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Case presentation

Progeria and the early aging in children: a case report

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Abstract

The Hutchinson-Gilford syndrome or progeria is a rare autosomal dominant syndrome characterized by premature aging and involvement of internal systems, such as the circulatory and locomotor. The diagnosis is essentially clinical and the manifestations become more evident from the first year of life. Long term outcome data from Progeria Research Foundation clinical trials have demonstrated an increase in survival in recent years. Even though new trials are ongoing, the recognition of this syndrome is essential to prevent cardiovascular and cerebrovascular complications. A patient, initially asymptomatic, who developed characteristic signs of the syndrome at the age of 6 months is reported. She was referred for evaluation only when she was two years and eleven months old. The diagnosis of Hutchinson-Gilford syndrome was suspected owing to clinical characteristics. The diagnosis was confirmed by genetic testing. A mutation c.1824C> T in exon 11 of the LMNA gene was detected. She was registered in the Progeria Research Foundation and was invited to participate in the weighing and supplementation program. She was included in the lonafarnib protocol study. This medication is a farnesyl transferase inhibitor that prevents the production of progerina and slows cardiovascular and neurological complications of the syndrome. This case highlights the importance of diagnosing progeria patients because they may be referred to the Progeria Research Foundation, which offers genetic screening and inclusion in clinical and therapeutic follow-up protocols without any costs. Progeria trials and research may also contribute to new drug developments related to prevention of aging and atherosclerosis in the near future.

Keywords: Progeria, Hutchinson-Gilford syndrome, drug therapy, prevention and control.

Introduction

The Hutchinson-Gilford Progeria syndrome (HGPS) is an autosomal dominant syndrome, affecting 1 out of 4 million people [1]. The incidence is similar throughout the world and there is no predisposition by gender, geographic area, or ethnicity. The manifestations begin during the first two years of life. At birth the child is apparently healthy and most patients present with abnormalities between 6 and 12 months of age when problems such as failure in gaining weight, skin changes (areas of scleroderma), and alopecia appear [2]. The present patient is one of the 114 children with progeria identified worldwide, one among 10 in Brazil and the only one in the state of Paraná [3].

Case synopsis

Our female patient was seen for the first time when she was six years and eleven months old. She was born on January 7th, 2008, at normal term delivery without complications. Her weight was 2.675 grams and her height 49 cm. Apgar score was 8/10. Her parents were not consanguineous. She received exclusive maternal breastfeeding up to age seven months and weaning occurred at age one year and six months). Progressive facial changes, such as prominent eyes and perioral cyanosis, as well as thinning hair were noted beginning at the age of 6 months (Figure 1A,B). From six months old she presented with failure to thrive, with abnormality of her growth curve (Figure 2). She said first words at age two and began using phrases at age three.

At two years and eleven months old she was admitted to a tertiary hospital for investigation and Hutchinson-Gilford syndrome was suspected. At that time, weight and height deficit, sparse hair, prominent blood vessels on the scalp, hypoplasia of the midface, micrognathia, perioral cyanosis and dyspigmentation were noted (Figure 1A).

A nutritional assessment determined that the patient´s diet was qualitatively and quantitatively inadequate. Her weight was 8.770 g and her height was 83 cm, both below the 3rd percentile. Muscle mass and subcutaneous tissue were significantly decreased. Nutritional counseling was offered and supplementation three times a day was indicated. Echocardiogram evaluation identified tricuspid reflux with a maximum gradient of 12 mmHg. The audiometric test and the Brainstem Auditory Evoked Potentials (BAEP) were normal. Orthopedic assessment identified plano valgus feet and increased knee joints with mild contracture. The karyotype was normal (46, XX).

The patient was registered in the Progeria Research Foundation and she has been participating in the weighing and supplementation program. The result of genetic sequencing confirmed the diagnosis of Hutchinson-Gilford syndrome by demonstrating the mutation c.1824C> T in exon 11 of the LMNA gene in January 2011. The Progeria Research Foundation granted a visit to Boston for patient assessment and for her inclusion in a protocol study with lonafarnib. Her treatment started in August, 2014 and she will be receiving it for two years. She is using lonafarnib, 75mg per oral, in the morning and 100mg in the afternoon. Supplementation of vitamin A and D and formula supplement three times a day is being administered. Daily broad spectrum sunscreen is being used.

Currently the patient exhibits a worsening appearance of the skin. Hair and skin are thinning and muscle atrophy is also more notable (Figure 1B). There was an improvement in weight and height gain, although still insufficient for age and still below the third percentile.

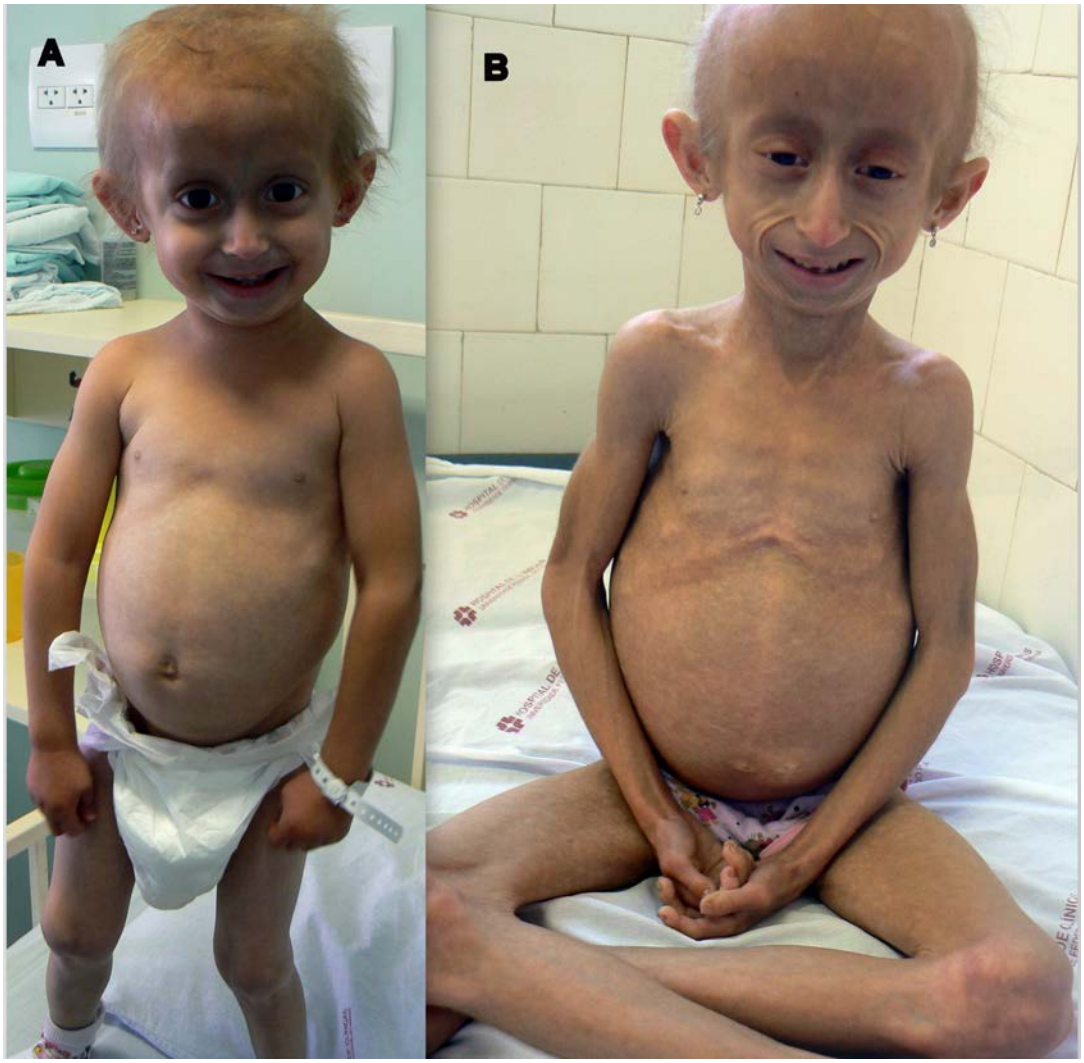

Figure 1A. Perioral and periorbital cyanosis,typical facies with cranifacial desproportion,thinning hair,wrinkles, and atrophied skin with lipodistrophia at 2 years and 11 months. **Figure 1B**. Aspect of the patient at 6 years and 6 months old.

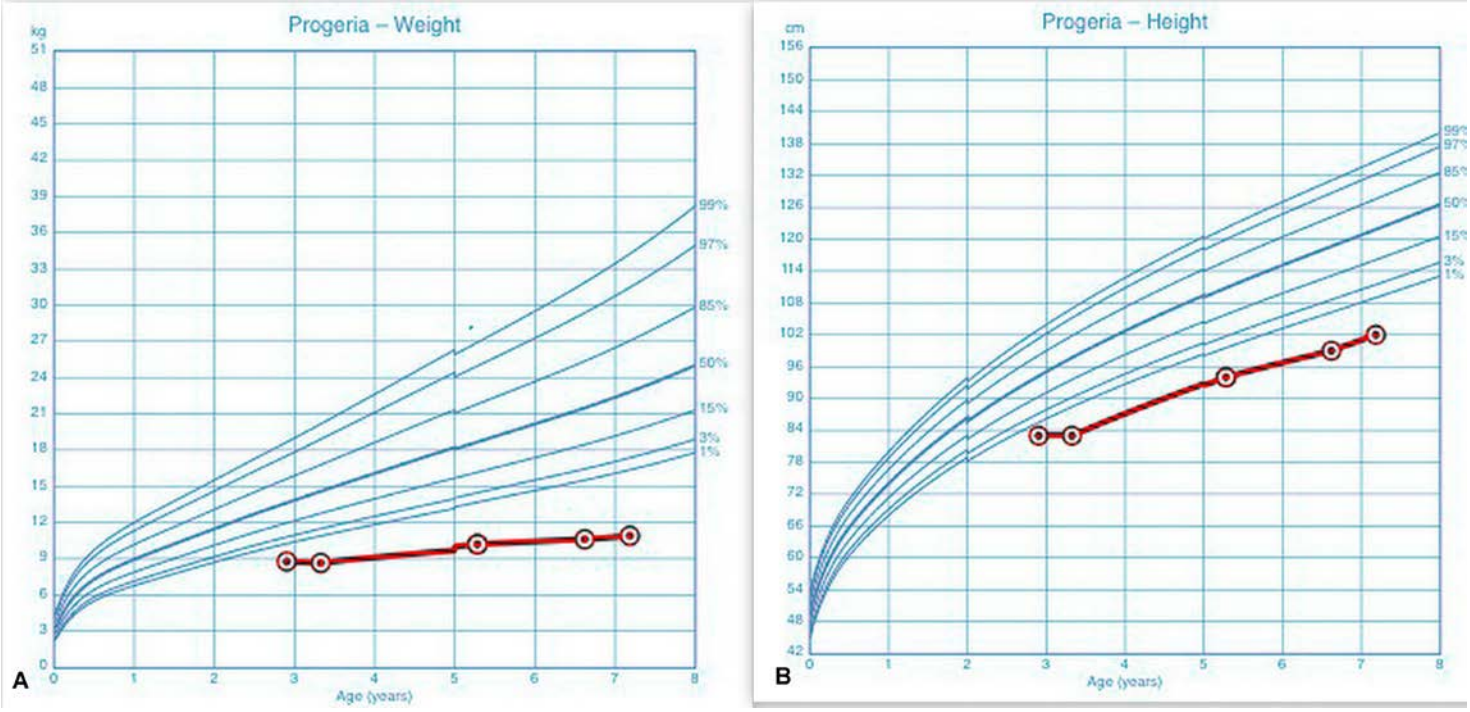

Figure 2. Percentis of Weight (A) and Height (B) from 3 to 6 years of the patient.

Discussion

The progeria is an extremely rare and fatal genetic syndrome known by the early development of aging sings. It was described by Hutchinson Gilford in the late nineteenth century, when there was no knowledge about the existence of cellular cytoskeleton. It was only in 2003 that LMNA gene was isolated. It is the producer of Laminin A, which is responsible for the structural stability of the cell nucleus [4]. A mutation in this gene leads to formation of an aberrant protein that undergoes farnesylation and becomes the progerina, a molecule which, among other effects, gives the the cell nucleus of patients with progeria a characteristic form [5].

The progerina accumulation and the consequent nuclear instability lead to telomere shortening, which is related to aging. Shorter telomeres make the aging process patent in children who have not completed one year old. Signs such as growth restriction, falling pelage, aging skin and joint stiffness precede the atherosclerosis process, which often leads to death due to myocardial infarction and stroke in patients with an average of 14 years old.

The patient reported had the progeria typical facies, with wrinkled skin, head proportionally larger than the body, sharp nose, prominent eyes, small ears without lobe, micrognathia and narrow face [3]. The main complaints reported by the mother were the skin changes and the facial dysmorphism, which are fundamental to the clinical suspicion [3]. This syndrome can go unrecognized if clinicians are unaware of these characteristics and drug treatment possibilities. From the age of six months the lipodystrophy and widespread alopecia appears. Therefore, the skin becomes hardened, infiltrated and swollen, acquiring aspect of scleroderma [6,7]. Up to two years old the scleroderma disappears and the skin becomes thin, dry and atrophic. With lipodystrophy progression, thinning of the lips and superficial veins highlighting on the scalp occurs. The skin treatment is non-specific and must be done with hydration and sun protection.

The patient in this report had an important speech delay, which is not common in progeria. The communication of the patients is partially affected by restriction of tongue movement, but so far cognitive delay or hearing disability associated with this syndrome has not been reported. The neurological symptoms in progeria syndrome are largely dependent on the neurovascular status and most of the children have transient ischemic attack and stroke with underlying carotid stenosis [2].

The tricuspid regurgitation presented by the patient is not common in progeria classical cases. In progeria the echocardiogram is usually normal and the electrocardiogram shows biventricular hypertrophy after certain age [2]. Cardiovascular substantial modifications would include high blood pressure and increased heart rate. Clinical or eletrocardiographic manifestations of ischemia appear at later stages in the end of life [8]. The plano valgus feet reported here, however, is a characteristic in both, progeria and natural aging. The valgus deformation with semiflexion of the lower limbs is due to premature atherosclerosis in these patients, which affects vessels of the connective tissue [9].

All of these clinical signs together with the acro-osteolysis findings on X-ray are used to diagnose progeria. Currently, the diagnosis is confirmed by a genetic test that amplifies the LMNA gene and identifies possible mutations. The patient has the c.1824C> T mutation in 11 exon (p.Gly608Gly), which was described as the cause of the syndrome by Eriksen et al. [4]. The genetic test with the identification of the mutation is important to differentiate progeria from other progeroid syndromes, such as Werner syndrome and Cockayne syndrome. When there is a suspected case of the progeria syndrome, a doctor in the Progeria Research Foundation (PRF) may be contacted. The patient's history will be evaluated and they will decide about the test, which is fully paid by the foundation.

The PRF was established in 1998 by two American doctors, which were parents of a child with Progeria. Since then, the organization has been stimulating research on the progeria syndrome, which has a huge importance in the scientific field because these children mimic the normal aging process. The LMNA gene was discovered with PRF support. Through active study of these children and their diagnosis, performed by PRF, it was possible to identify 114 patients with progeria worldwide. The inclusion of progeria patients in clinical trials with new drugs could shed light on aging processes in general including atherosclerosis.

The main medication in current study is called lonafarnib, which is a farnesyltransferase inhibitor. Progerina synthesis is occurs not only via the pre-progerina production by the mutant LMNA gene, but also by the synthesis of farnesyl groups (related to cholesterol) and its insertion in the molecule of the pre-progerina. This insertion is prevented by lonafarnib, which is an inhibitor of progerina synthesis at the end of this reactions chain [10]. A clinical trial had been initiated in 2007 comparing patients that took this drug to control groups. After five years of follow up, the results were encouraging. In the untreated group 21 deaths occurred among 43 patients, whereas among the 43 treated children there were just five deaths. There was a mean increase in survival of 1.6 years in the group that received the drug [1]. Other studies have shown a great neurological benefit, with reduction of adverse cerebrovascular occurrences [11]. Another two clinical trials are evaluating pravastatin and zoledronic acid, which inhibits the production of farnesyl groups.

Even though it is a rare syndrome, the most common clinical manifestations should be recognized by the pediatrician. The patient may be referred to the Progeria Research Foundation, allowing correct diagnosis and appropriate treatment. As mentioned, new clinical trials are being conducted and new drugs are being developed to improve quality of life and reduce morbidity and mortality. In the future these clinical trials might shed further light on the therapeutic potential of these drugs in prevention of aging and atherosclerosis.

This case highlights the importance of diagnosing progeria patients because they may be referred to the Progeria Research Foundation, which offers genetic screening and inclusion in clinical and therapeutic follow-up protocols without any costs for patients. Progeria trials and research may also contribute to new drug developments related to prevention of aging and atherosclerosis in the near future.

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