The Application of Clinical Genetics

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CASE REPORT

Hutchinson–Gilford Progeria Syndrome: Clinical and Molecular Characterization

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Abstract: Hutchinson–Gilford progeria syndrome (HGPS) is a rare congenital disease caused by mutations in the *LMNA* gene. Children with HGPS are phenotypically characterized by lipodystrophy, short height, low body weight, scleroderma, reduced joint mobility, osteolysis, senile facial features, and cardiovascular compromise that usually lead to death. We aimed to describe the case of a patient who reached above-average age expectancy for children with HGPS in Latin America and describe the clinical and molecular characteristics of the patient. A 14-year-old female patient was presented with progeria-compatible phenotypic characteristics. HGPS was confirmed via *LMNA* gene sequencing that detected a heterozygous c.1824C>T (p. Gly608Gly) mutation. The primary aim is to describe the HGPS case, the molecular gene mutation finding, and make a short review of the limited available treatment options for children with HGPS. Such as the farnesyl transferase inhibitors in conjunction with other pharmacological therapies that have insinuated improvement in health, and survival rate.

Keywords: HGPS, progeria, premature aging, genetic assessment, laminopathy, treatment

Introduction

Hutchinson–Gilford progeria syndrome (HGPS) is a rare sporadic autosomal dominant segmental premature aging disease, with a prevalence of 1 in 20 million births in the United States.[1] Associated with de novo missense heterozygous mutations of the LMNA gene in most cases.[2,3]

Little is known of the prevalence of HGPS in middle-income-countries, but in 2013, there was a report of 16 cases in Central and South America[4] that described a life expectancy of 13 years of age. Taking this into account we will describe the clinical and molecular characterization of a female patient with HGPS that reached above-average age expectancy in Latin America, and review some available treatment options.

Case Report

A 14-year-old female previously diagnosed with HGPS was the firstborn child of non-related, healthy parents, with no previous family genetic disorders and a healthy 9-year-old sibling. The mother was aged 20 years during conception, and the father was aged 26 years. Normal weight and height data were recorded throughout pregnancy. According to the parents, the patient appeared to be a healthy newborn, and the patient's development and growth was normal until her second year of age.

Subsequently, she had trouble gaining weight, even with an adequate diet, started losing hair, and her skin thickened and hardened. Her cognitive development

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was normal until she was 13 years old, when she had to stop school owing to Chikungunya viral infection that triggered secondary medical conditions.

The physical examination of our patient was compatible with a classic progeria phenotype she had alopecia, posterior low hair implantation with prominent scalp veins and eyes, beaked nose, micrognathia, partial anodontia, and senile facial features. Her thorax had "rosary" costal grating, and abdominal outpouching, with the absence of subcutaneous fat. Genitals were normal. Skin showed altered skin pigment, with scleroderma. Her extremities presented with tufting of fingers, osteoarthritis, and joint fibrosis (Figure 1).

Additionally, she had dilated cardiomyopathy, severe aortic and mitral valve insufficiency, congestive heart failure, severe insulin resistance and, altered lipid metabolism. Owing to these complications, she was receiving congestive heart failure treatment: furosemide, digoxin, and propranolol, and had concomitant follow-ups with pediatric gastroenterology, endocrinology, and pediatric palliative

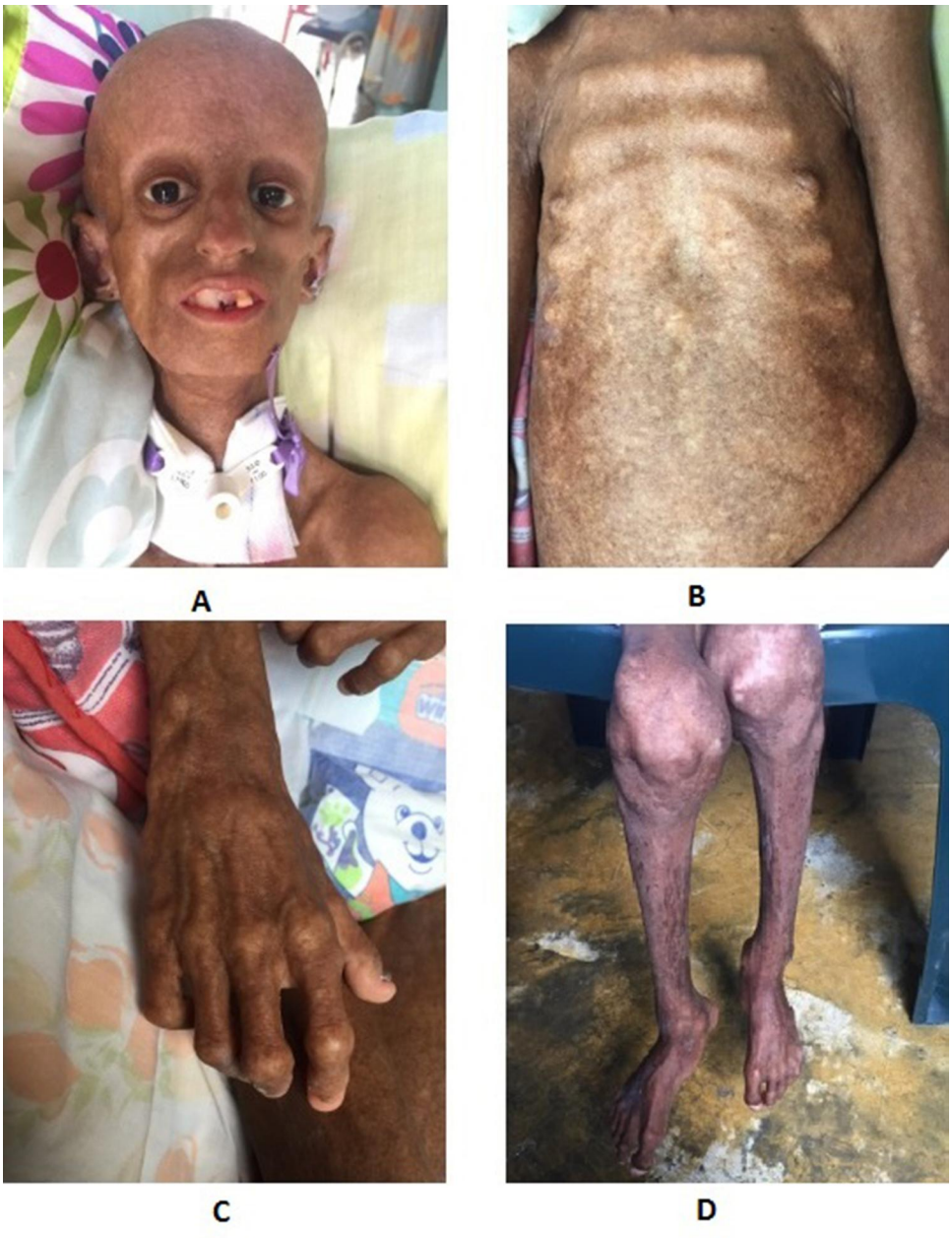

Figure 1 Alopecia, posterior low hair implantation with prominent scalp veins and eyes, beaked nose, micrognathia, partial anodontia, and senile facial features (**A**). Her thorax had "rosary" costal grating, and abdominal outpouching, with absence of subcutaneous fat (**B**). Her extremities presented with tufting of fingers (**C**), osteoarthritis, and joint fibrosis (**D**).

care. Patients' physical alterations through time were documented in a picture time-line (Figure 2).

Via a blood test, we sequenced the LMNA gene. A heterozygous mutation detected in exon 11 of the LMNA gene at c.1824C>T (p.Gly608Gly) confirmed the molecular diagnosis of classic HGPS. The present study was previously approved by the institutional Internal Review Board, Comite de etica en investigacion biomedica. A written informed consent was signed by the parents authorizing to perform genetic test, use case details, pictures and publish the case.

Discussion

HGPS follows an autosomal dominant inheritance pattern.[2,3] But, most patients with HGPS have de novo missense mutation in the *LMNA* gene leading to activation of a cryptic splice site, which means children do not inherit the disease from their parents.[5] Although at birth, these patients appear healthy, the symptoms begin to appear after the first year of life, and the average age of diagnosis is 2.9 years.[2] These children have a life expectancy of 13.4 years[6] and experience accelerated atherosclerosis usually resulting in early death associated with myocardial infarction or less commonly, stroke.[7–9] Therefore, children with this life-threatening condition must be followed up by a pediatric palliative care team.

In 2003, two independent studies reported on the mutation c.1824C>T (p.Gly608Gly) within exon 11 of the *LMNA* gene, now referred to as the "classic" mutation that occurs in ~90% of HGPS patients,[6,10,11] including the patient in the present study.

Although this mutation is usually silent, it activates a cryptic splice that deletes 150 nucleotides, extending to the beginning of exon 12.[2,3,10,11] Therefore, the final post-translational process of prelamin A (suppression of the 15C-terminal amino acid) is halted, resulting in abnormal

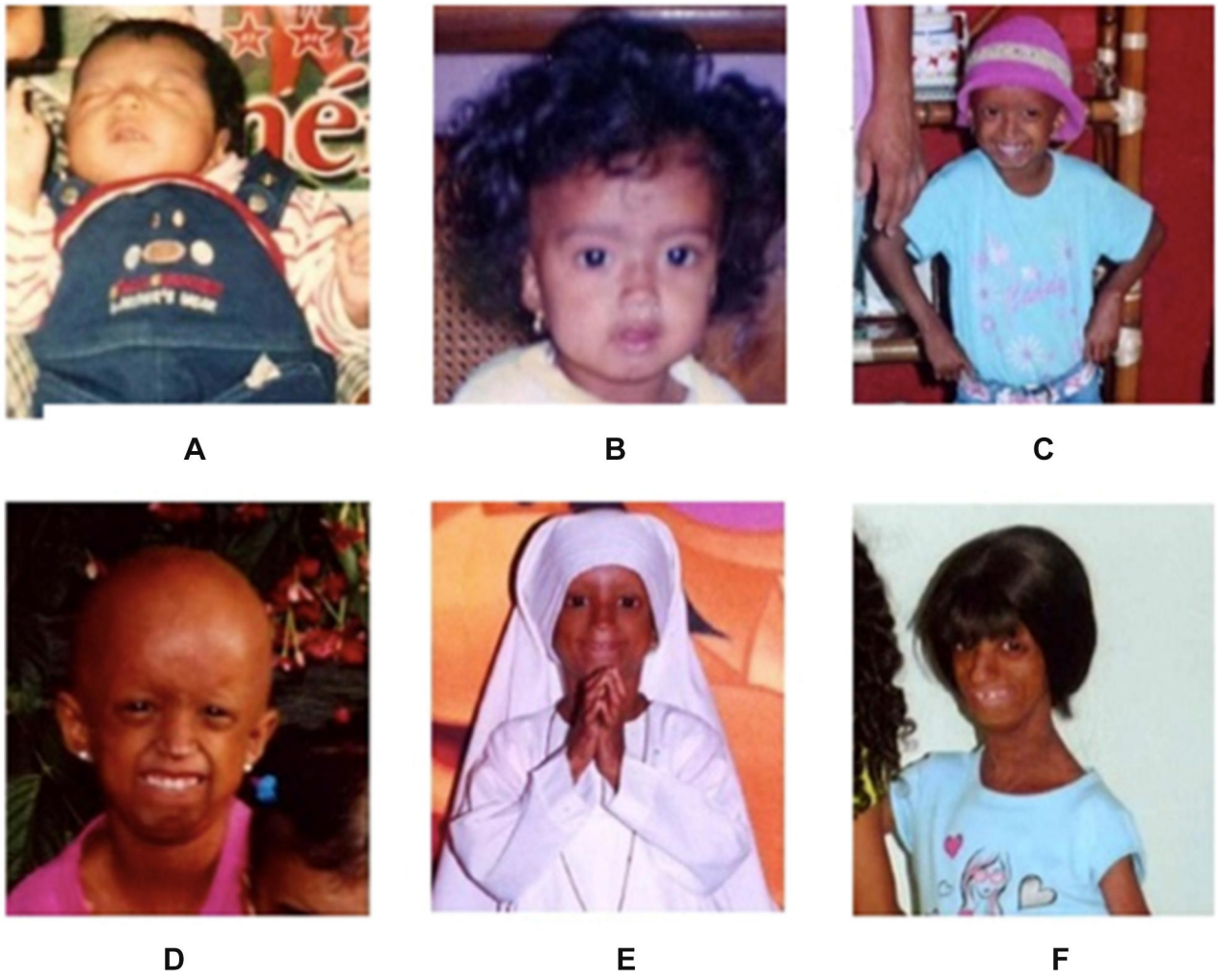

Figure 2 Patient at one month-of-age (**A**), six months-of-age (**B**), five years-of-age (**C**), six years-of-age (**D**), seven years-of-age (**E**), and thirteen years-of-age (**F**).

farnesylation, and a mutant lamin A called progerin. Scaffidi and Mistelli[12] evaluated fibroblasts of patients with classic HGPS and concluded that the presence of progerin and not the absence of lamina A causes the phenotype.[12] Additionally, with the insertion of a modified oligonucleotide that targets the cryptic splice and causes mutation of p. G608G, fibroblasts recover nuclear distribution of the studied proteins and normal morphology.[13] Other authors like Fong et al[14] demonstrated that toxicity caused by progerin is responsible for the abnormal HGPS phenotype.

Although currently, there are no Food and Drug Administration-approved treatments for HGPS, some clinical trials have been directed to test farnesyl transferase inhibitors such as lonafarnib.[3,8,10,15] Gordon et al conducted two single-arm non-randomized, age and gender-matched clinical trials on farnesyltransferase inhibitors. In the first trial, they administered lonafarnib as monotherapy[15] with no concurrent control group. The primary outcome was an improvement in weight gain rate, followed by cardiovascular distensibility, increase in bone rigidity and sensorineural hearing, but the duration of the trial was insufficient to demonstrate an improvement in survival. In the second trail, they compared triple-therapy[16] (farnesyltransferase inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor and a bisphosphonate) with historic and concurrent untreated control participants enrolled in the prior lonafarnib monotherapy treatment trial. Concluding that triple-therapy did not provide any additional benefit compared to lonafarnib monotherapy.[16] There was a third observational cohort study, age, gender and continent matched derived from the previous two treatment trials conducted to compare contemporaneous treated patients with lonafarnib vs untreated patients. Showing lower mortality rate after 2.2 years.[17] Despite these results, it is important to highlight that farnesylation inhibitors do not reverse the disease and therefore are not curative.[15]

Currently, CRISPR/Cas9 gene editing seems a promising strategy for the treatment of genetic diseases, including HGPS.[18] Another important scenario to keep in mind with HGPS children is to prevent secondary complications; therefore, some authors recommend the use of aspirin (2–3 mg/kg per day) as a cardio-cerebrovascular protector.[9]

Although most HGPS cases are associated with a new mutation, Wuyts et al[19] described an affected individual whose mutation was transmitted by his asymptomatic mother, who presented somatic and germline mosaicism to the classic mutation. Therefore, promoting genetic counseling to parents of children with HGPS is essential because prenatal tests are available, and the risk of recurrence is 1 in 500 siblings.[9]

Differential diagnoses for HGPS include the following autosomal recessive syndromes: Wiedemann-Rautenstrauch syndrome, neonatal progeroid disorder characterized by lipodystrophy, growth retardation, triangular face, and dental anomalies suggested to be caused by biallelic variants in POLR3A;[20] Rothmund–Thomson syndrome that compromises the RECQL4 gene and is associated with baldness, short stature, skin pigmentation, cataracts, and abnormalities

Table 1 Extremely Rare Genetic Lipodystrophy Syndromes

Lipodystrophy	Gene	Clinical Features
MAD Type B	*ZMPSTE24*	Craniofacial, cutaneous and skeletal abnormalities, premature renal failure and progeroid features, generalized loss of fat[22]
MDP syndrome	*POLD1*	Mandibular hypoplasia, deafness and progeroid features, progressive lipodystrophy[23]
Neonatal progeroid syndrome type a	*FBN1*	Marfanoid/ progeroid appearance, dilated aortic bulb, bilateral subluxation of the lens, myopia in addition to severe generalized lipodystrophy, and muscle mass, no significant metabolic abnormalities associated with insulin resistance[24]
Nestor-Guillermo Progeria Syndrome	*BANF1*	Growth retardation, decreased subcutaneous fat, thin limbs and stiff joints[25]
Keppen-Lubinsky syndrome	*KCNJ6*	Severe intellectual disability, microcephaly, developmental delay, prominent large eyes, progeroid features with an open mouth, and generalized lipodystrophy.[26]
SPRTN mutations	*SPRTN*	Genomic instability, progeroid features, lipodystrophy, and hepatocellular carcinoma[27]

Note: The Werner Syndrome is also included in this category. Data from Wuyts et al[19] and Kashyap et al.[21]

Abbreviations: *BANF1*, barrier to autointegration factor1; *FBN1*, fibrillin-1; *KCNJ6*, potassium inwardly-rectifying channel subfamily J member 6; MAD, mandibuloacral dysplasia; MDP, mandibular hypoplasia, deafness, progeroid features, *POLD1*, polymerase (DNA) delta 1, catalytic subunit; *SPRTN*, spartan; *ZMPSTE24*, zinc metallopeptidaseSTE24.

of bones, nails, and teeth; Cockayne syndrome, caused by mutations in the ERCC8 gene and usually presents with cutaneous photosensitivity, retinal degeneration, short height, large ears, long limbs and feet, and large hands; Werner syndrome, caused by mutations in the RECQL2 or WRN gene, that manifests as bilateral cataracts, thinning and graying of the hair, short stature, ankle sores, hyperkeratosis, subcutaneous atrophy, and "bird-like" facial features,[21] that appears at 20–30 years of age.

There are two more lipodystrophy syndromes linked to the LMNA gene. One of them is the mandibuloacral dysplasia type A (MADA) characterized for craniofacial, skeletal and cutaneous abnormalities, loss of subcutaneous fat from the extremities along with normal or excessive fat in the face and neck.[22,23] The latter is associated with mutations that disrupt nuclear function and therefore premature cell death in many tissues.[24] The second one is the atypical progeroid syndrome caused by molecular defects in exon 1 through 6 of the LMNA gene. It presents with overlapping muscular symptoms, skin defects, cardiomyopathy and rhythm abnormalities, as well as variable progeroid features, and partial or generalized loss of subcutaneous fat.[22] Extremely rare genetic lipodystrophy syndromes are listed in Table 1.

This study suggests that patients with HGPS should be managed by a multidisciplinary health team that includes a geneticist, cardiologist, and pediatric palliative care, to meet all needs of children with this condition and their families.

Data Sharing Statement

Can be accessed contacting the corresponding author.

Ethics Approval

The present study was previously approved by the institutional Internal Review Board, Comite de etica en investigacion biomedica of Fundacion Valle Del Lili.

Consent for Publication

Written informed consent was signed by the parents authorizing to perform genetic tests, use case details, pictures and publish the case.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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