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Hutchinson-Gilford progeria syndrome a diagnostic phenotype - A case report.

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Introduction

Hutchinson–Gilford progeria syndrome (HGPS) is a rare, fatal pediatric segmental premature aging disease. HGP is a "premature aging" disease in which children exhibit phenotypes that suggest aging process at both the cellular and organismal levels. HGPS is characterized by extremely short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, and facial features that resemble an aged person.

Cases

A 4-year-old male, the only issue of a non-consanguineous marriage child presented with complaints of not gaining adequate height and weight since 2 years of age. The antenatal period was uneventful. He was born full term with a birth weight of 3 kg with no neonatal intensive care requirement. He achieved all the developmental milestones as per his age. There was no history of associated chronic infections, use of Medi cations, short stature in the family, recurrent infections, or diarrhea.

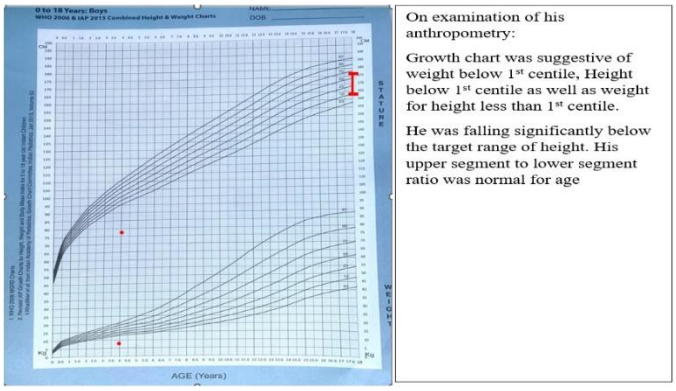

Figure 1:

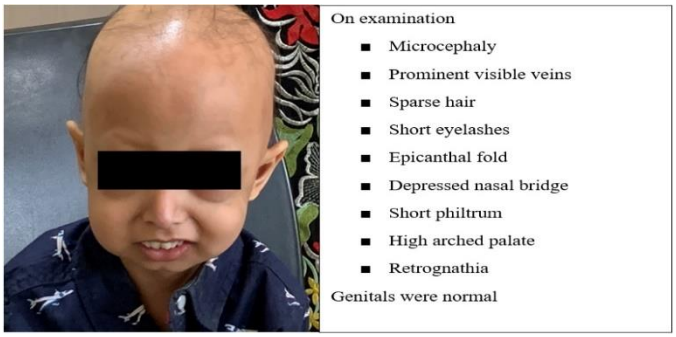

Figure 2:

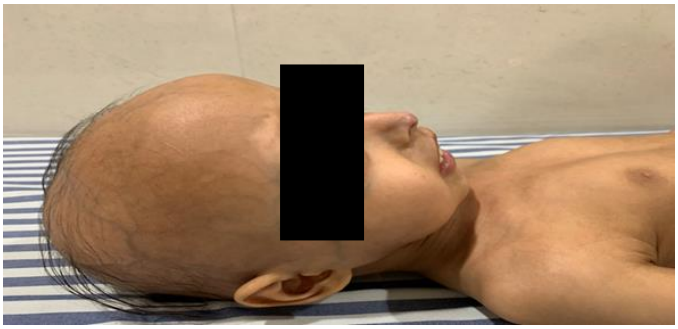

Figure 3:

There was no evidence of organomegaly.

After exclusion of chronic systemic causes, considering the dysmorphic facies with disproportionate short stature a possible diagnosis of syndromic short stature was considered. Basic investigations documented were normal.

Table 1:

Investigation	Values
Haemogram	Hb-13.7g/dl TLC-8700/cumm Neutrophils-44% Lymphocyte-42% Platelet count-2.56/cumm
Vitamin d	21 ng/ml
Calcium profile test	Serum Calcium (total): 93 mg/dl Serum Alkaline phosphatase: 167U/L Serum Phosphorous: 5.4 mg/dl
Serum Creatinine	0.3 mg/dl
Free T4 TSH	0.78 ng/dl 2.81 microIU/ml
IgA tTG	Normal Negative
2D Echo	Normal

Based on above history and clinical features, possibility of Hutchinson-Gilford progeria syndrome was con sidered. To confirm the diagnosis, a clinical exome was suggestive of coffin syndrome however no clinical relation, the whole phenotypic picture was suggestive of Hutchinson-Gilford progeria syndrome. In order to establish a confirmatory, entire genetic sequence is planned.

Table 2:

Gene	Location	Variant identified	Disorder	Inheritance	Zygosity	Classification
SOX4	Exon 1 chr 6	c.875A>G (p.Lys292Arg)	Coffin-Siris syndrome-10	Autosomal Dominant	**Detected Heterozygous**	Variant of Uncertain Significance
SON	Exon 3 chr 21	c.6070T>G (p.Leu2024Val)	ZTTK syndrome	Autosomal Dominant	**Detected Heterozygous**	Variant of Uncertain Significance

Clinical exome report of our patient.

Conclusion

Despite of genetic advances, some syndromes are still difficult to establish initially. A good history and correlation of clinical features can help to arrive at a diagnosis.

Discussion

Hutchinson-Gilford progeria syndrome (HGPS)is a rare genetic disorder characterized by accelerated aging with clinical involvement of the skin, bones, and cardiovascular system. The prevalence of HGPS is one in four million to one in eight million live births; males are more frequently affected than females, and the intellect of the affected children is unimpaired. The first descripttion of patients with HGPS was in 1886, by Jonathan Hutchinson (Hutchinson, 1886), and again later by his colleague Hastings Gilford (Hutchinson and Gilford, 1897), who named the condition progeria (prematurely aged) in 1904. The word progeria comes from the Greek word's pro, meaning "before" or "premature," and geras, meaning "old age." (1)

Genetics

Hutchinson–Gilford progeria syndrome is an autosomal dominant, rare, fatal pediatric segmental premature aging disease. Its extreme rarity (1:4–8 000 000) and mostly sporadic occurrence made it difficult to identify the underlying genetic cause. There is a little evidence of autosomal recessive inheritance of HGPS(2) Recently, denovopoint mutations in the LMNA gene have been found. LMNA encodes Lamin A and C, the A-type Lamins, which are an important structural com ponent of the nuclear envelope. This mutation leads to the production of a truncated toxic form of Lamin A, issued from aberrant splicing and called progeria. Progerin accumulates in HGPS cells nuclei and is a hallmark of the disease. (3)

Clinical features

HGPS is characterized by clinical features that typically develop in childhood and resemble some features of accelerated aging.(4)

Children with HGPS usually appear normal at birth but present as failure to thrive by first the first year. Common features include loss of subcutaneous fat, delayed eruption, abnormal skin with small outpour chings over the abdomen and upper thighs, alopecia, and nail dystrophy. Later findings include low-frequency conductive hearing loss, dental crowding, and partial lack of secondary tooth eruption. Motor and mental development is normal as described in our case as well. (5)

Growth

Inadequate nutrition is not responsible, since energy intake was sufficient for growth. Profound failure to thrive occurs during the first year of life.(5)

Facial features

Loss of subcutaneous fat, narrow nasal ridge, narrow nasal tip, thin vermilion of the upper and lower lips, small mouth, and retro- and micrognathia.(5). Plasivolia et all also found in his case diffuse frontal-temporal-occipital alopecia with absent eyebrows and eyelashes, and large open fontanelles which were also seen in our case.(2)

Patients are born with normal hair texture and coloring. At the age of 6 months–2 years, the hair usually falls out. Between 2 and 3 years, most children are found to be bald, apart from fine, downy hair, which has the tendency to curl. (6)

SKIN: The skin is thick, swollen, and shows a pitting edema. With time, the skin becomes more firm and sclerodermatous. Involvement of the skin of the lower

abdomen, upper gluteal regions, genitalia, and thighs is particularly seen. (6)

Musculoskelet on

Coxa valga, progressive joint contractures. decreased joint mobility, osteolysis are commonly observed (6)

Diagnosis

To confirm the clinical diagnosis of HGPS, DNA sequence analysis is performed.

Complications

Cardiovascular complications generally cause death in Hutchinson–Gilford progeria syndrome. Medial smooth-muscle cells are lost, with secondary maladaptive vascular remodeling, intimal thickening, disrupted elastin fibers and deposition of extracellular matrix causing sclerotic plaques in the aorta and coronary arteries can progress to stenosis. Primary morbidity and mortality for children with HGPS is from atherosclerotic cardiovascular disease and strokes with death occurring at an average age of 14.6 years. (5)

Initial ECG or blood pressures are not suggestive of cardiovascular problems. Murmurs are detectable from 4 years of age onwards. The children gradually develop shortness of breath with exertion and easy fatigability from 6 to 8 years, and pulse rates and blood pressure rise. Strokes have been reported at a median age of 9 years (4–19 years). They also present with (focal) seizures, hemiplegia, and dysarthria due to cerebral infarctions along with episodes of headaches, vertigo, and limb weakness. (6)

General phenotype and course

The general course in children with classical HGPS is very similar. Antenatally period is normal; the children are somewhat small for gestational age but do grow well during infancy. The first sign to notice is a clearly visible vein across the nasal bridge. From 6 to 12 months onwards, they start faltering in their growth with loss of hair and subcutaneous fat tissue. The diagnosis is often suspected between 2 and 3 years. The facial chara cteristics gradually develop wide veins over the scalp, eyes that look prominent, a narrow nasal bridge and ridge, thin skin that wrinkles around the mouth, irregular teeth with decay, a small chin, and prominent ears that lack lobules.

The body shows increasing loss of subcutaneous fat and muscle bulk, the joints protrude and contractures become more severe. But follow normal psychosocial and language development. Their appearance becomes increasingly that of an older person.

The main health problems that follow are from the vascular system. They can develop strokes, from a young age, with a sequel for mobility and speech. The cardiac problems can be slowly progressive or acute leading to sudden fatality. (6)

Treatment

Initially, treatment was focused on only symptomatic support including minimizing invasive medical interventions, avoidance of regular pain, and adequate psycho logical support to patients. A normal diet, accepting the severely impaired growth, non-surgical support of the limited joint mobility, and sealing of the teeth were achievable goals that help patients and families to cope with the disorder. (6) Monitoring for complications plays a vital role.

But over the last ten years, extensive efforts have been directed at developing genetic/ pharmacological interventions. A few studies have mentioned to treating HGPS by using protein therapy, diet control, or fecal microbiota therapy.

Among different modalities of pharmacological treatment, protein farnesyltransferase inhibitors (FTIs)

are the most commonly used therapeutic agents, being adopted in 22.5% of studies involving pharmacological treatment. Many more agents are still in the pipeline for the treatment. (7)

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