A case of Hutchinson-Gilford Progeria Syndrome (HGPS) due to pathogenic LMNA variant c.433G<A (p.Glu145Lys): Growth hormone administration failed to improve growth and long-term outcome

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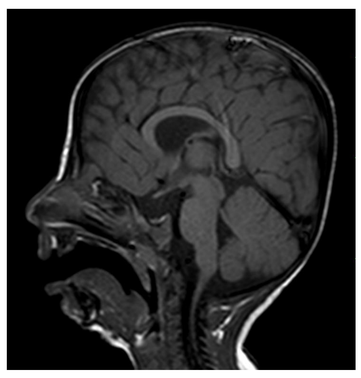
Introduction

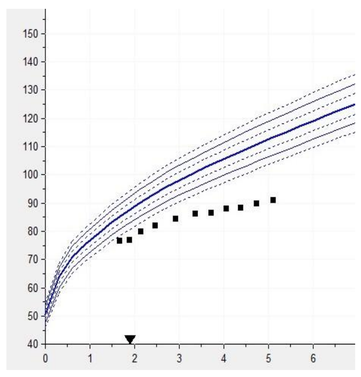
Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare condition (estimated incidence 1:4-8 million), caused by mutations in *LMNA* gene, which leads to premature aging. Median life expectancy is shortened to 13 years due to vascular complications such as stroke or myocardial infarction. We present below the history of a child born with a pathogenic LMNA variant c.433G>A.

Case presentation

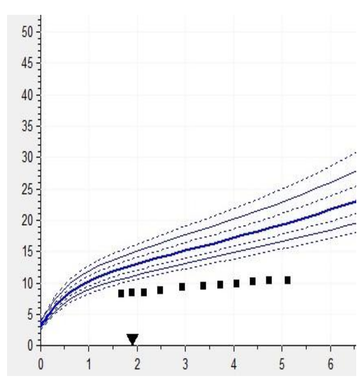
A male patient was referred for failure to thrive and low growth velocity at age 18 months. He was born short for gestational age (39th GW, BW 3270g, BL 46 cm). Since his early life he had feeding problems, runny stools, his motoric development was slightly delayed and he had loose hair, visible blood veins on the forehead, pinched nose and small recessed jaw. Due to severe short stature (height -2.38 SD) and low IGF-I (39 ug/l; -1.45 SD) he was tested and finally diagnosed with growth hormone (GH) deficiency (peak GH 2.43 ug/l after clonidine stimulation). The subsequent MR revealed partial empty sella. GH therapy was initiated when 23 months old. Unfortunately, GH failed to improve growth velocity, despite a transient increase of IGF-I to 135 ug/l (-0.15 SD). The treatment was stopped at age 4.4 years (height -3.93 SD).



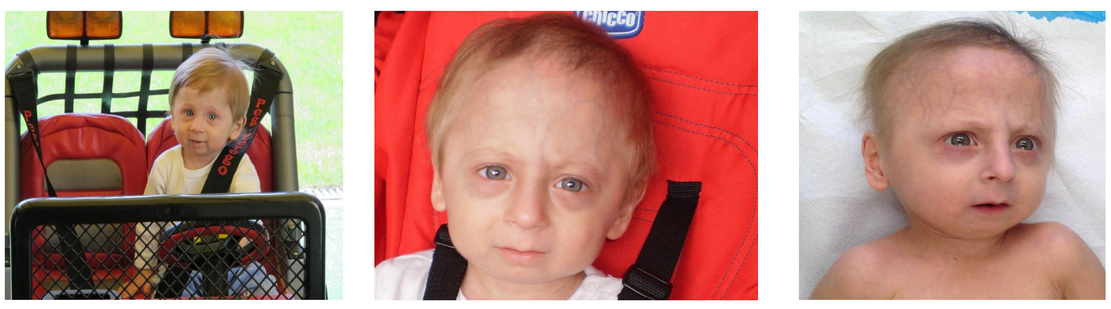
Partial empty sella on MRI



Length for age chart



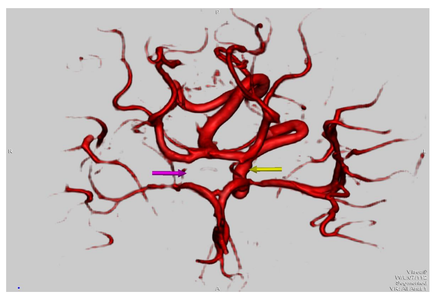
Weight for age chart



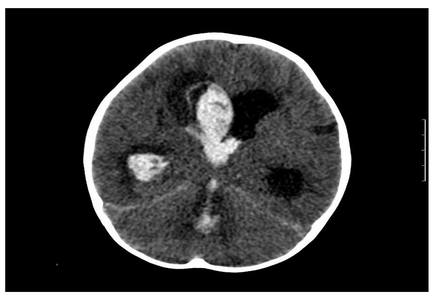
Typical features of HGPS become apparent in the first years of life.
(A) 1,5 years old, (B) 2,5 years old, (C) 4 years old

His phenotype became suggestive of progeria when 2,5 years old. We sequenced all exons of *LMNA* gene and identified a heterozygous base substitution c.433G>A (p.Glu145Lys), which is known to disable lamins to form dimers and higher structures. The previous patient described in the literature carrying the same mutation had severe cerebral stroke by the age of 4.

His first ischemic complication manifested via transient hemiparesis at age 4.2 years. When 7 years old, he presented with seizures and unconsciousness due to a massive haemorrhagic stroke which led to a fatal outcome.



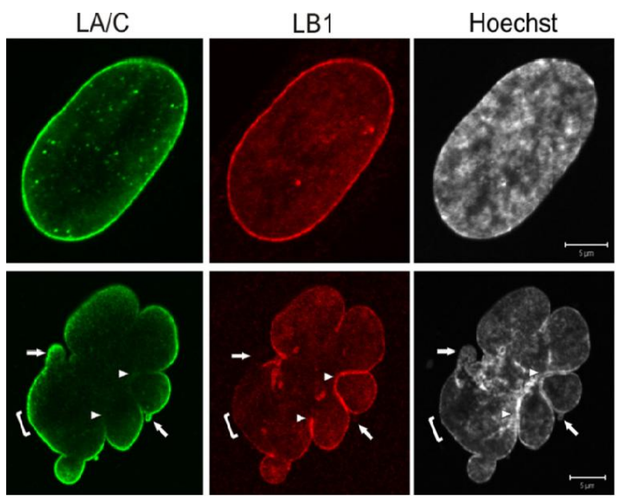
Severely reduced flow in in the right internal carotis



Massive haemorrhagic stroke

Discussion

The *LMNA* gene provides instruction for formation of lamin A and lamin C. Lamins are supporting intermedial filaments of the nuclear envelope. The mutation described here is located in segment 1B of the central rod domain of lamin A/C where it directly impacts the assembly of lamins into dimers and higher order structures, which leads to their premature senescence. Cells carrying the described mutation show extensive lobulated nuclei after being stained with anti-LA/C, anti-LB1 and Hoechst.



Severly lobulated nuclei

Conclusions

This is our first case of Hutchinson-Gilford Progeria syndrome. In contrast to the most common pathogenic variant which leads to formation of an abnormal version of lamin A called progerin, the c.433G>A substitution does not alter the posttranslational processing of the C terminus, which is why the FTI treatment is not succesful in these patients and unfortunately no other therapy is available. Our single-case observation revealed failure of GH therapy, not only to improve growth, but to prevent or postpone vascular complications as well, despite transient increase of IGF-I levels.

References:
Smith AS, Wiznitzer M, Karaman BA, et al. *MRA detection of vascular occlusion in a child with progeria. AJNR Am J Neuroradiol 1993;14:441–43*
Taimen P, et al.*(2009) A progeria mutation reveals functions for lamin A in nuclear assembly, architecture, and chromosome organization. Proc Natl Acad Sci USA 106:20788–20793.*

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Pictures are published with the consent of the patient's parents.
Declaration of interest: the authors report no conflicts of interest. The authors alone are responsible for the content and writing of the poster.