Noonan Syndrome Presenting Growth Hormone Neurosecretory Dysfunction

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Noonan syndrome has been diagnosed by the characteristic physical stigmata for more than two decades. Recent studies of growth hormone secretory pattern provide a new category of growth hormone neurosecretory dysfunction to characterize short stature. We describe herein a case of growth hormone neurosecretory dysfunction in a 16-year-old boy with Noonan syndrome. Growth hormone neurosecretory dysfunction was diagnosed primarily based on the low amplitude and small numbers of the spontaneous bursts of growth hormone secretion during 12-hour nocturnal growth hormone sampling. Treatment with synthetic human growth hormone has markedly accelerated the growth velocity for one year and a half. This case notes the wide spectrum of short stature in Noonan syndrome and the effectiveness of treatment with human growth hormone.

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Introduction

Noonan syndrome was first recognized as a clinical entity by Noonan and Ehmke in 1963 (1). The principal clinical features of Noonan syndrome include characteristic facial appearance, short stature, mental retardation, neck signs, congenital heart lesions, somatic anomalies, and the lack of a significant chromosomal anomaly. However, the cause of short stature found in the majority of the patients with this syndrome has not been elucidated yet (2-4). Herein, we describe a patient of Noonan syndrome in whom growth hormone neurosecretory dysfunction is responsible for the short stature and the growth velocity after replacement therapy with exogenous synthetic human growth hormone (hGH) has been markedly accelerated for a period of one year and a half.

Case Report

The patient, a 16-year-old male, was admitted to this hospital in October 1988 for the endocrinological evaluation of short stature. He was born of a full-term pregnancy and thereafter had been in a good state of health except for the short stature and mental retardation. At the age of nine, he was noted at another facility that growth hormone (GH) release by provocative testings was normal. His parents and a brother were physically and mentally normal. Physical examination on admission was remarkable for short stature (136cm) well below 2 SD (Fig. 1), the characteristic appearances of face, head and neck such as ocular hypertelorism, downward slanting palpebral fissures, low-set ears, webbed neck, low posterior hairline, and cubitus valgus, but did not show congenital heart lesions, thoracic cage deformities, nor cryptorchism (Fig. 2). His body proportions were appropriate for his height. Axillar and pubic hair did not develop and the genitalia showed a small penis and testes (Tanner stage I). The results of neurological examination were negative. Bone age determined from hands and wrists roentgenograms was four years behind the chronological age. Admission laboratory examination was normal except for elevated alkaline-phosphatase activity (93 IU/l). High-resolution computed tomography scanning of the sella turcica and hypothalamus showed no abnormalities. Chromosomal analysis showed 46 XY karyotype with normal banding. The patient’s intelligence quotient (IQ) by Wechsler Adult Intelligence Scale (WAIS) was estimated to be verbal IQ 61, per-
Performance IQ 79 and the Full Scale IQ 67. The results of endocrinological examinations showed thyroxine 95.5 nmol/l, triiodothyronine 2.02 nmol/l, normal diurnal rhythm of plasma cortisol (8:00 AM; 190.4 nM, 4:00 PM; 146.3 nM, and 11:00 PM; 35.9 nM), testosterone 0.12 nmol/l, urinary 17-hydroxycorticosteroid 7.45 μmol/day and 17-ketosteroid 17.7 μmol/day. Basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations were 14 U/l and 13 U/l and increased 30 minutes after intravenous administration of luteinizing hormone-releasing hormone (LHRH) (100 μg) to 66 U/l and 26 U/l, respectively. Basal thyrotropin (TSH) and prolactin (PRL) concentrations were 1.6 mU/l and 25 μg/l, and increased 30 minutes after intravenous administration of thyrotropin-releasing hormone (TRH) (500 μg) to 6.2 mU/l and 75 μg/l, respectively. GH after intravenous administration of arginine (0.5 g/kg) and growth hormone-releasing hormone (1 μg/kg) increased from the basal values of 2.1 and 3.1 μg/l to the peak values of 16.0 and 15.2 μg/l, respectively (Fig. 3). The endogenous nocturnal pulsatile secretion of GH of which samples were obtained every 20 minutes for 12 hours from 9:00 PM to 9:00 AM disclosed that there were only 4 GH peaks greater than 3 μg/l and the mean GH concentration for over the 12 hours was 2.31 ± 2.26 (SD) μg/l (Fig. 4). The low baseline level of insulin-like growth factor 1 (IGF-1) of 0.37 U/l responded to the acute administration of hGH intramuscularly for three days with an increase in IGF-1 level of 0.85 U/l. After the tests, the patient was treated with hGH 4 U (0.125 U/kg).
The period of sleeping clock time

Fig. 4. The twelve-hour growth hormone secretory profile. Samples were obtained every 20 minutes from 21:00 to 9:00. The patient's sleeping period was from 23:00 to 7:00. Growth hormone secretory peaks over 3 \( \mu g/l \) were four and the mean (±SD) growth hormone concentration was 2.31 ± 2.26 \( \mu g/l \).

three times a week for a period of one year and a half. The growth velocity accelerated more than three fold compared to the mean growth velocity of the previous five years [1.9 ± 0.2 (SD) cm per year] (Fig. 1).

Discussion

Noonan syndrome has been diagnosed for more than two decades by the characteristic stigmata consisting of facial appearances, short stature, undescended testes, heart lesions, cubitus valgus and mental retardation, since the exact etiologic factors and possible mode of inheritance of the syndrome have not been determined yet (2-4). This case represented most of the diagnostic stigmata of Noonan syndrome and occurred sporadically since his parents and a brother were normal. We were interested in the cause of the short stature in this case since short stature in Noonan syndrome is a common but not invariable feature. There is no definite agreement to date on the cause of short stature, that is, genetic, prenatal, perinatal or postnatal. Collins and Turner (3) suggested that it might be, at least in part, postnatal in origin, although there was no constant relationship between a reflection of the difficulties in the early years of life such as feeding problems, failure to thrive and recurrent infection and the shortness of stature. In addition, they suggested that the shortness of stature was best considered as a component of the syndrome (3).

Since this patient had normal GH reserve confirmed by the conventional provocative testings, non-GH-deficient growth retardation was most likely. GH neurosecretory dysfunction (GHND) was reported by Spiliotis et al in 1984 and criteria for the diagnosis of GHND was proposed (5): 1) height <1 percentile, 2) growth velocity <4 cm/year, 3) bone age ≥2 years behind chronological age, 4) abnormal 24-hour GH secretion pattern, 5) normal provocative tests (peak GH ≥10 \( \mu g/l \)), 6) low somatomedin-C (IGF-I) for age. Rather than a 24-hour GH secretion study, in this patient we examined the 12-hour nocturnal GH secretory pattern which was suggested most useful to identify GHND (6). Magnitude and numbers of the spontaneous bursts of GH secretion are age-related and transition from early puberty to adolescence is associated with increased numbers of GH surges (7, 8). The result of 12-hour nocturnal GH secretion showed a conspicuously low amplitude and small numbers of bursts of spontaneous GH secretion, compatible with GHND. This case fulfilled the criteria for GHND. The marked slowing of growth velocity noted before the age of ten is thought to be the result of GHND that probably had been in his childhood. Bercu and Diamond mentioned the association of Noonan syndrome and GHND though data were not shown (6). Kitajima et al reported a 14-year-old girl with Noonan syndrome presenting GHND who responded to the administration of propranolol (20 mg a day); she grew 1.9 cm over a three-month period but did not present any effect of hGH administration (9). In the present case the marked acceleration of growth velocity after hGH treatment indicates the effectiveness of hGH treatment in short stature. Although GHND is most responsible for short stature in this case, it is difficult to identify the primary abnormality in complex neural pathways of GH secretion including growth hormone-releasing hormone, somatostatin, and neurotransmitters at many levels (10). In children of GHND, a disruption at any level in the neurotransmitter-neurohormonal pathways could modify GH secretion ultimately expressed as poor growth velocity and short stature. Therefore, the pathways and levels impaired in GHND seem to differ among individual cases.

Another concern is that the appearance of the sexual characteristics of puberty was delayed in the present case. It has been reported that puberty is delayed in GH-deficient children (11, 12). The precise signal that initiates and maintains puberty is not known although a critical level of body fat has been hypothesized to be a signal (13). The significant increases in LH and FSH after intravenous administration of LHRH in this case indicate that the pituitary-gonadal axis was normal and these responses suggest that puberty is imminent (14). Since it was reported that GH administration in GH-deficient children initiates puberty (11), we expect the appearance of sexual characteristics of puberty under hGH treatment in this patient.

The present observations of a patient of Noonan syndrome presenting GHND resulting in short stature, who was treated effectively with hGH suggest that short stature in Noonan syndrome has a wide spectrum of causes. Further analysis of short stature in Noonan syndrome could help to elucidate its etiology.
References
