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Familial idiopathic short stature and beyond: a case-report of a novel heterozygous NPR2 mutation.

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Abstract

Background: NPR2 gene encodes for B-type natriuretic peptide receptor (NPR-B), a positive regulator of the growth plate. Recently, heterozygous NPR2 mutations were reported in 2–6% cases of idiopathic short stature (ISS) and 13.6% of familial ISS.
Case report: A 9-years-old boy was referred to our Outpatient Clinic of Pediatric Endocrinology for short stature. Analysis of growth chart revealed severe short stature since early childhood. At first evaluation he presented with a stature of 117.3 cm (-3.20 SDS), below the target height (-2.68 SDS), with normal body proportions and delayed bone age. Some dysmorphic features (small and stubby hands, slightly prominent frontal bosses) were observed. Laboratory investigations ruled out the main causes of short stature. A growth hormone (GH) stimulation test was performed, showing elevated GH levels at baseline (9.781 ng/ml) with low insulin-like growth factor-1 (IGF-1) levels (61.98 ng/ml). GH receptor resistance was therefore excluded. Genetic analysis highlighted a novel heterozygous mutation in the NPR2 gene (c.938del; c.953G>A), inherited from the mother.
Conclusion: Our case-report highlights that ISS represents a diagnosis of exclusion, that can only be formulated after a detailed diagnostic evaluation. The identification of a genetic aetiology in many ISS patients may contribute to better characterize the diagnosis, with potential implications in terms of growth outcome and response to treatment, allowing tailored management besides familial genetic counselling.

Keywords: Idiopathic short stature, familial short stature, NPR2

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Introduction

Idiopathic short stature (ISS) is characterized by a height more than - 2.0 standard deviation scores (SDS) for age, sex and population group, in patients with adequate birth weight and length, normal body proportions and without evidence of systemic, endocrine, psychosocial or nutritional disorders and chromosomal abnormalities. Therefore, ISS is considered a diagnosis based on the exclusion of other recognizable causes of short stature through an accurate history taking, physical examination and additional laboratory investigations (1-4). The definition includes a subcategorization into familial ISS and non-familial ISS, based on the height of the patient in relation to the familial target range (2,3). Recently, genetic investigations have emerged as a potential tool to better characterize the aetiology of ISS. Next generation sequencing (NGS) technologies have gained importance and several studies have already been

published using this methodology in children with ISS (5-6). Most of the genetic defects found in children with ISS involve genes related to the growth plate, including ACAN (Aggrecan gene), IHH (Indian hedgehog gene), SHOX (Short stature homeobox-containing gene), NPR2 (Natriuretic Peptide Receptor 2 gene), COL2A1 (Collagen type II alpha 1 chain gene) and FGFR3 (Fibroblast Growth Factor Receptor 3 gene), thus emphasizing that a disruption at any stage of the endochondral ossification may affect the physiological process of growth (7). Recently, heterozygous NPR2 mutations were reported as responsible for short stature in many patients initially classified as ISS. NPR2 gene, located on chromosome 9p13.3, encodes for the B-type natriuretic peptide receptor (NPR-B), with high affinity for c-type natriuretic peptide (CNP). The CNP/NPR2 signalling cascade acts as a crucial regulator of endochondral ossification, promoting bone matrix synthesis and stimulating the proliferation and differentiation of chondrocytes (8). Biallelic loss-of-function mutations in NPR2 gene are responsible for Maroteaux-type acromesomelic dysplasia (AMDM; OMIM *602875), a skeletal dysplasia with severe short stature and body disproportion (9). Heterozygous NPR2 mutations are associated with mild/variable growth impairment without serious skeletal alterations, and account for 2–6% cases of ISS (10, 13) and 13.6% of familial ISS (11). Data on the efficacy of recombinant human growth hormone (rhGH) treatment in these patients are still limited and controversial (10-11).

Case Report

We describe the case of a 9-years-old boy who was referred to the Outpatient Clinic of Pediatric Endocrinology of our Hospital for short stature. The boy was born at term, appropriate for gestational age, with normal psychomotor development. Growth chart evaluation revealed a severe short stature (< -3 SDS) since early childhood. Family history was positive for short stature: mother's height was 142 cm (sitting height/height ratio = 0.49), with target height of 157.5 cm (-2.68 SDS).

Our first auxological evaluation confirmed a condition of harmonic short stature (height -3.20 SDS, sitting height/height ratio 0.53) with bone age more than 2 years delayed using Greulich and Pyle method. On physical examination, the boy presented with some dysmorphic features (small and stubby hands, slightly prominent frontal bosses). Tanner stage was prepubertal (G1, P1). Laboratory tests, including complete blood count, iron status, liver, kidney and thyroid function, electrolytes, and screening for celiac disease, were within normal range. A growth hormone (GH) stimulation test with oral clonidine (Table 1) was performed, showing elevated GH levels at baseline (9.781 ng/ml) together with insulin-like growth factor-1 (IGF-1) values (61.98 ng/ml) below the normal range for sex and age.

Table 1. Growth Hormone (GH) stimulation test (with oral clonidine) performed in our patient.

Time (minutes)	GH (ng/ml)
T0’	9.781
T30’	5.341
T60’	6.468
T90’	3.233
T120’	1.653

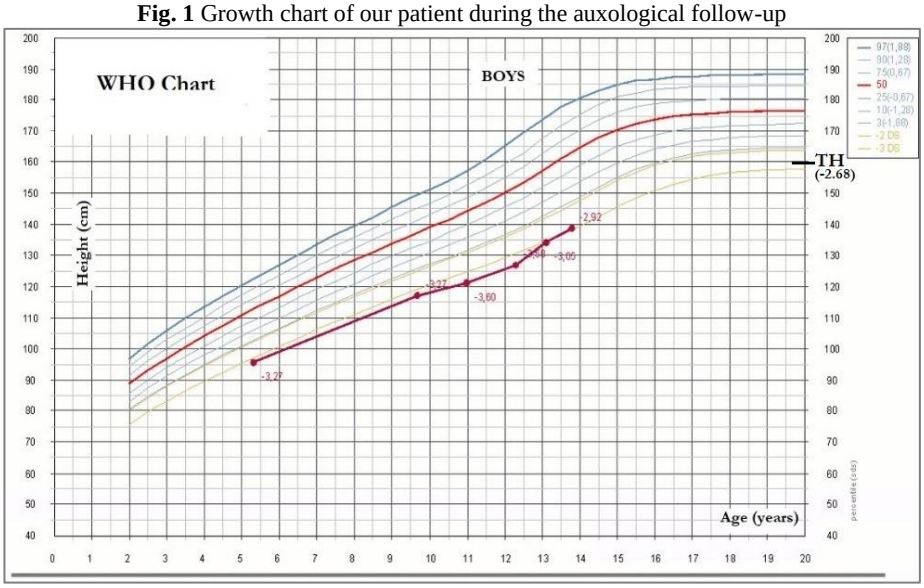
Table 2 Insulin like growth factor-1 (IGF-1) generation test: IGF-1 levels doubled if compared to baseline

IGF-1	Value
Baseline	84.76 ng/ml
After GH administration (0.1UI/kg/die for 4 days)	175 ng/ml

Therefore, an IGF-1 generation test (IGFGT) was performed by administering 0,1 U/Kg/day of GH for four nights. IGF-1 levels measured twelve hours after the last GH administration doubled if compared to baseline, thus excluding GH receptor resistance (Table 2).

Due to the association of severe short stature, subtle dysmorphic features and family history for short stature, genetic investigations were performed. SHOX gene analysis by MLPA (Multiplex Ligation-dependent Probe Amplification) was negative. Next-generation sequencing (NGS)-based panel for short stature highlighted a novel compound heterozygous NPR2 variant (c.938del; c.953G>A), classified using ACMG guidelines as likely pathogenic (class 4) and VUS (class 3) respectively. Puberty started spontaneously at the age of about 12 years old. At our last auxological evaluation (14 years old), the boy had reached a height of 138.8 cm (-2,92 SDS) with a pubertal growth spurt of about 12 cm (figure 1).

Fig. 1 Growth chart of our patient during the auxological follow-up



Discussion

The association of NPR2 heterozygous mutations with short stature was first described by Olney et al. (12). Subsequent reports (10,11,13) identified heterozygous pathogenic NPR2 variants in patients evaluated for ISS with significant phenotypic variability. Affected patients may present mild and variable degrees of short stature without a distinct phenotype. According to Ke et al. (14), non-specific manifestations presented in patients with NPR2 heterozygous mutations are mainly short stature, facial anomalies including high-arched palate, low nasal bridge, strabismus, dental malposition, frontal bossing, and skeletal deformities such as brachydactyly, shortened metacarpals or metatarsals, clinodactyly, mesomelic limb shortening, cubitus valgus, short and wide fingers and toes, and cone-shaped epiphysis. Notably, none of the patients with NPR2 heterozygous mutations have a Madelung deformity (14). Phenotype variability is likely due to differences in the type of NPR2 mutations carried by the individuals, as well as variable expressivity. Our report describes a novel compound heterozygous NPR2 variant associated with short stature and some dysmorphic features (small and stubby hands, slightly prominent frontal bosses). In 2003 GH therapy was approved by FDA for ISS children with a height below -2.25 SDS, while in Europe this treatment is still off-label (upon approval of local committees). The decision to treat a child with a height below –2.25 SD needs to be evaluated carefully and should be shared with the family, considering risks and benefits and variability of response to treatment (15). Unfortunately, our patient received the genetic diagnosis of NPR2 mutation too late to take into consideration GH therapy, mainly because at that time the bone age was yet advanced (13 years). In this regard, some authors (14, 16-18) demonstrated that GH treatment of ISS caused by NPR2 heterozygous variants may sometimes be effective, even if response to GH seem to vary significantly among different patients. Conversely, Vasques et al. (10) reported a relatively

poor response to GH treatment (height gain of 0 to 0.4 SDS). Such great variability may be due to differences in treatment initiation age, dose and adherence to GH therapy, parental height, and different variants in NPR2 (14). Of course, considering the small number of patients currently treated, further studies are necessary to confirm the efficacy of GH treatment in these subjects.

Conclusions

ISS represents a diagnosis of exclusion, that can only be formulated after a detailed diagnostic evaluation. Our case-report is notable, as it expands the number of known NPR2 variants, shedding new light on the genetic causes of ISS. In the last decades, genetic analysis emerged as a potential tool to better characterize the aetiology of many cases of ISS, not only allowing genetic counselling, but also opening new scenarios of potential positive implications in terms of growth outcome and response to treatment.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose.
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