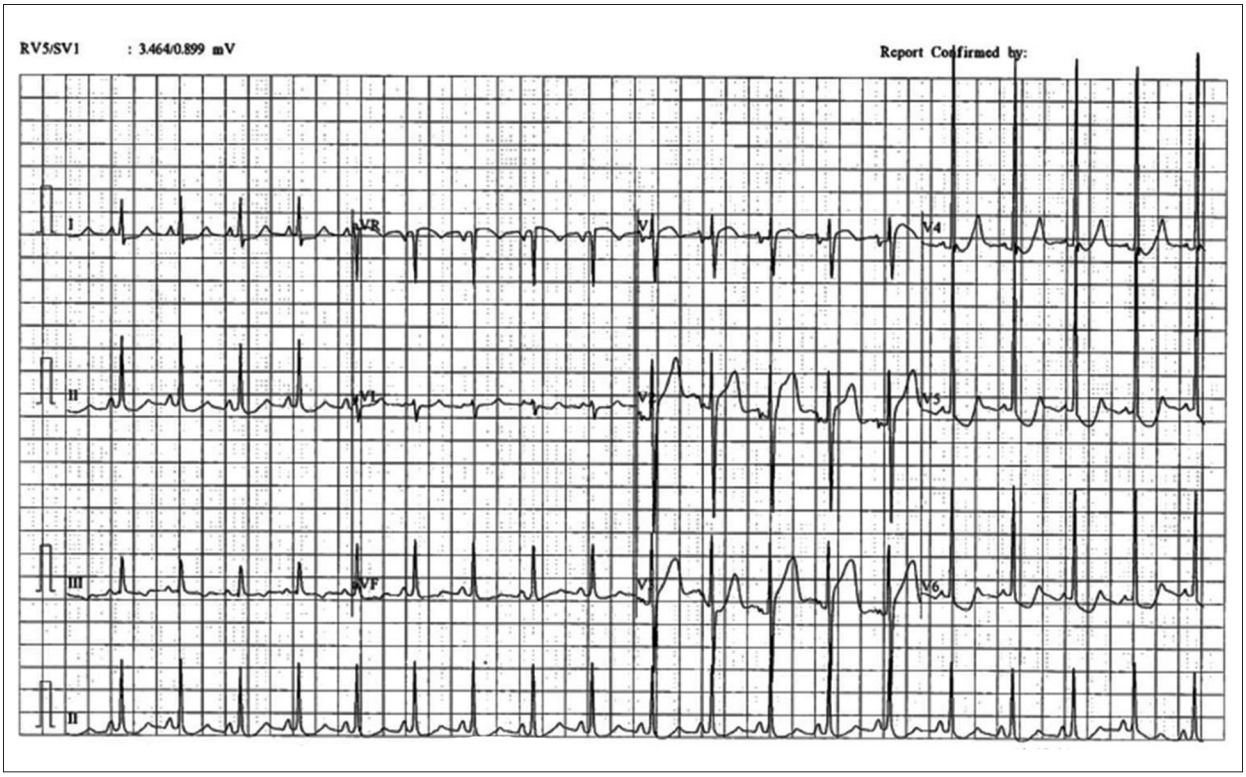

Figure 3. The 12-lead ECG showed sinus tachycardia, normal axis, left ventricular hypertrophy, and widespread horizontal ST-segment depression in I, aVL, II, III, aVF, and V4–V6, and ST elevation in aVR and V1. In the setting of acute coronary syndrome, this ECG usually indicates left main heart disease or a significant proximal LAD occlusion.

a loss of subcutaneous fat (**Figure 2**). The results of a bedside cardiovascular and respiratory examination were unremarkable. His mother reported that the patient appeared normal at birth, but during the first year of life he developed alopecia and delayed growth development, followed by skin changes and dysmorphic features. His mental and cognitive functions were normal for age. During the last 2 years, he had a traumatic right hip dislocation. A previous plain-film hip X-ray showed a right posterior hip dislocation with generalized osteopenia. During that hospital admission, blood tests revealed an elevated level of high-sensitivity troponin I (3995 pg/ml). A 12-lead electrocardiogram (ECG) showed sinus tachycardia, normal axis, left ventricular hypertrophy, widespread horizontal ST-segment depression in I, aVL, II, III, aVF, and V4–V6 and

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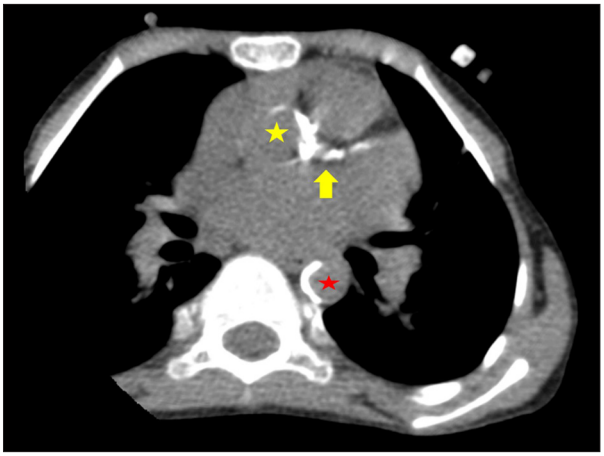

Figure 4. Cardiac computed tomography for coronary calcium score showing calcification of the aortic valve (yellow asterisk), coronary artery (arrow) including left main and proximal left anterior descending artery (LAD), and along the descending thoracic aortic wall (red asterisk). The calcium score was 126 Agatston units (AU). This appearance indicates the presence of progressive arteriosclerosis and associated cardiovascular abnormalities.

ST-segment elevation in aVR and V1 (**Figure 3**). In the setting of acute coronary syndrome, this ECG is usually a sign of left main disease or significant proximal left anterior descending artery occlusion. Echocardiography by a pediatric cardiologist showed good left ventricular function without regional wall abnormalities. There was no significant valvular heart disease and no pericardial effusion and there was a normal coronary artery origin. He was diagnosed as having NSTEMI based on clinical chest pain, 12-lead ECG, and cardiac enzyme levels. Metabolic disturbances included dyslipidemia, total cholesterol 239 mg/dl, low-density lipoprotein (LDL) 175 mg/dl, triglyceride 145 mg/dl, and non-HDL 204 mg/dl. Thyroid function and blood sugar were normal.

Cardiac computed tomography for coronary calcium score was performed to evaluate additional risk stratification. The calcium score was 126 Agatston units (AU), with calcification of the aortic valve, left main coronary artery, proximal LAD, and along the descending thoracic aortic wall (**Figure 4**). This appearance indicates the presence of progressive arteriosclerosis and associated cardiovascular abnormalities.

Unfortunately, the mutation status in the LMNA gene was not available for testing in Thailand. The diagnosis of Hutchinson-Gilford progeria syndrome was established in our patient based on the age at onset of disease and the phenotypic characteristics. The problem of greatest concern was coronary artery disease caused by premature atherosclerosis. Clinically, anginal pain, ECG pattern, and high cardiac troponin were compatible with NSTEMI. A multidisciplinary team discussion included a pediatric cardiologist, an adult cardiologist, and a coronary interventionist. In accordance with the wishes of the patient and his family, the treatment was mainly symptomatic and supportive. He and his family refused coronary angiography and coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting. We administered a low-dose oral antiplatelet, high-potency statin, anti-hypertensive drugs, dietary magnesium supplement, and antianginal drugs after weight-adjusted dosing. After 3-month follow-up, the patient reported no recurrence of anginal chest pain and the LDL level had decreased by up to 50% from baseline after medications.

Discussion

We reported the case of a 13-year-old boy from Thailand with Hutchinson-Gilford progeria syndrome with coronary artery and aortic calcification and NSTEMI. Because the mutation status in the LMNA gene was not available for testing in Thailand, the diagnosis of HGPS was based on the age at onset of disease and the presence of typical phenotypic characteristics.

The differential diagnosis of premature aging diseases includes Wiedemann-Rautenstrauch syndrome, also known as neonatal progeroid syndrome. For this diagnosis, the signs and symptoms of aging must present during the neonatal period. The second differential diagnosis is Werner syndrome, also known as adult progeria. These clinical conditions of premature aging begin during the teens or early adulthood. Progeria is the one of premature aging diseases in which the patients usually appear normal at birth. The clinical manifestations are expressed within the first year of life, as in our case [23,24].

Probable mechanisms of progerin-induced arteriosclerosis were previously reported [25]. A mutation of the Lamin A gene produces nuclear instability and dysregulation of the affected gene expression function, and DNA repair induces cellular senescence [16,26]. The accumulation of un-repairable DNA damage in progeria is caused by mitochondrial reactive oxygen species (ROS)-mediated cell damage and the loss of antioxidant capacity [27–31]. The effect of gene mutation results in loss of vascular smooth-muscle cells and adventitial fibroblast dysfunction [32]. The abnormalities in nuclear morphologic features and function cause cellular stiffening [33–36]. Cell death encourages extracellular matrix growth in the dense vascular walls. The excessive vascular calcification found in progeria is mainly caused by the loss of pyrophosphate synthesis due to ROS-induced mitochondrial dysfunction [37]. The vascular calcification promotes osteogenic differentiation of vascular smooth-muscle cells [38]. Patients are affected by decreased creation and production of extracellular pyrophosphate [37], which is generally a strong inhibitor of vascular calcification [39]. In combination, these processes reduce the compliance of blood vessels. Cardiovascular

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problems include interstitial myocardial fibrosis, myocardial infarction, hypertension, and thickening and calcification of the mitral and aortic valves [40–42]. Due to the rarity of this disease, limited information is available on the natural history of related cardiovascular disorders [16,43]. Therefore, clinical trials have been difficult to perform.

The coronary calcium score is another noninvasive strategy currently used for risk stratification in a coronary artery disease [44]. In our patient, the coronary calcium score was high, indicating the presence of coronary artery disease. Use of coronary angiography and coronary artery bypass grafting (CABG) may be the best option for revascularization. However, according to coronary artery disease management guidelines [45,46], the data on the safety and efficacy outcome of coronary revascularization in the pediatric population are limited. The patient and his family's prerequisites are the most important aspects that we are concerned with. Symptomatic and atherosclerosis risk factor control might be the best option for patients such as ours. Recent advances in basic research have raised new hopes regarding targeted therapies [47].

Previous studies demonstrated some improvement in lifespan and delayed progression of degenerative processes in a mouse model of Hutchinson-Gilford progeria syndrome using farnesyl transferase inhibitor [48], combined treatment with statins and zoledronate [49], salicylic acid [50], methionine restriction [51], fecal microbiota transplantation [52], ATP-based therapy [53], and dietary magnesium supplementation [54]. Previous phase 2 clinical trials established that the protein farnesyltransferase inhibitor lonafarnib ameliorates some aspects of cardiovascular disease among these patients [55].

Conclusions

Our patient with Hutchinson-Gilford progeria syndrome is unusual in that most do not live beyond 13 years of age. This patient presented with typical accelerated degenerative changes of the cardiovascular system, including NSTEMI. The disease is caused by a point mutation in the LMNA gene. The patients usually appear normal at birth. The clinical manifestations are expressed within the first year of life, as in our patient. Progressive arteriosclerosis of coronary arteries is potentially life-threatening. Treatment of coronary artery disease remains a challenge in this population due to lack of guidelines and clinical trials.

Acknowledgments

We are grateful to the patient for providing consent for publication.

Ethics approval

The study was approved by the Ethics Committee for Research in Human Subjects, Chiang-Rai Prachanukroh Hospital.

Conflict of interests

None.

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