PERSISTENTLY INCREASED IGF-I LEVELS AND EXCELLENT AUXOLOGICAL RESPONSE DESPITE LOW DOSES OF RECOMBINANT GROWTH HORMONE IN A GH-DEFICIENT PATIENT WITH A HETEROZYGOUS VARIANT OF THE GROWTH HORMON RECEPTOR (*GHR*) GENE

M L NICOLOSI[1], A CATTONI[1], S MAITZ[1], S DI MARCO[1], A BIONDI[1], S MOLINARI[1]

1. Paediatric Department, Università degli Studi di Milano-Bicocca, Fondazione MBBM, San Gerardo Hospital - Monza (MB), Italy

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INTRODUCTION

Homozygous loss-of-function mutations of the growth hormone receptor **(*GHR*)** gene result in GH insensitivity due to a dysfunctional receptor protein.
Heterozygous mutations may result in a variable clinical *spectrum* ranging from normal height to severe short stature.

CASE REPORT

Age and gender

7.25 years-old male patient

Family history and previous medical history

Unknown (adopted child)

Mid-parental height and birth weight and length not available

Reason for referral

Faltering growth

Height -3.17 SDS (WHO growth charts) upon the time of consultation.

Lab test

- Baseline IGF-I: - 1.57 SDS
- Two pathological GH-stimulation tests
  (GH peaks: 4.7 and 3.4 ng/mL, respectively)

Radiology

- Remarkably delayed bone age (2.7 years versus 7.3 years)
- Brain MRI: pituitary hypoplasia with intrasellar arachnoid diverticulum

IDIOPATIC GH DEFICIENCY

THERAPY

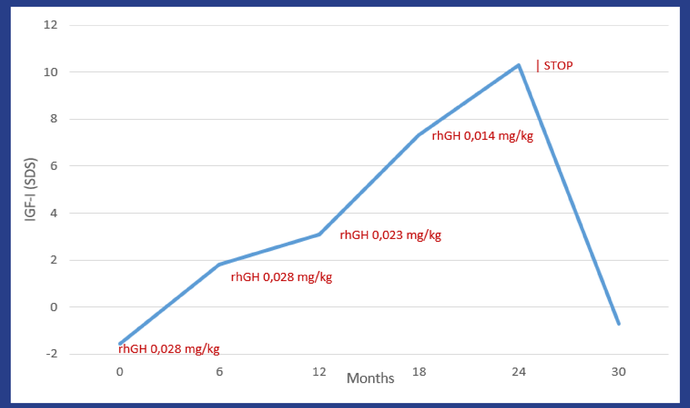
Treatment with recombinant human GH (rhGH) was undertaken, with a daily starting dose of 0.028 mg/Kg.

Excellent auxological response, with an overall height gain of 1.57 SDS in 24 months.

After the first year of treatment, IGF-I levels persistently above + 2 SDS were detected, with the maximum value recorded being + 10.64 SDS.
Increased IGF-I levels were sequentially recorded subsequently, despite a stepwise down-titration to a daily dose of 0.015 mg/kg.

Treatment discontinuation.
Timely normalization of IGF-I levels (-1.24 SDS).

UNEXPLAINED RESPONSIVENESS TO rhGH



GENETIC ASSESSMENT

A NOVEL HETEROZYGOUS *c.535C>T (p.Arg179cys)* VARIANT INVOLVIG THE *GHR* GENE IN A FUNCTIONAL DOMAIN WAS IDENTIFIED

It has been classified as «Likely disease-causing» by 4 different bioinformatic pathogenicity prediction tools.

DISCUSSION

Increased responsiveness to rhGH associated to polymorphisms of the *GHR* gene has already been described in patients with idiopathic short stature (1,2).

The novel variant hereby described may positively affect the sensitivity to treatment, as demonstrated by the combination of an excellent auxological response and remarkably increase of IGF-I despite low dosed of rhGH.

CONCLUSION

Growth hormone-deficient patients presenting with an excellent auxological response and persistent IGF-I levels above +2 SDS despite low rhGH doses may be carriers of ***GHR* gene polymorphisms.**

To date, rhGH doses are customized on the basis of IGF-I levels and individual clinical response. **In the future, ideally, systematic genetic profiling may provide additional information to tailor tHe optimal GHR genotype-based rhGH dose.**

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CONTACT INFORMATION

m.nicolosi5@campus.unimib.it

alessandro.cattoni@unimib.it

s.molinari3@campus.unimib.it