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Craniofacial features associated with Hutchinson – Gilford progeria syndrome – A case report

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SUMMARY

Hutchinson – Gilford Progeria syndrome (HGPS) is a very rare syndrome characterized by early onset senescence. It is manifested as premature aging with involvement of hair, skin, nail, cardiovascular and bone manifestations. This syndrome has also been reported to be associated with craniofacial anomalies. With regard to these craniofacial phenotypes of Hutchinson – Gilford Progeria syndrome several studies are being undertaken all around the world. Here we present one such rare case of HGPS associated with craniofacial anomaly along with cleft lip and cleft palate in an eleven year old boy.

Keywords: Hutchinson – Gilford progeria syndrome, craniofacial anomalies, cleft lip and cleft palate, early onset senescence.

INTRODUCTION

Hutchinson Gilford Progeria syndrome (HGPS) is an extremely rare genetic disorder, characterized by segmental premature aging process with involvement of cardiovascular system, bones as well as skin (1). The prevalence rate of this syndrome is one in four to one in eight million live births with a male predominance (2). The most common cause of death in individuals with HGPS is myocardial infarction (2). Here we present a rare case of HPGS with association of craniofacial anomalies as well as clefts of the lip and palate which is rarely reported.

CASE REPORT

An eleven year old male patient reported to the Department Of Oral Medicine and Radiology with the chief complaint of defect in the face since birth. On eliciting the history, the patient's elder brother reported that, he was the younger child of the parents and was born with low birth weight. The patient did not have any pre-natal or natal history of trauma. The patient's mother had no history of consumption of medication for any disease or condition and the delivery was normal. The patient had delayed milestones of development like speech, walking and delayed response. The previous medical reports showed that the patient had undergone primary surgery for correction of cleft lip and palate. Cleft palate repair was done in 2012 followed by Cheiloplasty in 2013 at Baby Memorial Hospital, Calicut. The family history of the patient revealed that the parents had a consanguineous marriage. The patient has an elder brother and a twin brother; both of them lead a normal healthy lifestyle. Patient also has family history of his grandfather and first degree relatives being affected by cleft lip and cleft palate.

On general examination the patient had short stature with dry skin all over the body and docile child like features. The nails of hands and feet were hypoplastic. On extra oral examination features noticed were macrocephaly, sparse hair, absence of eyebrows and eyelashes, hypertelorism, hypoplastic maxilla, relatively prognathic mandible, depressed zygomatic region due to malar hypoplasia, scarred upper lip secondary to primary cleft lip surgery, incompetent lip with a concave profile. The skin of the scalp was pigmented with minute areas of hypo pigmentation, sparse hair, and dry and scaly skin mimicking scleroderma. The patient also displayed features of obliterated nostril on right side, deviated nasal septum secondary to cleft lip and palate deformity. Altered anatomy of external pinna of the ear was also seen. The face was disproportionately small in relation to the cranium. Mandibular angle was obtuse with prominent ante-gonial notch.

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Fig. 1. Extra oral photograph of the patient showing short stature with typical features of progeria

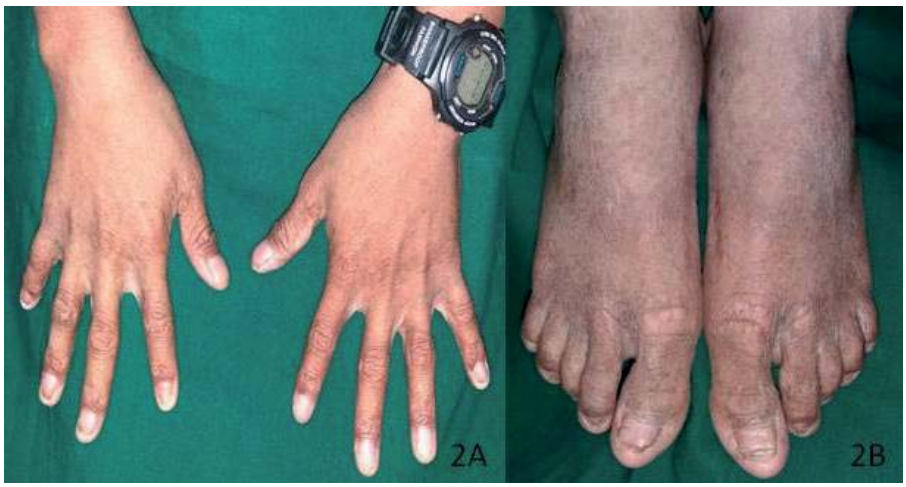

Fig. 2. Clinical photograph showing sclerodermatous changes of the hands and feet

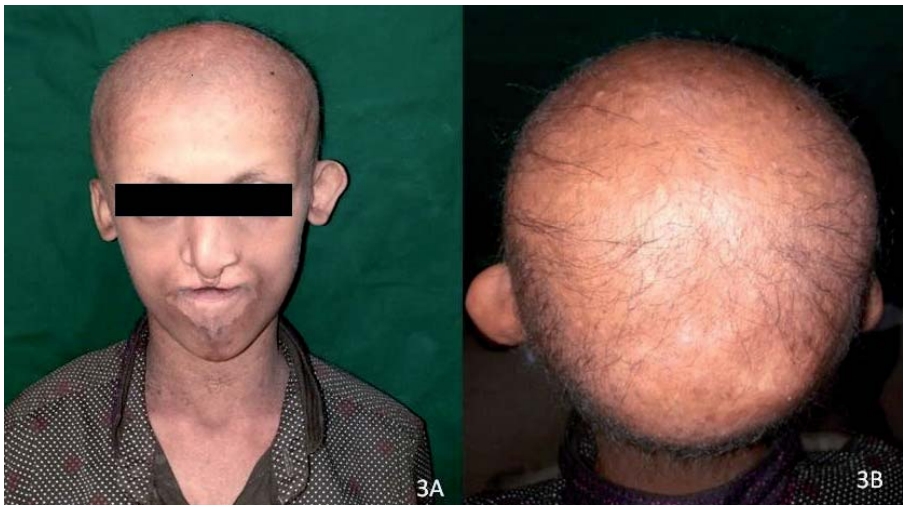

Fig. 3. Clinical photographs: A – facial appearance; B – cephalic view showing disproportionate cranial form, alopecia, sclerodermoid features, prominent scalp veins

On intra oral examination multiple missing teeth were noticed. Retained rootstumps were seen with respect to 16, 55, 54, 53, 64, 74, 75, 84, 85, 46. A palatal fistula was also noticed which was a post surgical remnant of primary cleft palate surgery.

Based on the above clinical findings, a provisional diagnosis of Hereditary Ectodermal Dysplasia was considered. A differential diagnosis of progeroid syndromes was given.

The patient was then subjected to radiographic examinations which included an Orthopantomogram, Lateral Cephalogram and Posterio- Anterior Cephalogram followed by a Cone Beam Computed Tomography.

The orthopantomogram revealed normal condylar and coronoid morphology. Multiple root stumps were present in the region of 54, 55, 65, 31, 32, 41 and 42. Also grossly decayed 16, 26, 36 and 46 were noticed. Tooth buds were noticed in the region of 17, 15, 27, 35, and 45. No permanent teeth counterparts were noticed in the region of 11, 12, 13, 14, 21, 22, 23, 23, 24, 25, 37, 34, 33, 43, 44 and 47 suggesting partial anodontia. The mandibular angle was obtuse with prominent ante- gonial notch which confirmed the inspectory findings. There was decreased vertical height of the body of the mandible and the width of the ramus. The lateral cephalogram revealed a hypoplastic maxilla and relatively prognathic mandible with a concave profile and a beaten skull appearance. Mastoid air cells were absent and the fronto nasal angle appeared obliterated. skull table, diploe appeared to be placed in a relatively lower position. Also the mandibular plane angle was steep with prominent ante gonial notch. The postero anterior view revealed beaten skull appearance with increased dimension of the orbit, missing frontal sinus and deviated nasal septum, hypoplastic maxillary sinus and zygomatic arch.

The patient was then subjected to a Cone Beam Computed Tomography (CBCT) to know about the

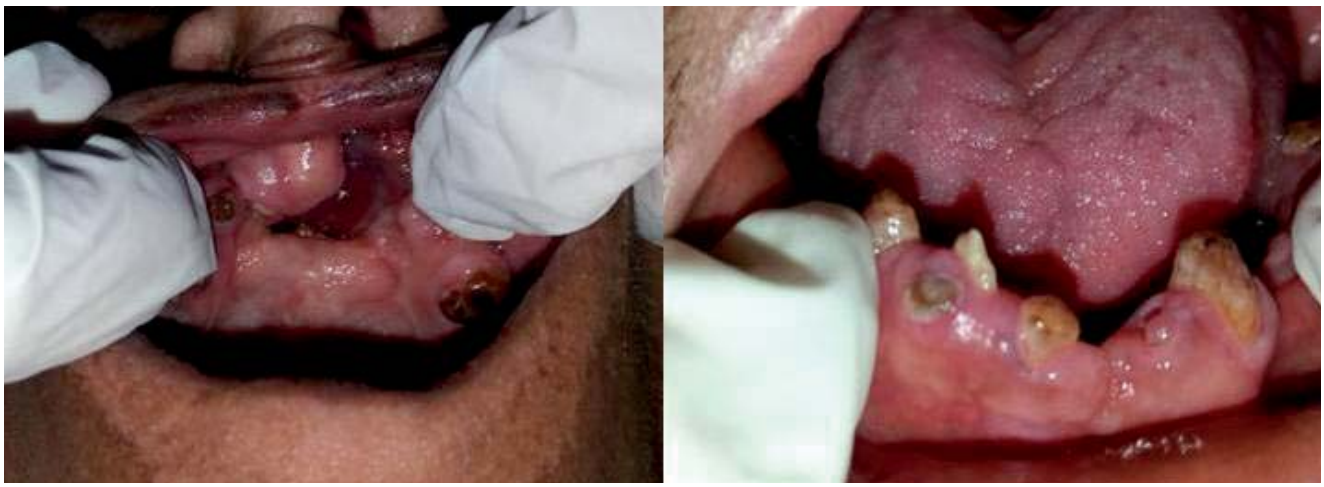

Fig. 4. Intra oral photograph showing micrognathia with multiple missing teeth, root stumps and unilateral cleft palate on left side

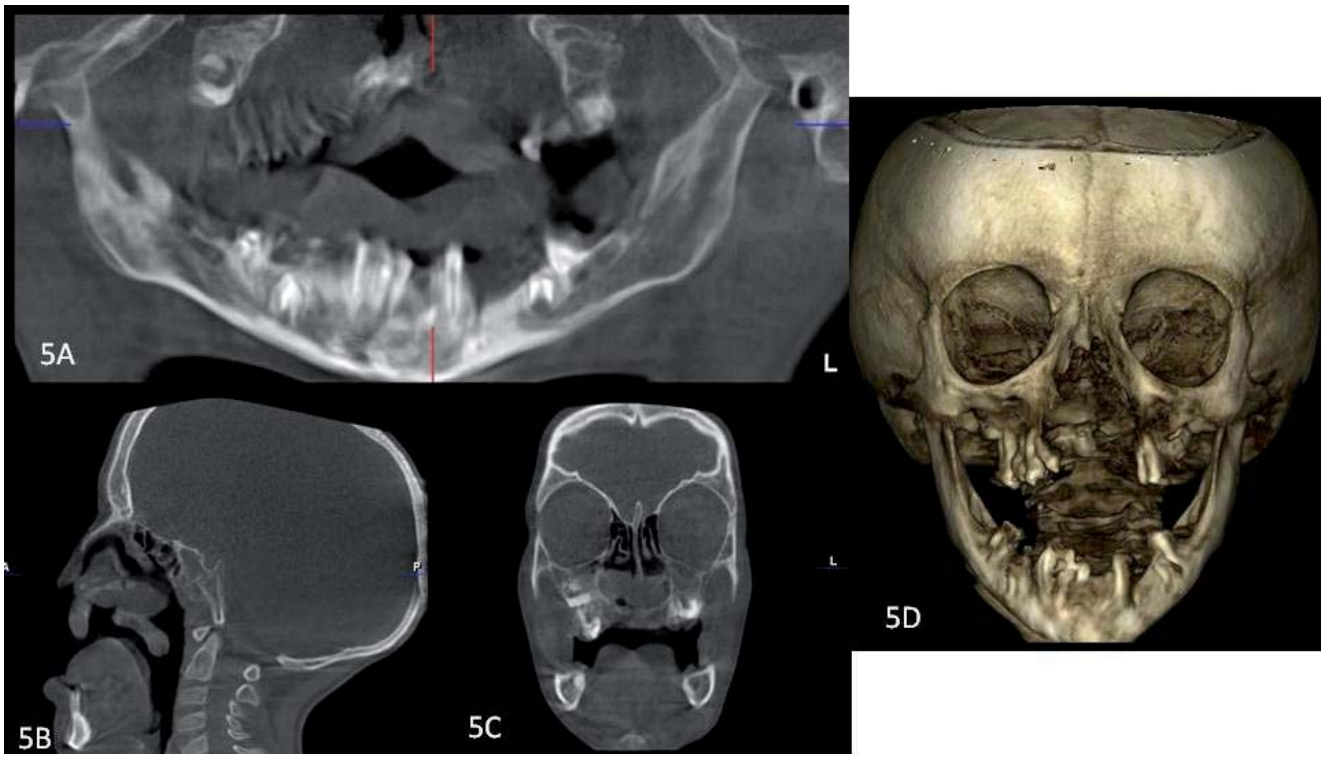

Fig. 5. Cone beam computed tomography images: A – reconstructed orthopantomogram – altered condylar and coronoid morphology, multiple root stumps, partial anodontia and few erupting tooth buds. The mandibular angle is obtuse with prominent ante- gonial notch and decreased vertical height the mandible. B – sagittal section – hypoplastic maxilla, concave profile, ethmoidal sinuses miniature in size and cleft palate. C – coronal section – enlarged orbital fossa, missing frontal sinus, mastoid air cells, hypoplastic maxillary sinus and zygomatic arch. D – CBCT 3D reconstruction.

involvement of deeper anatomic structures. The coronal section of the CBCT images revealed the presence of deviated nasal septum, hypoplastic maxillary sinus and missing frontal sinus as well as mastoid air cells. Also the orbit appeared larger on compared to the CBCT of the patients within same age group. The sagittal view confirmed the presence of cleft palate. The 3-Dimensional reconstructed view of the CBCT showed the presence of prominent antegonial notch and altered shape of the condyles, concave profile with decreased vertical height of the mandibular ramus with an obtuse mandibular angle and prominent ante- gonial notch.

Based on the history, clinical findings and radiographic examination a diagnosis of Hutchinson – Gilford Progeria Syndrome (HGPS) was considered.

DISCUSSION

Hutchinson – Gilford progeria syndrome is a rare genetic disorder characterised by early onset

accelerated senescence. Progeria is the term derived from greek word "geras" meaning old age. This condition was renamed by De Busk in 1972 as Hutchinson-Gilford Progeria Syndrome (HGPS). The affected individuals appear normal at birth, but begin to display the features of accelerated aging by the first year of life. The mean age of diagnosis is at 3 years. But the present case was diagnosed at the age of 4 years when the parents approached a surgeon for the repair of associated cleft lip and palate. The mode of inheritance of progeria is commonly autosomal recessive with most of the affected individuals found in families with history of consanguineous marriage, which was present in this case also. But there are reported cases of sporadic autosomal dominant inheritance. The prominent clinical features include involvement of bone, skin, cardiovascular and respiratory systems which was true in our case also. There is marked growth retardation, bone changes including resorption of the clavicles, which are replaced by fibrous tissue, osteolysis of distal phalanges and joint dislocations. Death occurs at an average of 13 years, most commonly due to coronary artherosclerosis. The typical facial features of HGPS include prominent eyes and beaked nose giving characteristic "bird like" facies with missing skin appendages such as eyelashes, eyebrows and earlobes. Typical craniofacial features are alopecia with prominent scalp veins, craniofacial disproportion and micrognathia. hypoplasia of both maxilla and mandible has been reported with irregular eruption of the teeth, crowding and presence of localised enamel hypoplasia. All the above features were present in our case also. The commonly seen dental manifestation of HGPS is hypodontia, commonly involving the third molars, second premolars and canines (4). But the feature seen in the present case is partial anodontia with only the presence of deciduous root stumps. Other features include abnormalities of joint motion, low frequency hearing loss and oral motor abnormalities like labial weakness, decreased lingual range of motion and vertical chewing (6). The common ocular manifestations are loss of eyebrows and eyelashes, lagophthalmous and prominent eyes (5). The cardiovascular complications are the major cause of early death in patients with HGPS. The medial smooth muscle cells are lost with thickening of the tunica intima, disrupted elastin fibres, formation of sclerotic plaques in aorta and coronary artery stenosis (6). Also there are reports of elevated systolic and diastolic blood pressure levels in these patients.

The important skull and craniofacial features include thinning of the calvarium and paucity of the scalp fat. Also mottled appearance of the skull has been reported, commonly in frontal, parietal and sphenoid regions. The anterior fontanellae remains patent in these patients. Widening of the lambdoid, sagittal and squamous sutures was also reported. The facial features include thin zygomatic arch, short mandibular ramus, shallow glenoid fossa with hypoplastic articular eminence and flattening of the condyle, "V" shaped palate is most commonly seen but cleft palate associated with HGPS are rare that make the present case different from other reported cases. Radiographic features that are commonly seen in these patients include retrognathic facial appearance with obtuse gonial angle, steep mandibular plane angle and lack of development of pogonion. An alteration in the morphology of the crown of mandibular first molars, with increased width and cervical constriction, giving it an appearance of the crowns seen in dentinogenesis imperfecta has also been reported. However obliteration of the pulp chambers and canals were not observed in HGPS. Other features include diffuse osteopenia, bone resorption of the distal phalanges and clavicles (acroosteolysis), widened metaphysic, attenuation of cortical bone thickness and fish mouth vertebral bodies (4).

The differential diagnosis of HGPS include Wiedemann Rautenstrauch syndrome, Cockayne syndrome, Gerodermia osteodysplastica, Petty Laxova Weidemann syndrome, Berardinelli Seip congenital lipodystrophy, Ehlers Danlos syndrome, Rothmund – Thomson syndrome, Mandibuloacral dysplasia, Acrogeria, Hallermann Streiff syndrome, NestorGuillermo syndrome and Werner's syndrome (9). Cockayne syndrome is manifested by facial erythema in butterfly distribution with photosensitivity, ocular defects and disproportionately large hands and feet with protruding ears (3). Werner's syndrome is usually seen between 14-18 years with short stature, immature sexual development, cataract, glaucoma, and sclerodermatous changes. Rothmund Thomson syndrome is seen between 3-6 months of age with poikilodermatous skin (3 which were not seen in our case.

Even though HGPS has been discovered 10 years ago, it still remains incurable with no therapy other than symptomatic treatment. Many studies have been carried out with regard to the management following the discovery of the pathogenesis of HGPS i.e the mutation of LMNA gene. In the ongoing clinical trial is being carried out at present at the Progeria Research Foundation at USA after successful animal studies, which includes all the children who are diagnosed with HGPS have to

register under the progeroid research foundation following which they will be a part of the clinical trial. In the disease process, as progerin is permenantly farnesylated, so farnesyl transferase inhibitors are used as a pathogenic treatment for HGPS. In 2004, it was first hypothezised that farnesylated progerin might be a key player in pathogenesis of HGPS. Positive results from animal trials led to the intiation clinical trial with FTI in patients with HGPS. 28 patients with classic HGPS were enrolled for the first round of clinical trial which had started in 2007. Also statins and aminobisphosphonates effectively inhibit farnesylation geranylgeranylation of progerin and pre-laminin A. More recently rapamycin has gained attention in the treatment of HGPS. Cao et al demonstrated that HGPS cells showed enhanced progerin degradation, slowed senescence and reduced nuclear blebbing when treated with rapamycin compared to non treated cells (8). Every child who are diagnosed with HGPS have to be registered with the Progeria Research Foundation and are enrolled in the clinical trial which takes place at the Children's hospital at Boston where Farnesyl Transferase Inhibitor (FTI) drugs are given in phases (11).

CONCLUSION

The pathogenesis and management of Hutchinsons Gilford progeria syndrome still remains a mystery even after the invention of all the modern technologies of medicine. Till date only 146 cases have been registered with the progeria research foundation. The report of oldest person with progeria was that of Leon Botha from South Africa who died at the age of 26. An Indian family hailing from Uttar Pradesh have five children affected with the disease. The parents who are first cousins who had eight children, four of them born with progeria died between 12 and 24 years, another child who died shortly after birth is thought to have the same disease, while two of their daughters are unaffected.

This case is hereby reported because of its rarity.

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None

STATEMENT OF CONFLICTS OF INTEREST

The authors state no conflict of interest.

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