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Case Report

Ocular manifestations of Hutchinson-Gilford-Progeria syndrome: A rare presentation

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ABSTRACT

The Hutchinson-Gilford Progeria (HGP) syndrome is an exceptionally rare genetic condition characterized by premature and accelerated aging in children. It is demonstrated by developmental delay along with progressive degenerative changes of the integumentary, musculoskeletal, cardiac, and vascular systems. In this case report, we describe the ocular manifestations of Hutchinson-Gilford Progeria (HGP) syndrome of a 20-year-old Bangladeshi boy. The patient had the classic triad of prominent eyes, loss of eyebrows or madarosis and lagophthalmos, which are the most common ocular manifestations.He also developed dry eye, keratinized ocular surface, Meibomian gland dysfunction, vascularized cornea, symblepharon, corneal opacification, and cataract. He had several systemic manifeastations that included senile facies, prominent scalp veins, generalized alopecia with plucked bird appearance, and sclerodermatous changes.

1. Introduction

Hutchinson-Gilford Progeria Syndrome (HGPS) is a unique hereditary disorder with a prevalence of one in 4-8 million new births.[1] The word Progeria came from the Greek word "Progeros," which means "prematurely elderly." HGPS is characterized by growth retardation, premature aging, and accelerated degenerative changes, most notable in the integumentary, cardiovascular, and musculoskeletal systems.[2] Accelerated carotid and coronary artery atherosclerosis cause considerable morbidity and death, contributing to early death in the first or second decade of life.[3] The male-female ratio is 1.5:1.[3] Dr Hutchinson and Dr Gilforddescribed the first two patients with HGPS; the disease was named after them.[3]

1.1. Genetic Basis

HGPS is activated by mutations in two different genes, LMNA and ZMPSTE24.[4] The LMNA gene is an autosomal dominant trait where the mutation occurred at position 1824(C-T).[5] Although De novo mutations with advanced paternal age are responsible for most cases, maternal transmission of a mutant LMNA gene which expressed somatic and gonadal mosaicism has also been testified.[3] Progerin is a mutant Lamin A protein which is responsible for maintaining nuclear stability, establishing nuclear chromatin, regulating gene expression, D.N.A. synthesis, and D.N.A. repair.[6] The outcome of these shortcomings are genomic unsteadiness, reduced cell proliferation, premature cell senescence.[7]

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1.2. Biochemical changes

A typical finding in HGPS is the rise in hyaluronic acid excretion. The fibroblasts from progeria patients show a three times increase in total glycosaminoglycan production, particularly hyaluronic acid production, compared to the normal population. These changes in the level of hyaluronic acid are solely responsible for morphological development.[3]

1.3. Clinical findings

Early infancy is characterized by a normal physical appearance in progeria children,[8] while symptoms emerge throughout the first two years of life.[9] The ocular manifestations are described in Table 1. Surprisingly, patients with HGPS develop no senile ocular features such as presbyopia, arcus senilis, or age-related macular degeneration. The systemic manifestations are demonstrated in Table 2. They also develop subcutaneous fat and muscle loss, skin atrophy, osteoporosis, arthritis, poor growth, and alopecia.[8] Excessive lipofuscin deposition in several organs is an indicator of aging that is seen in HGPS patients. A consistent finding in patients with HGPS is a marked lack of vascular smooth muscle cells inside the great arteries, which is synonymous with sclerosis and fibrosis.[9] With a range of 7-27 years, the average life expectancy is 13 years.[10] About 75% of HGPS patients die as a result of cardiovascular disorders. Stroke, marasmus, inanition, epilepsy, and accidental head trauma are among the other causes of death. Sequential E.C.G., echocardiography, and radiological evaluation should be performed to monitor cardiac and musculoskeletal complications.[3] The differential diagnosis of HGPS is Werner's syndrome (adult progeria), Wiedemann-Rautenstrauch syndrome (neonatal Progeria), Cockayne's syndrome, Rothmund-Thomson syndrome, Metageria, and Acrogeria.[10]

1.4. Treatment

Patients with Progeria require a multidisciplinary approach in their care. Treatment is mainly symptomatic and supportive. Lonafarnib is a farnesyl transferase inhibitor, the first F.D.A. (U.S.A Food and Drug Administration) approved drug for HGPS.[11] The medicine has shown considerable weight gain, bone development, increase in musculoskeletal system integrity, and blood vessel flexibility. The cardiovascular and cerebrovascular disease must be closely monitored. The use of low-dose aspirin is commended as prophylaxis against cardiovascular and cerebrovascular atherosclerotic disease.[3]

2. Case Report

A 20 years old boy from Thakurgaon, Bangladesh, came to the cornea clinic two years back with complaints of the diminution of vision in both eyes (BE) for the last couple of years. On examination, his best-corrected visual acuity (BCVA) in the right eye (RE) was hand movement close to face (HMCF) and in the left eye (LE) was 1.00 in LogMAR charts. External ocular examination showed excessive forehead wrinkling, thickened eyelids, pseudoproptosis, superior sulcus deformity, lagophthalmos, lid lag in downgaze, total loss of eyelashes and eyebrows in BE (Figure 1). Systemic examination revealed a typical senile look with craniofacial disproportion, frontal and parietal bossing called pseudo hydrocephaly, beaked nose (Figure 2), mandibular and maxillary hypoplasia, prominent scalp veins (Figure 3), protruding ears, thin lips, thin limbs, prominent and stiff joints, thin and high-pitch voice, generalized alopecia (Figures 2 and 3), absence of subcutaneous fat, thin and wrinkled 'sclerodermatous' skin, fleck like hyperpigmentation in sun-exposed areas, prominent superficial veins, and nail dystrophy (Figure 3). He could write his name (Figure 3).

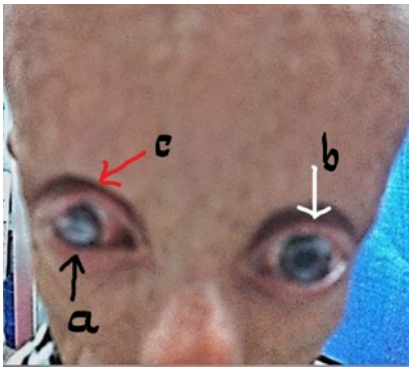

Fig. 1: (**a-c**) External ocular features shows: **a:** Thickened eyelid (Black arrow), **b:** Superior sulcus deformity (White arrow), **c:** Total loss of eyelash and eyebrows (Red Arrow)

Slit-lamp examination revealed dry and keratinized ocular surface and blocked meibomian gland orifices in BE. In his RE, the cornea was opacified with symblepharon (Figures 2 and 3). Due to a permanent lateral tarsorrhaphy done around seven years ago, there was substantial adhesion of the upper and lower eyelids at the lateral region. (Figure 4). In his LE, there were punctate epithelial defects (Figure 5). There was grade 3 nuclear sclerosis in RE and grade 1 nuclear sclerosis in the left eye. Intraocular pressure was 15mmHg and 13mmHg in RE and LE respectively, measured by air-puff tonometry. Fundus was not visible in the right eye due to cataract & corneal opacity. The fundus examination under mydriasis showed a mild dilated and tortuous vessel with a normal disc and macula in the left eye. The cause of decreased vision is probably due to surface

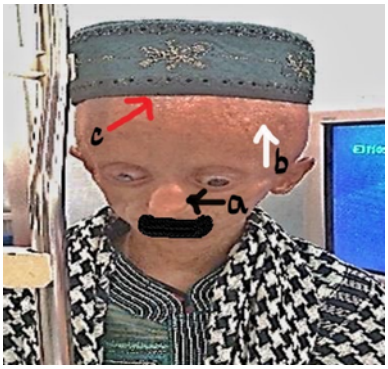

Fig. 2: (**a-c**): Systemic manifestation of HGPS shows typical face of Progeria with the senile look, associated with: **a:** Beaked nose (Black arrow), **b:** Fleck-like hyper pigmentation with aged-appearing skin (White arrow), **c:** Alopecia (Red arrow)

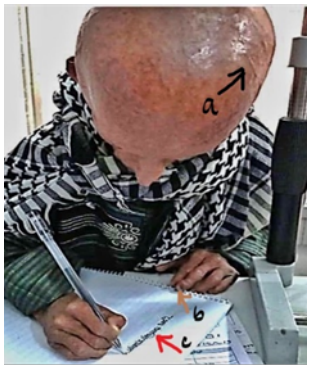

Fig. 3: (**a-b**). Systemic manifestation of HGPS shows: **a:** Generalized alopecia with prominent scalp veins (Black arrow), **b:** Nail dystrophy (Brown arrow), He could write his name (Red arrow)

irregularity, astigmatism, and cataract.

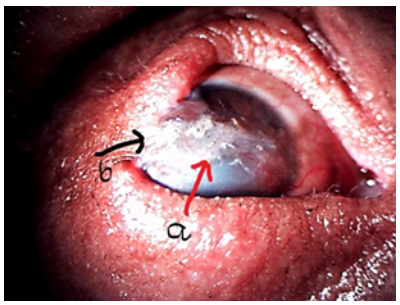

Fig. 4: Right eye of cornea shows, **a:** Keratinized ocular surface with opacified cornea (Red arrow), **b:** Symblepharon with permanent lateral tarsorrhaphy (Black arrow)

The antenatal period of the mother of this patient was uneventful, and delivery was normal at 41 weeks of gestation. His parents gave no history of consanguinity of marriage. A general physical examination of the patient

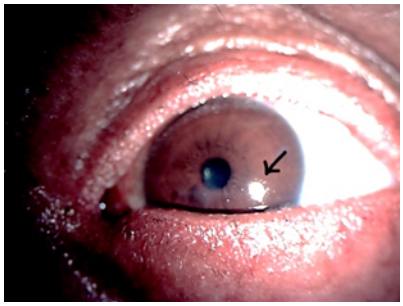

Fig. 5: Left eye of cornea shows punctate epithelial erosion (Black arrow)

Table 1: Ocular manifestations of HGPS syndrome

Ocular structures	Features
Globe and orbit	Prominent eyes with pseudoproptosis, Superior sulcus deformity
Extraocular Muscle (EOM)	Strabismus, Irregular nystagmoid movements
Eye Lid	Madarosis, Eyelid retractions, lagophthalmos, lid lag in downgaze, Senile ectropion, Ptosis with Marcus-jaw-winking phenomenon
Cornea	Dry-eye syndrome, Corneal scar, Pterygium, Corneal clouding
Anterior chamber	Irido-corneal adhesions,
Pupil	Poor pupillary dilatation
Lens	Cataract
Retina	Retinal arteriolar narrowing and tortuosity, Retinal angiosclerosis
Refractive changes	Myopia, hyperopia, and astigmatism

showed a height of 131 cm, a weight of 35 kg. Pulse was 72/min, and Blood pressure was 110/70 mm of Hg. We did a complete neurological examination of the boy—his I.Q. Scoring was average (90-109).[12]

Because of the characteristic clinical presentation, the child was diagnosed with HGP syndrome. We prescribed spectacle for the improvement of vision. Tear substitute was given four hourly for dryness as a supportive treatment. The patient was advised for radiological examinations to evaluate the bony deformity and urine examination for hyaluronic acid. He was referred to other specialities to evaluate cardiac disease and systemic anomaly. But unfortunately, he did not return. After two months, when we contacted his father, he informed us that his son had died from an acute myocardial infarction.

3. Discussion

HGPS is a rare genetic disorder that describes specifically premature aging. 97% of the reported cases were Caucasian.[13] More than 142 cases with the HGP syndrome have been recorded globally as of now.[14] The clinical diagnosis of the HGP syndrome is based on

Table 2: Systemic manifestations of HGPS

Cutaneous Manifestations of HGPS	Oral and craniofacial anomalies	Musculoskeletal system	Cardiac and vascular anomalies [11]	Miscellaneous Clinical findings
Sclerodermatous skin [10]	Plucked bird appearance [2]	Weight decrease for height [2]	Vascular smooth muscle cell loss	Inadequate sexual maturation
Generalized Alopecia (first appeared clinical features) [12] with lipodystrophy	Pseudohydrocephaly, micrognathia with midface hypoplasia	Thin limbs with prominent joints	Generalized atherosclerosis of cerebral and coronary arteries	Intellectually sound with normal personality [13]
Prominent superficial scalp veins	Large anterior fontanel [3]	Pyriform (pear-shaped) thorax [2]	Electrical, structural, and functional anomalies in the heart	High pitched voice
Nail dystrophy	Prominent eyes with a Beaked nose	Short, dystrophic clavicles	Myocardial infarction	Hyaluronuria [2]
Progressive freckle-like hyperpigmentation in sun-exposed areas	Protruding ears with absent lobes and shortened ear canals [3]	Bilateral hip dislocations	Heart failure	The reduced amino acid level in blood [2]
Loss of scalp hair resulting in baldness [3]	Thin lips with Centro-facial cyanosis	Avascular necrosis of the femoral head [3]	Stroke	Abnormal kidney and liver functions
Hypertrophic scars and Hypoplastic nipples.	Hypodontia with palatal anomalies	Resorption of distal phalanx		

the identification of distinguishing symptoms.[15] These children have a characteristic facial appearance that includes a disproportionately small face compared to the head, micrognathia, delayed dentitions, dental malformation and crowding, a beaked nose, prominent eyes, nasolabial circumoral cyanosis, and loss of scalp hair, brows, and eyelashes.[15] Most of the clinical features were present in our case. Additional features that we reported, which other researchers previously recorded, include generalized atherosclerosis, prominent scalp veins, lipodystrophy, nail dystrophy, and joint stiffness.[13,15]

Ocular menifestations reported by different authors are prominent eyes, loss of brows and eyelashes, skin attaching the upper lid to the cornea, senile ectropion, ptosis with Marcus-jaw-winking phenomenon, dry-eye syndrome, keratopathy, iridocorneal adhesions,corneal clouding, cataract, strabismus, irregular nystagmoid movements, myopia, hyperopia, retinal arteriolar narrowing and tortuosity.[15] We have discovered many of these ocular manifestations. In our case, we found some new features like punctate epithelial erosion, keratinized cornea and symblepharon (Figure 4), which were not previously recorded in the HGP condition, to our knowledge.

The average longevity of Progeria is 13 years.[16] But our patient survived for 20 years without any treatment. Cardiac problems are a principal cause of death,[16] and our patient also died due to acute myocardial infarction.

4. Conclusion

We have reported a patient with HGPS that demonstrates multiple systemic involvements. The diagnosis was made on clinical findings. Due to the poor socioeconomic condition of the patient, the diagnosis was delayed, and the patient died unfortunately due to acute myocardial infarction before completing other systemic evaluations.

5. Source of Funding

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6. Conflict of Interest

The authors have no conflicts of interest to declare.

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