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Case Report

Unprecedented report: First female monozygotic twins as carriers of Hutchinson-Gilford progeria syndrome

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ABSTRACT

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic condition characterized by premature aging resulting from an autosomal mutation in the LMNA gene. This article presents a groundbreaking instance of the first female monozygotic twins affected by HGPS, originating from Brazil, highlighting the exceptional nature of this case.

Keywords: Hutchinson-Gilford progeria syndrome, monozygotic twins, female, progeria

INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS) is an exceedingly rare condition characterized by premature aging. It arises from a spontaneous autosomal mutation in the LMNA gene, which is responsible for producing the Lamina A protein. This protein plays a crucial role in maintaining the structural integrity of the cell nucleus. However, due to the mutation, cellular instability ensues, leading to various abnormalities in nuclear morphology, dysregulated gene expression, deficiencies in deoxyribonucleic acid (DNA) repair, telomere shortening, and genomic instability, resulting in the impairment of the cell's ability to proliferate. The primary manifestation of HGPS is the early onset of aging-related features, which become evident in the affected individuals. As the condition progresses, complications arising from atherosclerosis, such as myocardial infarction, stroke, and heart failure, become a significant cause of death. Unfortunately, individuals diagnosed with HGPS typically have a life expectancy that extends only into their teenage years or early twenties.[1,2]

Progeria was first described in 1886 by Hutchinson and confirmed by Gilford in 1904. It occurs sporadically, with an incidence of 1 in every 8 million live births, and its diagnosis is merely clinical, based on physical manifestations.[3] According to data from the Progeria Research Foundation in March 2023, an estimated 193 children live with progeria, encompassing both HGPS and Progeroid Laminopathy. Progeroid Laminopathy refers to cases wherein individuals have mutations in the lamin pathway but do

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not produce progerin, the characteristic protein associated with HGPS. Since the foundation's inception in 2001, 373 Progeria cases have been registered.[4] To date, the only reported instance of monozygotic twins affected by progeria has been documented in the study conducted by Viégas et al.[5] However, this present work introduces a groundbreaking discovery — the first case of female twins affected by progeria, specifically Hutchinson-Gilford Progeria Syndrome. Notably, both twins have undergone laboratory confirmation, which involved the collection of genetic material. This significant finding expands our understanding of progeria and highlights the importance of further exploration in diverse populations and gender-specific presentations of the syndrome.

CASE REPORT

We present the case of female monozygotic twins born through vaginal birth at 32 weeks of gestation in Boa Vista, Roraima, Brazil. The maternal history involves a healthy Brazilian woman, 38 years old, who has had ten natural deliveries from different relationships, with no complications during pregnancy, although she did not receive prenatal care. The father is a healthy 27-year-old Brazilian man and the twins' sole father. Both parents met while working in a mine in the Amazon rainforest.

At birth, no syndromic features were observed in either twin. However, when the twins reached four months, the family noticed a progressive onset of hair loss, changes in skin thickness, prominent veins in the cranial region, and difficulty gaining weight. Concerned about their health, the twins were admitted to the hospital at six months of age due to suspected pneumonia and malnutrition. Given their low weight and the presence of phenotypic changes, their pediatrician initiated a comprehensive clinical investigation. Karyotype analysis, among other tests, was conducted to identify any underlying abnormalities. However, the results of the tests did not reveal any apparent irregularities. At nine months of age, during a pediatric consultation at the Reference Center for Women's Health, located in the capital of Roraima–Boa Vista, the twins were clinically diagnosed with Hutchinson-Gilford Progeria Syndrome (HGPS). The diagnosis was based on the progression of the HGPS phenotype becoming more evident over time. The twins exhibited characteristic features associated with HGPS, including accelerated aging, craniofacial abnormalities, and vascular changes.

In their concern for their children's health and in search of guidance and support, the family turned to the Progeria Research Foundation (PRF). In June 2023, genetic testing confirmed the diagnosis of HGPS in the twins, detecting c.1968+1 G>C heterozygous mutation in the LMNA gene. This gene variant is associated with Hutchinson-Gilford progeria, which exhibits autosomal dominant inheritance, alongside various clinical phenotypes associated with both autosomal dominant and autosomal recessive inheritance. This confirmation played a crucial role in initiating appropriate management strategies and exploring access to Lonafarnib, the only FDA-approved drug known to delay the disease's progression potentially.[6]

The anthropometric measurements of both twins fall below the normal range. As of November 2023, at the age of 2 years and six months, the twins weighed 4690 and 4350 grams, with heights of 64.9 and 61.9 centimeters, head circumferences of 42.3 and 41.8 centimeters, and Body Mass Index (BMI) values of 11.13 and 11.35 kg/m2, respectively. Additionally, both twins exhibit a global developmental delay relative to their age milestones. Early recognition of developmental delays is crucial as it allows for timely interventions and support, ultimately facilitating positive progress in their future development.

Anthropometric parameters vary significantly between individuals and change according to sex due to genetic potential and environmental factors. Specifically, in childhood and adolescence, body measurements change according to the growth and development stage, in other words, according to age and Tanner pubertal stage. Consequently, evaluating the normality of these measures becomes complex. In daily pediatric practice, scores like the Z-score are used to compare measurements with children of the same age and sex. Any alteration beyond three standard deviations from the mean is considered severe. Tables and charts for children of up to 5 years of age of both sexes can be freely downloaded from the WHO website (www.who.int/childgrowth/standards/en). Regarding the twins in the study, both girls have a Z-score < -3 for weight, classified by the WHO as very low weight for age, and for length, both have a Z-score < -3, classified as very short stature.

The proactive engagement of a multidisciplinary healthcare team is pivotal in overseeing the well-being and developmental progress of twins affected by Hutchinson-Gilford Progeria Syndrome (HGPS). Within this team, the pediatric neurologist assumes a central role in assessing the twins' overall developmental trajectory, particularly providing guidance on speech and social delays. Concurrently, the twins' nutritionist ensures they receive optimal nourishment to preempt malnutrition, even in the absence of current dietary challenges or restrictions. The physiotherapist adopts a proactive stance in advocating for recreational activities to bolster mobility, resulting in noteworthy enhancements to the twins' daily functioning. This includes engaging in intra-household activities utilizing familiar

toys introduced by the family in a playful manner strategically designed to stimulate cognitive and motor skills. Moreover, the recommendation of late afternoon walks has proven efficacious, effectively addressing early-onset walking challenges to foster improved mobility and independence as the twins progress through development.

Given the tropical climate and heightened sun exposure in Roraima, the twins' dermatologist maintains vigilant oversight of their skin health. Emphasis is placed on rigorous photoprotection and hydration regimens to mitigate the elevated risks of sunstroke and skin dehydration prevalent in the region. Diligent care management can effectively alleviate skin-related symptoms associated with HGPS, enhancing the twins' overall comfort and well-being. The collaborative synergy between the family, medical specialists, and the PRF underscores the imperative of early identification and intervention in HGPS cases. By harnessing available resources and exploring potential therapeutic avenues, the collective goal is to optimize the quality of life and long-term outcomes for these remarkable female monozygotic twins.

DISCUSSION

HGPS is a single sporadic autosomal alteration in the LMNA gene, which produces a defective Lamin A protein that cannot maintain cell nucleus stability.[7] This makes the cells unstable, which leads to the fatal process of premature aging. However, progeroid syndromes encompass a group of diseases, HGPS or not, that are characterized by signs of premature aging.[8]

Previously, it was only possible to diagnose HGPS using error-prone clinical information, as other progeroid syndromes existed. With the advent of genetic testing and gene identification, it is possible to make a more accurate diagnosis that may allow early medical intervention that favors a better quality of life for children.[4]

In November 2020, Lonafarnib was the first drug to receive US Food and Drug Administration (FDA) approval for Progeria and Progeroid Laminopathies.[6] Preclinical studies involving the farnesyltransferase protein inhibitor Lonafarnib, originally an experimental drug in oncology, resulted in better life expectancy in children with the disease and minimized the impact of cardiovascular events due to the syndrome.[9,10]

This work announces the first recorded case of female monozygotic twins with HGPS worldwide. Two Brazilian women residing in the capital of the state of Roraima, Boa Vista. Both were born 32 weeks premature and have been fighting for life ever since.

The use of mercury in gold mining is one of the main sources of methylmercury contamination in Brazil. Methylmercury exposure during pregnancy is indeed a concerning issue, as it has been associated with various complications and adverse effects on both maternal and fetal health.[11] Since the mother remained until the fifth month of pregnancy in the mining area, a place with high contamination with mercury, the question arises of the participation of this metal with the predisposition to the syndrome. Although there is currently no literature data directly linking HGPS to mercury exposure during pregnancy, Khan et al.'s work in 2019 demonstrated that mercury exposure could induce epigenetic alterations, leading to behavioral outcomes, atherosclerosis, and myocardial infarction, and miRNAs in the cervix of pregnant women are responsive to maternal mercury exposure, suggesting a novel pathway of influence. The same work has shown that mercury-induced epigenetic alterations in kidney tissues have revealed a significant disruption in renal function, with DNA methylation and histone post-translational modifications being the predominant types of mercury-induced epigenetic changes.[12] Indeed, it was postulated that exposure to adverse environmental factors during fetal life determines the chronic disease risk during adult life due to epigenetic alterations or changes in the genetic material.[3,4]

The physical characteristics of progeria begin to manifest themselves only from 4 months of age. The family suspected, based on this event, that they might have a syndrome. However, doctors were still determining what it could be since most of the tests requested had negative results.

In one of the routine consultations with the pediatrician, at nine months of age, both received the clinical diagnosis of HGPS based on clinical experience and the characteristic phenotypes of premature aging.

The twins periodically carry out several multidisciplinary follow-ups with health professionals to maintain their well-being. Initially, there was a significant barrier, as the professionals were unaware of HGPS, and the caregiver stated that he often needed to explain the syndrome based on previous research carried out for self-knowledge of the subject. From these searches on internet sites, the family found information about PRF. They contacted the institution that instructed them on the collection of genetic material for laboratory confirmation of HGPS, in addition to clarifying doubts about the drug Lonafarnib.

The family has great positive expectations with the test result confirming HGPS and is anxiously awaiting PRF's response to the possible use of the farnesyltransferase protein inhibitor since the drug helps to minimize this effect of vascular stiffness, allowing for a longer life expectancy.[9]

Figure 1 represents the twins' clinical journey, showcasing the changes in their physical appearance and syndromic features as they age.

All the information presented in this article, including laboratory tests and photos, was provided by the family to the researchers through formal written consent. Moreover, the family has requested to disclose the twins' social media, such as their Instagram account (https://www.instagram.com/elis_e_eloa/), YouTube channel (https://www.youtube.com/@Elis_e_Eloa), and TikTok page (https://www.tiktok.com/discover/elis_e_eloa), which allows interested individuals to follow the twins' routine. The twins are public figures virtually, accompanied by their caregiver (brother) on these platforms. By sharing their experiences, the family aims to raise awareness about HGPS and provide insights into the daily lives of individuals living with this rare genetic disorder.

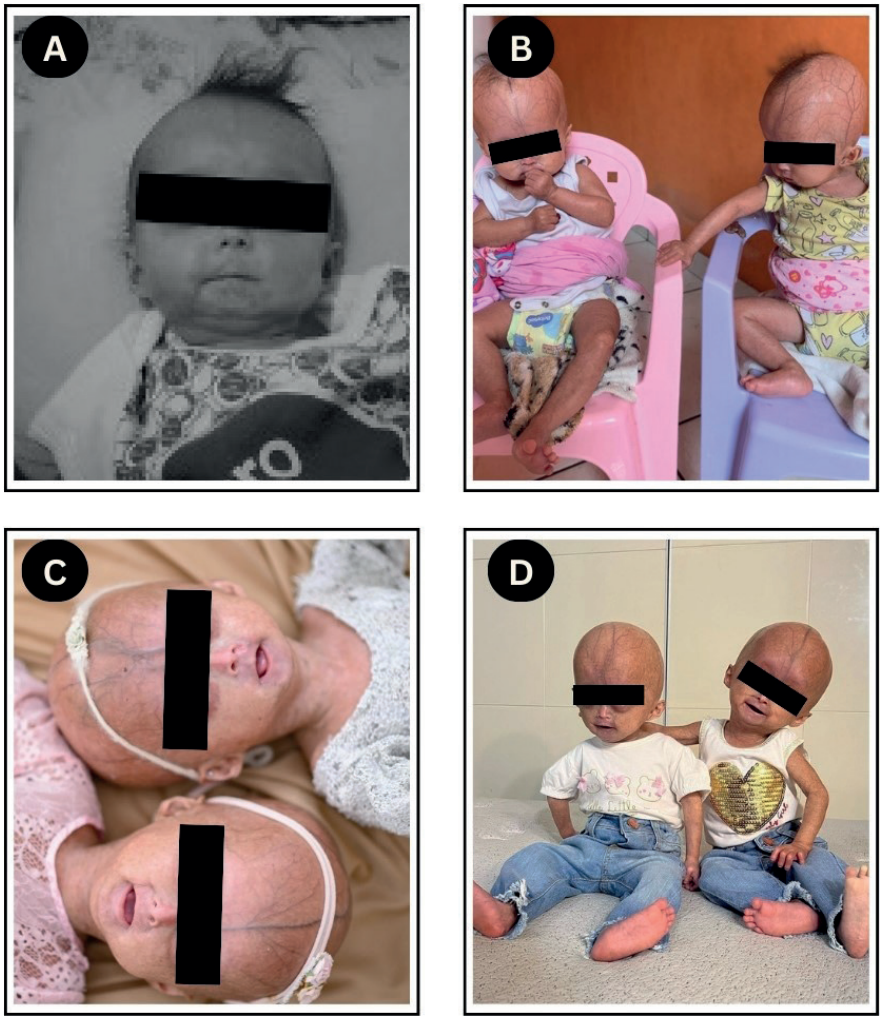

Figure 1. Progression of alopecia and syndromic characteristics in female monozygotic twins affected by HGPS.

(A) One of the twins at an early age with only a few phenotypic manifestations. The child still has preserved hair at 12 months of age, indicating an early phase in the development of the syndrome. **(B-C)** Both twins are at a later stage of development (15 months of age). They exhibit changes characteristic of HGPS, including vascular alterations, noticeable hair loss, and low weight. These manifestations highlight the progression of the disease over time. **(D)** HGPS Twins in February 2024 at three years old with the syndrome's full range of phenotypic characteristics evident.

HGPS: Hutchinson-Gilford Progeria Syndrome Hutchinson-Gilford Progeria Syndrome

CONCLUSION

This is the first confirmed case of progeria in female twins in the world, an extremely rare syndrome with premature cellular aging as a hallmark. The diagnosis is made according to clinical aspects and confirmed by laboratory tests from the genetic material, which are very difficult in some poor and underdeveloped regions. There is currently no cure, but there is a drug treatment, approved in 2020 by the FDA, capable of delaying the impacts of the syndrome, which therapy can be supported by the Progeria Research Foundation (PRF).

Ethical approval

This study has been approved by the Federal University of Roraima (approval date 01.08.2023, number 99168103204). Written informed consent was obtained from the participants.

Author contribution

All authors collected information and analyzed the results. All authors also contribute to writing and reviewed and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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