SHOX-HAPLOINSUFFICIENCY INTRA-FAMILIAL PHENOTIPIC VARIABILITY AND THE IMPACT ON FINAL HEIGHT: REPORT OF A PEDIGREE

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SHOX haploinsufficiency (SHOX-D) is a genetic cause of disharmonic short stature. However, the different impact on phenotype can show differences between patients with the same genotype.

GH ameliorates final height, with significant differences between patients for the putative role of environmental factors who can influence growth.

We describe the case of two sisters with SHOX-D (target height: 146.8 cm (-2.6SDS); mother: 146.5 cm; father: 160 cm). ZM was first evaluated at the age of 6.8 years for disharmonic short stature: stature: 103.5 cm; SPAN: 99 cm. She was affected by SHOX-D (heterozygous missense mutation c414G>C: p.Glu138Asp of the exon 3). The same mutation was first confirmed in the mother, and later in the sister who had not a stature < -2SDS at the first clinical evaluation. Both the patients did not show GH deficiency and IGF-1 levels were in the normal range.

GH treatment was started at 6.8 years for ZM (BA: 6 years): stature: 103.5cm: -3SDS; SPAN: 99cm; and at the age of 6.8 years (BA: 6.1 years): stature: 113cm: -1.38SDS; SPAN: 112.5cm; for ZS, when the patient showed a reduction of height velocity, despite the progression of BA. At the follow-up the patients showed increased growth velocity, progression of puberty and progressive increased BA, with an early near-adult height of ZM at 13.7 years of 143.1cm (-2SDS), SPAN 138,5cm, BMI 18 kg/mq; weight: 37.5kg (-2SDS); bone age: 18 years. ZS at the age of 14.4 years showed a stature of 150.8cm (- 1.8SDS), SPAN: 155cm; BMI 22 kg/mq; weight: 50kg (-1SDS).

This family shows a different phenotype of SHOX-D: the mother, spontaneously reached a stature of 146.5cm. The sisters started GH treatment at the same age, however they showed a different response. Bone age rapidly increased at puberty.

ZM, with the most severe phenotype, had a near-final height of 143.1cm, with a low SPAN. ZS reached a higher stature and a SPAN at this time higher than the stature.

This case series show that SDS of stature before GH therapy is a prognostic parameter for final height in SHOX-D patients.

1) Iughetti L et al. Impaired GH secretion in patients with SHOX deficiency and efficacy of recombinant human GH therapy. Horm Res Paediatr. 2012;78(5-6):279-87.
2) Auger J et al. Genotype-Phenotype Relationship in Patients and Relatives with SHOX Region Anomalies in the French Population. Horm Res Paediatr. 2016;86(5):309-318.

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Growth and syndromes (to include Turner syndrome)

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