CLINICAL IMAGING FINDINGS IN A GIRL WITH HUTCHINSON-GILFORD PROGERIA SYNDROME

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Summary: *Clinical imaging findings in a girl with Hutchinson-Gilford progeria syndrome:* We report an 8½-year-old girl with premature aging, a karyotype of 46,XX and a *de novo* c.1824C>T mutation encoding p.G608G in the lamin A gene. The clinical features of accelerated aging and the molecular finding were consistent with the diagnosis of Hutchinson-Gilford progeria syndrome (HGPS). In this presentation, we demonstrate the radiological imaging findings of skeletal, oral and craniofacial phenotypes of abnormalities associated with HGPS. The oral and craniofacial abnormalities caused dental caries, severe malocclusion, and swallowing, feeding and speech problems. Dural calcification, and granulation in the ear drum and external ear canal were additionally observed.

Key-words: Hutchinson-Gilford progeria syndrome – *LMNA* – Oral and craniofacial phenotypes – Radiology.

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INTRODUCTION

Hutchinson-Gilford progeria syndrome (HGPS; OMIM 176670) is a rare genetic disorder characterized by acceleration of aging process affecting a variety of organ systems in children. Up to date, fewer than 150 cases of HGPS have been reported since the first report of Hutchison in 1886 (8), with approximately one third of those affected individuals currently diagnosed (15). Herein, we present the clinical and molecular features of a Chinese girl with HGPS.

CLINICAL REPORT

The 8½-year-old girl was the second child of healthy non-consanguineous parents. When she was born, the mother was 27 years old and the father 34 years old. The family history was unremarkable. She was delivered at 39 weeks of gestation with a body weight of 2,790 g. When examined at 2 months of age, she was found to have sclerodermatous skin with loss of subcutaneous fat over abdomen, back, buttocks and trunks, sparse hair and prominent veins. The findings were consistent

with the features of premature aging. When examined at 2 years of age, she manifested alopecia, a characteristic facial appearance of frontal bossing, a nose with broad and mildly concave nasal ridges, prominent eyes, thin lips and micrognathia. At the age of 4 years, X-rays showed short clavicles with early osteolysis at the lateral ends (Fig. 1) and distal phalangeal osteolysis (Fig. 2). At the age of 5 years, pelvis X-rays showed coxa valga of femurs (Fig. 3) and dental X-rays showed dental crowding and double rows of teeth (Fig. 4). She was found to have bilateral conductive hearing loss, and granulation over right external ear canal and ear drum, which was excised surgically. At the age of 6 years, magnetic resonance imaging (MRI) showed craniofacial disproportion and a short mandible (Fig. 5), and computed tomography (CT) scans showed dural calcification adjacent to the superior sagittal sinus (Fig. 6). She had multiple dental caries, severe malocclusion, an ogival palatal arch with a median sagittal palatal fissure, and problems of swallowing and speech. At the age of 8½ years, her body weight was 9.7 Kg (< 3rd centile) and height 97 cm (< 3rd centile). Cytogenetic analysis revealed a karyotype of 46,XX. Molecular analysis revealed a *de novo* c.1824C>T mutation encoding p.G608G in the lamin A gene (*LMNA*; OMIM 150330). The clinical features, and radiographic and molecular findings confirmed the diagnosis of Hutchinson-Gilford progeria syndrome.

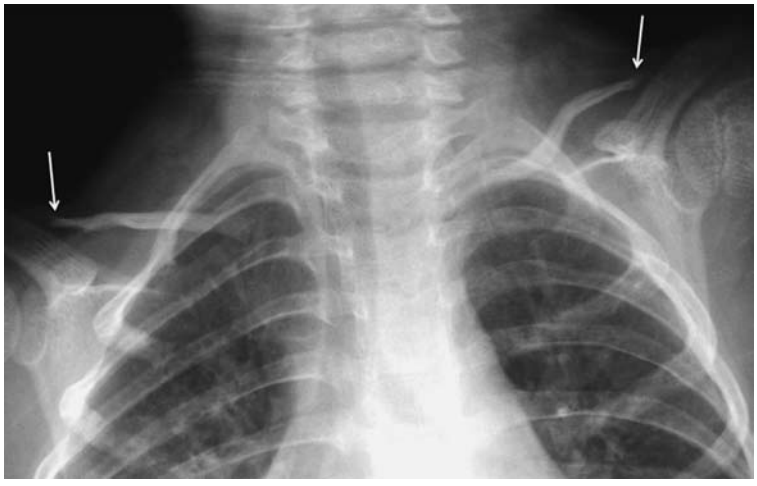

Figure 1: X-ray of the chest shows short clavicles with early osteolysis at lateral ends (arrows).

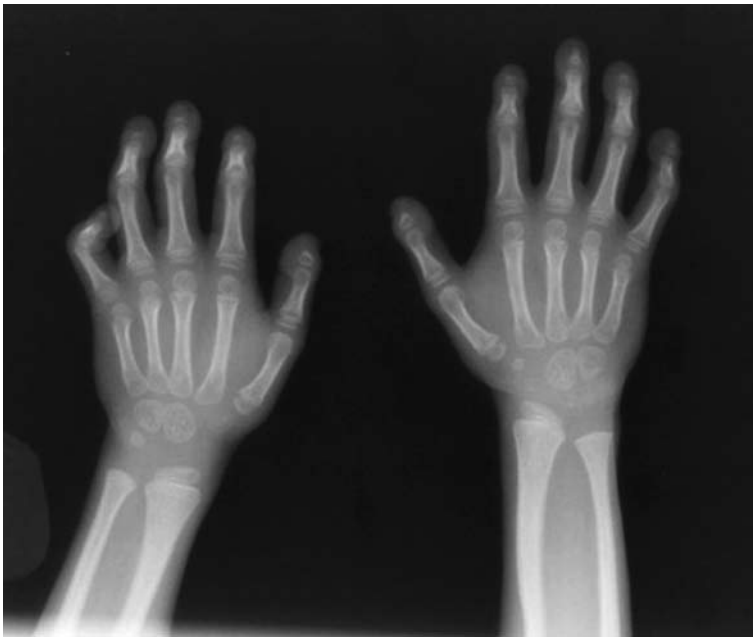

Figure 2: X-ray of the hands shows distal phalangeal osteolysis.

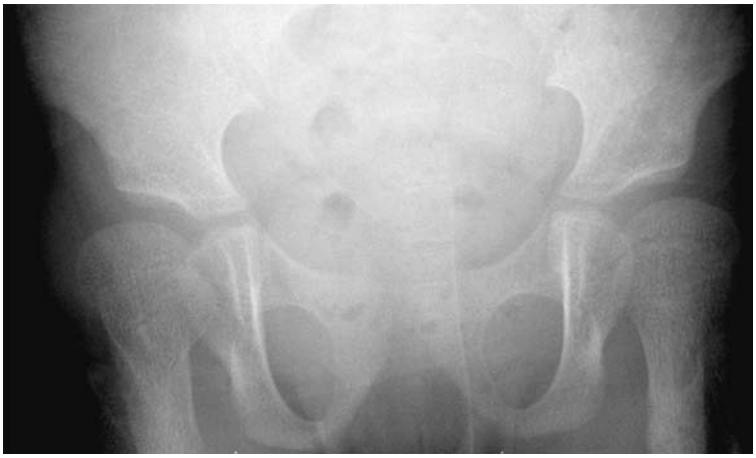

Figure 3: X-ray of the pelvis shows coxa valga of the femurs.

DISCUSSION

HGPS is a rare sporadic laminopathy which affects nuclear lamins and causes accelerated aging in early infancy. HGPS has an incidence of 1 per 4-8 million live births (14). To date, the mutations in the genes of *LMNA* and *ZMPSTE24* (OMIM 606480) have been found in patients with HGPS (1, 4). The most common mutation associated with HGPS

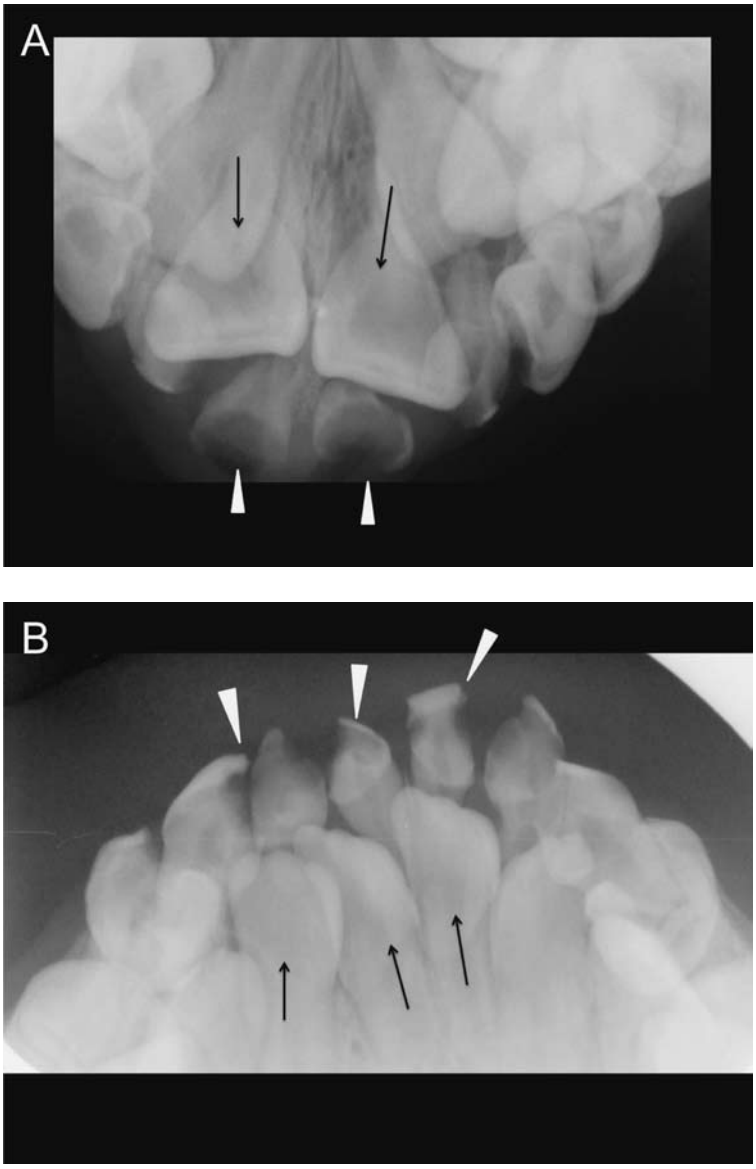

Figure 4: Dental X-rays of the maxillary teeth (A) and mandibular teeth (B) show dental crowding and double rows of teeth with permanent teeth (arrows) erupted lingual to the deciduous teeth (arrowheads).

is a *de novo* heterozygous single-base pair change (GGC>GGT) at codon 1824 within exon 11 of the *LMNA* gene, which does not cause an amino acid substitution (G608G) but activates a cryptic splice donor site and produces mutant farnesylated prelamin A or progerin with an internal deletion (p.Val607_Gln656del) (15). Lamins are structural components of the nuclear lamina, and lamin A contributes to chromatin regulatory mechanism and nuclear structural integrity (1, 10). The mutant lamin A or progerin acts as dominant negative and interacts

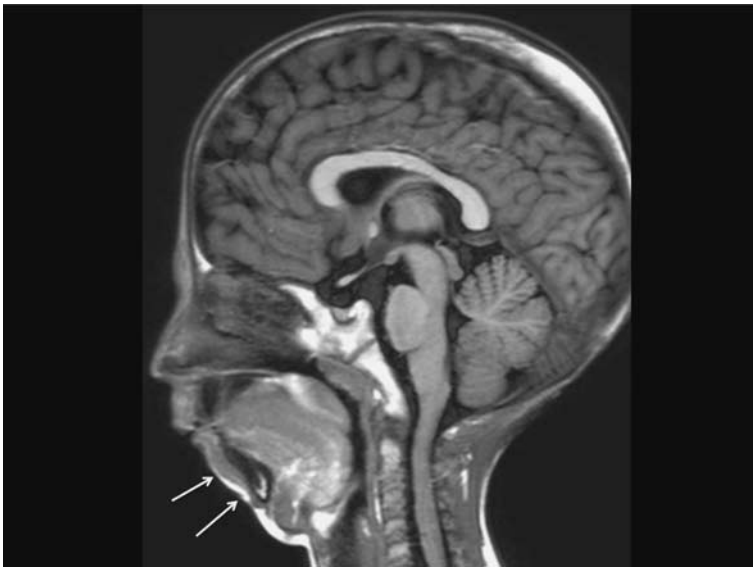

Figure 5: Magnetic resonance imaging of the skull shows a small mandible (arrows) with thin cranial vault, and relatively small viscerocranium compared to the neurocranium.

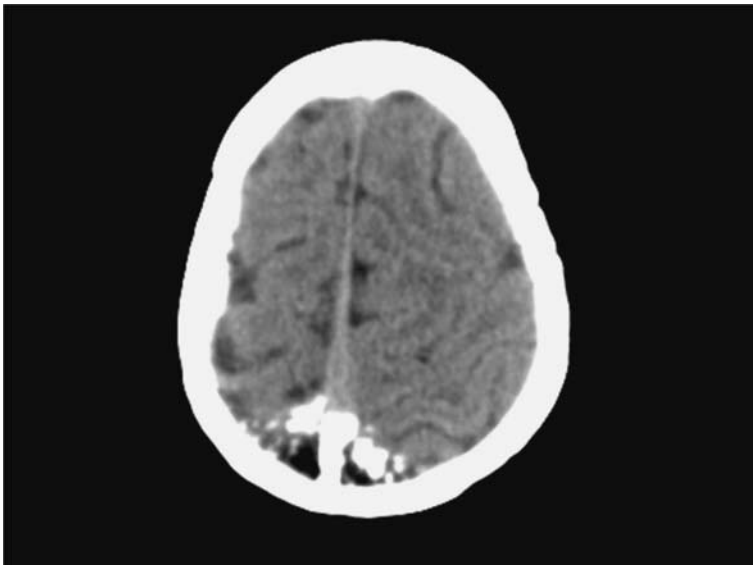

Figure 6: Computed tomography scan shows dural calcification adjacent to the superior sagittal sinus.

with lamin C to create heterodimeric multiprotein filaments causing nuclear membrane instability, progressive nuclear damage, and premature cell death (15).

Though the mechanism of *de novo* mutation in HGPS is unclear, paternal origin of *LMNA* mutations and the impact of advanced paternal age have been shown in 3 families with HGPS (3). Previous studies on the paternal effect in transmission *de novo* mutations indicate that the

mean paternal age at birth of patient was 35.6 years, compared to the mean maternal age of 28.8 years (2). The marital difference in age and parental age of 34 years at birth of this presented patient support the previous hypothesis. Nonetheless, asymptomatic somatic and gonadal mosaic carrier has been observed in the mother of an HGPS affected boy (17). Although sporadic dominant inheritance is likely in the majority of HGPS cases, rarity of recessive inheritance has been reported (9, 13, 16), suggesting the probability of germline mosaicism (5).
The clinical features of HGPS include failure to thrive, sclerodermatous thin skin, loss of subcutaneous fat, alopecia, prominent veins, characteristic facial appearance of frontal bossing, protruding ears, a nose with broad and concave nasal ridges, prominent eyes, thin lips, abnormal palate, micrognathia and a vertical midline groove in the chin, short clavicles, joint stiffness, osteolysis involving the distal phalanges and clavicles, short stature and cardiac and cerebrovascular complications (7, 11, 12, 15). In this presentation, we demonstrate the radiological imaging findings of skeletal, oral and craniofacial phenotypes of abnormalities associated with HGPS. The oral and craniofacial abnormalities will cause caries, severe malocclusion, and swallowing, feeding and speech problems (6). We additionally observed dural calcification, and granulation in the ear drum and external ear canal which may be in part caused by premature aging.

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