Experience in Growth Hormone Therapy in Noonan Syndrome in Japan

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Abstract

Thirty-nine children with Noonan syndrome were treated with growth hormone (GH). Prepubertal height velocity was $4.25 \pm 1.31$ cm/year ($M \pm SD$)(n=38) before GH therapy, which was increased to $6.23 \pm 0.87$ cm/year (n=33) in the first year, to $4.92 \pm 1.15$ cm/year (n=22) in the second year and $4.76 \pm 1.25$ cm/year (n=13) in the third year. Height velocity SDS for chronological age and height velocity (SDS) for bone age were also improved in the 1st year, but declined progressively during the subsequent years. No adverse effects were observed during GH treatment.

These data indicate that GH may be effective in Noonan syndrome, but further studies are required to evaluate the efficacy of long-term GH therapy on adult height and body proportions.

key words: Noonan syndrome, growth hormone
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 short stature, characteristic facial appearance, congenital heart disease, somatic anomalies, and lack of a significant chromosomal anomaly. Short stature is one of the main features of Noonan syndrome (2). The efficacy of GH therapy has been reported in Turner syndrome (3). The similarity of Noonan syndrome to Turner syndrome has led to the expectation that GH treatment might have a beneficial effect on final height, irrespective of biochemical demonstration of GH insufficiency or sufficiency. There are several reports on GH therapy in Noonan syndrome (4–7) but none on the effect of long-term GH therapy on final height.

The aims of this study were to investigate the status of GH secretion and the effect of GH treatment.

Patients and Methods

Thirty-nine children with Noonan syndrome, 30 boys and 9 girls, aged 3.8 to 13.5 years were studied. All patients were prepubertal before GH therapy. Thirteen patients reached puberty during the 3-year GH treatment. Data of the patients were excluded from this study when patients reached puberty. Therefore, all the following data were analyzed in the prepubertal stage during GH treatment. Bone age was assessed by the atlas of Greulich and Pyle in most patients and by the method of TW2 in some patients. Pretreatment height velocity was assessed over at least six months.

Standard GH provocative tests (L-dopa, arginine, insulin, clonidine, glucagon-propranolol) were performed. Complete GH deficiency was diagnosed when the peak GH value was less than or equal to 5 ng/mL in at least two provocative tests. In the glucagon-propranolol test, the peak GH value less than or equal to 7.5 ng/mL was considered to be complete GH deficiency. Partial GH deficiency was diagnosed when the peak GH value was between 5.1 and 10 ng/mL in at least two provocative tests. In the glucagon-propranolol test, the peak GH value between 7.6 and 15 ng/mL was considered to be partial GH deficiency. Serum IGF-I was not evaluated in this study.

For statistical evaluation, Student's t-test and one-way analysis of variance (ANOVA) were used. The results are presented as mean ± SD.

The patients received 0.5 IU/kg/week of recombinant GH.

Results

Of the 39 patients, 2 had complete GH deficiency and 13 patients had partial GH deficiency. Four of 13 patients with partial GH deficiency had a birth history of asphyxia or prolonged neonatal jaundice.

Congenital heart disease is one of the features of Noonan syndrome. Pulmonary stenosis (PS) was noted in 5 cases, PS associated with atrial septal defect (ASD) in 2 cases, ASD in 3 cases, patent ductus arteriosus in 2 cases and hypertrophic cardiomyopathy in 2 cases.

There was no significant sex difference in height velocity, height velocity SD score for chronological age (CA) and that for bone age (BA). Therefore, the following data were ana-
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lyzed with the sexes combined.

Table 1 shows the clinical characteristics of Noonan syndrome. BA was delayed. Height SDS, height SDS for CA and height velocity SDS for BA were all decreased before GH therapy. Both paternal and maternal heights were almost average. Birth length and weight were also normal. Gestational age was also normal.

Two patients reached puberty in the 1st year of GH treatment, 2 in the 2nd year and 4 in the 3rd year. As shown in Fig. 1, prepubertal height velocity (HV) was 4.25 ± 1.31 cm/year before GH treatment and it was increased to 6.23 ± 0.87 cm/year in the 1st year, to 4.92 ± 1.15 cm/year in 2nd year, and to 4.76 ± 1.25 cm/year in the 3rd year. HV SDS for CA and HV SDS for BA were also improved in the 1st year of GH treatment, but they declined progressively during the subsequent years (Figs. 2 and 3). There was no difference in BA advancement (Δ BA) during GH therapy (Fig. 4). There was no overweight nor adverse effect during GH therapy.

Discussion

In this study, 15 out of 39 patients (38 %) had impaired GH secretion. Four of them had asphyxia at birth or prolonged jaundice. Impaired GH secretion has been found in some cases of Noonan syndrome (4–7). The exact causes of impaired GH secretion in Noonan

Table 1

<table>
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<tr>
<th>Clinical Characteristics in Noonan Syndrome at the time of GH Tx</th>
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<td>CA (years)</td>
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<td>BA (years)</td>
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<tr>
<td>BA/CA ratio (%)</td>
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<td>Height (cm)</td>
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<td>Height SDS (SD)</td>
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<td>Height SDS for BA (SD)</td>
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<td>Height velocity (cm/yr)</td>
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<td>Height velocity SDS for BA (SD)</td>
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<td>Height velocity SDS for CA (SD)</td>
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Fig. 1 Height velocity (M ± SD)

Paternal height (cm) | 166.2 ± 5.4 (n = 37)
Maternal height (cm) | 155.2 ± 6.0 (n = 37)
Birth length (cm) | 49.2 ± 2.3 (n = 24)
Birth weight (g) | 3179 ± 690 (n = 24)
Gestational age (week) | 39.5 ± 1.5 (n = 39)
GH therapy indeed promotes height velocity and may improve final height for Turner syndrome (3). This has led to the acceptance of GH therapy for Turner syndrome in clinical practice in several countries. The similarity of Noonan syndrome to Turner syndrome led to the expectation that GH treatment may have a beneficial effect. There are several reports on GH therapy in Noonan syndrome but none on the effect of long-term GH therapy on final height (4-7). The efficacy of short-term GH therapy has been reported. Otten (4) investigated 55 patients with Noonan syndrome treated with GH enrolled in the Kabi International Growth Study (KIGS). The median GH dose was 0.6 IU/kg/week with a median frequency of six injections per week. The mean pre-treatment height velocity was 4.3 cm/year, and this increased to 7.0 cm/year in the 1st year, 6.0 cm/year in the 2nd year and 4.8 cm/year in the 3rd year. Ahmed et al. (5) observed a significant improvement in growth velocity (4.8 to 7.4 cm/year) in five children with Noonan syndrome after one year of treatment with GH in a dose regimen of 0.1 IU/kg/day administered subcutaneously six days a week. Moreover, Thomas et al. (6) treated five children with Noonan syndrome with GH in a dose regimen of 0.12 to 0.18 IU/kg/day as a daily subcutaneous injection. After one year of treatment, height velocity SDS increased from a mean of -2.1 to a mean of +3.1 and after two years of

![Fig. 2 Height velocity SDS for CA (M ± SD)](image1)

![Fig. 3 Height velocity SDS for BA (M ± SD)](image2)
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Treatment, mean height velocity SDS decreased to -0.4. A further reduction in height velocity SDS to mean -2.0 in the 3rd year of treatment was observed. An initial acceleration of growth was seen, but thereafter the growth waned. In this study, height velocity, height SDS, HV SDS for CA and HV SDS for BA were accelerated during the 1st year of GH treatment, but they declined progressively during the subsequent years in Noonan syndrome. The magnitude of this height velocity in GH treatment was similar to that in Turner syndrome (3), in achondroplasia (8), in GH-insufficient children (9) and in normal short children (10). Decreased effectiveness of GH treatment according to the duration of treatment might be due to resistance of the tissues against GH and/or IGF-I. However, the mechanism of this phenomenon is not clear at present. There was considerable variation in clinical response within the treated cases. Some patients with Noonan syndrome may respond well to long-term GH therapy. As with Turner syndrome, a greater dose of GH may be needed in order to promote growth.

Further studies are required to evaluate the efficacy of long-term GH therapy on adult height and body proportions and the optimal effective dosage and safety of GH in a large number of Noonan syndrome cases.

References

7. Matsuo K, Nakatsuka K, Aoki Y. Noonan

