Hutchinson–Gilford Syndrome (Progeria) with Heterozygous Mutation in the LMNA Gene-ENST00000368300.9 Presenting with Mandibuloacral Dysplasia and Acrogeroid Features—Overlap of Premature Aging Syndromes

Sir,

Hutchinson–Gilford progeria syndrome (HGPS) is a rare, fatal, genetic condition of childhood with striking features resembling premature aging and profound growth delays, resulting in short stature and low weight and systemic hyperlipidemia. Here, we report a rare case of Hutchinson–Gilford syndrome with diabetes and hyperlipidemia with a heterozygous gene mutation in the LMNA gene-ENST00000368300.9, with a variant of uncertain significance in the mutation (p.As47Tyr), but presenting with mandibuloacral dysplasia (MAD) and acrogeroid features suggesting overlap of premature aging syndromes.

The classic congenital premature aging syndromes include Werner’s syndrome, progeria, and acrogeria. These are rare genetic diseases associated with accelerated aging of the skin and other tissues. They come under the group of laminopathies due to mutations in the gene coding for lamin A (LMNA). Progeroid syndromes are a group of fatal, severe, and rare genetic disorders characterized by various clinical features and phenotypes of physiological aging prematurely. Among the different forms of progeria, the classical and most extensively studied type is the HGPS.[1] Acrogeria or Gottron’s syndrome begins at birth or soon afterward characterized by mild, non progressive form of skin atrophy involving the distal parts of the extremities with characteristic facies.[2] There have been many reports indicating that there is a considerable overlap between the premature aging syndromes as there is a common mutation in the gene LMNA in all these disorders.[3] Here, we report a rare case of Hutchinson–Gilford syndrome with a heterozygous gene mutation in the LMNA gene-ENST00000368300.9, with a variant of uncertain significance in the mutation (p. Asp47Tyr), but presenting with MAD and acrogeroid features suggesting overlap of premature aging syndromes.

A 23-year-old male patient born out of non-consanguineous marriage, with young onset diabetes mellitus presented with complaints of progressive skin thinning from birth and recurrent non healing ulcers over foot since the age of 8 years. The mother remembers that the child had hair on the scalp after birth and the head was normal in shape. There was no history of delayed milestones or seizures during childhood. There was no history of similar illness in family and siblings were normal. General examination revealed short stature with characteristic facies of beaked nose, hollowed-out cheeks, owl-eye appearance with thin lips, and micrognathia [Figure 1a] suggestive of acrogeria. The eyes were normal. The teeth were crowded and malformed. Dermatological examination showed sclerosis of the skin over distal third of all four extremities with dry, atrophic skin and loss of subcutaneous fat with prominent dilated veins and mottled pigmentation [Figure 1b]. Joint contracture was present over both knees [Figure 2a]. The patient had normal intelligence and the gonads were normal.

On investigations, patient had elevated triglyceride levels (1672 mg/dL) and increased blood sugar levels. X-ray of hands showed acral osteolysis [Figure 2b],

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while X-ray of the chest showed normal thorax and normal clavicles. Arterial Doppler of bilateral lower limbs showed diffuse atherosclerotic wall thickening. ECG and echo cardiography did not show any abnormalities. CT scan and ultrasound abdomen of the patient were normal. Skin biopsy revealed homogenization of collagen and mild perivascular lymphocytic infiltrate suggestive of sclerodermatous histopathology [Figure 3]. A clinical exome genetic study showed LMNA mutation (ENST00000368300.9) with a variant of uncertain significance in the mutation (p. Asp47Tyr), suggestive of Hutchinson–Gilford syndrome (Progeria) with MAD overlap [Table 1].

HGSP presents with macrocephaly and dilated scalp veins at birth or soon after birth. Scalp hair is absent or sparse. The patient has beaked nose and short stature, altogether giving a “plucked bird” appearance. The skin has sclerodermoid changes with mottled pigmentation and long bones have acro-osteolytic changes. MAD presents with typical facies of micrognathism and mandibular hypoplasia along with diabetes. Acrogeria presents with beaked nose, hollowed-out cheeks, “owl eye” appearance with thin lips, and micrognathia along with atrophy of the skin and subcutaneous tissue and with poikiloderma and telangiectasia. Our patient had facies of beaked nose, hollowed-out cheeks, “owl eye” appearance with thin lips, and micrognathia suggestive of acrogeria [Figure 1a]. Our patient has short stature, the teeth showed crowding and malformation, the skin of abdomen, and the limbs showed sclerodermoid features with mottled pigmentation, loss of subcutaneous fat, dilated veins, and joint contractures [Figures 1b and 2a]. Systemically there was elevated serum triglycerides levels. X-ray of the hands showed acro-osteolysis [Figure 2b]. All these are features of HGPS. However, the features of macrocephaly and alopecia at birth were absent in our patient. In addition, the patient had micrognathia and mandibular hypoplasia with diabetes which are features of MAD. Genetic study showed features of HGPS with MAD overlap [Table 1]. Therefore, we made a diagnosis of HGPS presenting with MAD and Acrogeroid features, indicating overlap of premature aging syndromes. However, MAD type A and HGPS are caused by the same gene and may represent a single disorder with varying degrees of severity.

The primary mutation in this patient was on the Exon 1 and qualifying for HGSP with MAD. But the genetic study also showed a variation in the mutation (p.As47Tyr) and we believe that this variation was responsible for the patient presenting with acrogeroid features and lacking some features of classical HGPS. Classical HGPS is usually caused by a sporadic autosomal dominant mutation in LMNA gene and/or abnormal posttranslational processing of ZMPSTE24 gene, both of which ultimately result in abnormally formed lamin A called progerin. Lamin A is a key protein component of nuclear scaffolding that holds the nucleus together by forming the inner layer of the membrane. This defect caused the typical phenotype of HGPS and cardiovascular defects at a very young age resulting in premature death. MAD can also present with short stature, bird-like facies, and micrognathism like HGSP, but in addition, there may be diabetes. Our patient was diabetic. There is considerable overlap between HGSP and MAD (MAD type A) as in both premature aging syndromes, the mutation is in the LMNA gene, even though it is in the Exon 8–10 region for MAD and Exon 1 for HGSP and this has been reported in literature.[4,5] However,
targeted mutation analysis could not be done in our case due to lack of resources.

There is no specific treatment for premature aging syndromes. HGSP patients must have frequent cardiovascular reviews. Imaging tests should be done at regular intervals as malignancy-like fibrosarcomas can occur.\(^6\) Mutation in the \textit{LMNA} gene forms a defective lamin A protein which causes accumulation of prelamin A in the nucleus which causes defective DNA synthesis. A class of anticancer drugs (Tipifarnib) which inhibits the enzyme farnesyltransferase in trials is known to reverse the aforementioned changes in the nucleus and could be a promising drug in the future.\(^7\)

We are reporting a very rare presentation of overlap of premature aging syndromes and overlap of HGPS and MAD with acrogeria has not been reported in literature to the best of our knowledge.

\textbf{Declaration of patient consent}

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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\textbf{Conflicts of interest}

There are no conflicts of interest.

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