

Clinical Experience

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GH treatment in a patient with Noonan syndrome



DR. I.P.S. KOCHAR
Senior Consultant
Pediatric & Adolescent Endocrinologist
Apollo Hospital and Fortis Hospital.



Introduction

Noonan syndrome is a heterogeneous genetic disorder characterized by short stature that was first recognized by Noonan and Ehmke in 1963 as a distinct clinical entity presenting with certain characteristic clinical features.^{1,2} The cause of short stature found in the majority of patients with this syndrome has not been well elucidated, and there exists a wide spectrum of short stature in Noonan syndrome. There is no single treatment for Noonan syndrome, and it focuses on the individual symptoms.

Growth hormone (GH) has been used successfully to treat short stature in individual patients with Noonan syndrome³, as in the case given below, and it constitutes a US Food and Drug Administration (USFDA) approved indication for GH therapy.⁴ The report given below presents a case of a 16-year-old boy with Noonan syndrome who exhibited markedly accelerated growth velocity with treatment with recombinant human GH (rhGH) for more than a year, thus, showing the effectiveness of treatment with rhGH.

Case report

A 15-year-old male presented to the endocrinology clinic for evaluation of his short stature. The patient was born of a full-term pregnancy, and thereafter remained in a good state of health except for the short stature and mental retardation.

Family history revealed that both parents were physically and mentally normal. A remarkable short stature (134cm), well below 2 standard deviations (SD), was noted on physical examination done on admission. Also, besides a short stature, he had characteristic appearances of face, head and neck (Table 1). He did show congenital heart lesions, mild pulmonary stenosis, thoracic cage deformities, and cryptorchidism.

Despite a short stature, his body proportions were appropriate for his height. Axillary and pubic hair had not developed and the genitalia showed a small penis and testes consistent with Tanner stage I. Neurological examination showed negative results. Hands and wrists x-rays were used to determine the bone age that appeared

TABLE 1. Characteristic physical appearances seen in the patient

- Short stature
- Ocular hypertelorism
- Downward slanting palpebral fissures
- Low-set ears
- Low posterior hairline.

about four years behind the chronological age. No abnormalities could be identified on Dynamic MRI of the Pituitary area. Wechsler Adult Intelligence Scale (WAIS) was used to estimate the patient's intelligence quotient (IQ); the Full Scale IQ, 66.

A 46 XY karyotype with normal banding was revealed on chromosomal analysis. Molecular genetic testing done in UK Lab appeared confirmatory for Noonan syndrome and identified mutation in PTPN11 gene. Laboratory examination at admission was normal except for elevated alkaline-phosphatase (ALP) activity (93 IU/l). GH stimulation test by insulin induced hypoglycemia showed decreased GH levels, maximum release being 4 ng/l.

Tests for other endocrinological examinations showed following results:

- Free Thyroxine 1.2 ng/dl
- Free Triiodothyronine 3.4 pg/ml
- Testosterone 0.11 nmol/l
- Basal luteinizing hormone (LH) concentration 15 U/l
- Vitamin D3 6 ng/ml
- Basal follicle-stimulating hormone (FSH) concentration 14 U/l
- Basal thyrotropin (TSH) concentration 1.7 mU/ml
- Basal prolactin (PRL) concentration 26 µg/l
- Baseline insulin like growth factor-1 (IGF-1) concentration 80 ng/ml which was low.

LH and FSH concentrations increased 30 minutes after intravenous (IV) administration of LH-releasing hormone (LHRH) (100 µg) to 64 U/l and 24 U/l, respectively. The low baseline level of IGF-1 responded to intramuscular rhGH administration for 3 days, and the levels increased to 240 ng/ml.

Further, the patient was treated with rhGH 4 U/day (0.125 U/kg) (Norditropin® Nordilet®-The only liquid human growth hormone) 7 times a week for more than a year. There was appreciable rise in growth velocity that accelerated > 3 fold compared to the mean growth velocity of the previous 4 years [2.0 ± 0.2 (SD) cm per year]. Also treated with Vitamin D, and there was improvement in the follow up of vitamin D level.

Discussion

Earlier, Noonan syndrome was used to be called Turner like syndrome because certain symptoms (webbing of neck and abnormally shaped chest) resembled those seen in Turner syndrome.⁸ It causes abnormal development of multiple parts of the body, and presents with characteristic signs and symptoms (Table 2).

Clinical examination may show an extra fold of skin above the eyes, near the nose (epicanthal

TABLE 2. Principal clinical features of Noonan syndrome

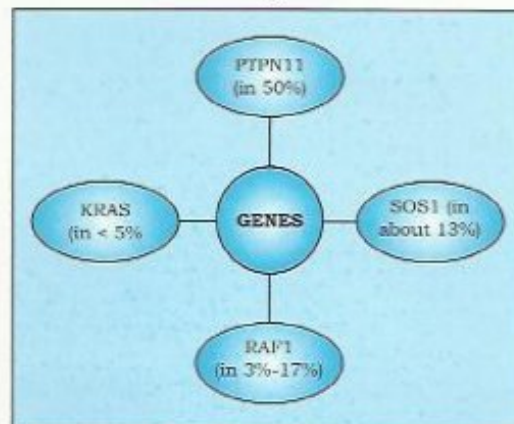
- Delayed puberty
- Short stature
- Down-slanting or wide-set eyes
- Sagging eyelids (ptosis)
- Low-set or abnormally shaped ears
- Webbed and short-appearing neck
- Mild mental retardation (only in about 25% of cases)
- Undescended testicles
- Small penis
- Unusual chest shape (usually a sunken chest called pectus excavatum).

folds) and arms that may be held at an unusual angle.⁹ Though there may be signs of congenital heart disease, and blood tests may reveal signs of a bleeding tendency, specific tests depend on what the symptoms are. Genetic testing can be used to identify the mutations in the genes which cause Noonan syndrome.

Although the exact etiologic factors and possible mode of inheritance of the syndrome have not been well determined, defects in 4 genes (KRAS, PTPN11, RAF1, SOS1) can cause Noonan syndrome.³ The syndrome is inherited in an autosomal dominant manner, and each child of an individual with Noonan syndrome has a 50% chance of inheriting the mutation.⁵ Molecular genetic testing for the 4 genes known to be associated with Noonan syndrome identifies mutations in PTPN11 in 50% of affected individuals, KRAS in fewer than 5%, SOS1 in approximately 13%, and RAF1 in 3%-17% (Figure 1).

In the present case, the patient had most of the diagnostic features of Noonan syndrome, and

FIGURE 1. Genes showing mutations in Noonan syndrome



or with primary or secondary amenorrhea, and a cytogenetic analysis should be performed, even in absence of other obvious abnormalities associated with Turner's syndrome.

The dose of the GH and the duration of therapy are important for favorable height outcomes, and the growth promoting therapy may be continued until attaining a satisfactory height, or until little growth potential remains; there is greater height gain with longer treatment with GH.⁹ In addition to promoting linear growth, GH also has favorable physiologic effects on adipose tissue, bone metabolism, and muscle accretion.⁸ It directly stimulates osteoblast and osteoclast differentiation, and promotes accretion of bone mass during childhood and adolescence.

Together with growth issues, it is also important to consider the patient's desire to begin puberty in order to establish an optimal hormonal treatment plan. The dose and timing of the hormonal therapy in Turner's syndrome patients should reflect the process of normal puberty, and should not interfere with the positive effect of GH treatment on the patients' final adult height.

References

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