A Patient with Short Stature with Normal Growth Hormone Provocative Tests and Low Physiological 24 hr Growth Hormone Concentration

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Abstract. We report a patient with short stature with normal GH provocative tests and low physiological 24 hour GH concentration. After starting GH treatment, growth velocity increased similarly to that seen in patients with a severe type of growth hormone deficiency. This is the first precise case report of a patient with typical neurosecretory dysfunction without any other complications.

Key words: growth hormone neurosecretory dysfunction, GH provocative tests, 24 hr mean GH concentration

Introduction

Traditionally, the diagnosis of growth hormone deficiency (GHD) has been made from the results of GH provocative tests and GH treatment was given only to patients with GHD [1]. After the development of recombinant technology, GH therapy has been given to quite a number of patients other than GHD such as Turner syndrome [2, 3] and so-called normal short children [4-8]. Among normal short children who have been conventionally defined by the results of GH provocative tests, the concept of GH neurosecretory dysfunction

(NSD) was proposed [9] and it was reported that GH therapy would increase the height of patients with NSD at least in a short range of the treatment years [10-13].

Originally, patients with NSD have short stature with delayed bone age, normal results of GH provocative tests, a low level of insulin-like growth factor-1 (IGF-1) and a low mean level of physiological 24 hr GH concentrations [9]. Since the concept was published, 24 hour or 12 hour overnight measurements of GH concentration (24-M-GH, N-M-GH, respectively) have been reported to be useful in analysing who should be treated among short children [10-14].

It remains to be clarified whether NSD is commonly seen in patients with short stature, although there are some reports where spontaneous GH secretion is low in patients with Turner syndrome [15], and brain tumor with irradiation [16]. As far as we know, there

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has been no single, precise case report of NSD, although there have been several reports about the data of NSD as a group [9-13].

Here we present a patient with normal GH provocation tests and low mean levels of 24-M-GH. Height gain after GH treatment was obtained similarly to that in a severe type of GHD.

Methods

All the GH levels were measured by a commercially available GH IRMA kit (Eiken, Tokyo, Japan). Serum IGF-1 and IGF binding protein-3 (IGFBP-3) levels were measured by previously reported methods [17-20].

Arginine and insulin tests were done as previously described [21].

Mean levels of 24-M-GH were calculated based upon the GH levels every 30 minutes as previously described [22]. Mean levels of N-M-GH were calculated based upon the GH levels every 30 minutes from 8 p.m. to 7:30 a.m.

Case Report

This Japanese girl was first seen in our clinic because she was short (mean-6.5 SD for Japanese girl standard [23]) at the age of three years and nine months. She was born as one of twins, by spontaneous vaginal, breech delivery at 35 weeks' gestation. Her Apgar score was nine at five minutes. She measured 45 cm and weighed 2.10 kg at birth. Her father and mother were 170 cm and 160 cm tall, respectively.

At the age of three years and four months at the regular health check at a local health center, she was referred to a local hospital because of short stature. At this hospital, her GH peak of insulin tolerance test was 16 ng/ml (Table 1).

At the age of three years and nine months, she was referred to our hospital. Her growth chart was as in Figure 1. Physical examination

Table 1. IGF- I, IGFBP-3, GH peaks during arginine (Arg.) and insulin (Ins.) tests, and physiological GH mean concentration. Physiological GH mean concentration was measured for a whole day and overnight (24-M-GH and N-M-GH, respectively. See in Methods). Normal mean levels of 24-M-GH and N-M-GH (mean±SD, range, n=21) are 4.4 ± 1.2 , $2.2-6.7$ and 5.4 ± 2.1 , $2.4-10.0$ ng/ml, respectively.

CA	IGF-1 (ng/ml)	IGFBP-3 (mg/L)	GH peak Arg. Ins. (ng/ml)	24-M-GH (ng/ml)	N-M-GH (ng/ml)
3:04			16.0		
3:09			14.4	0.82	1.17
3:11		0.80	8.0	0.81	1.23
					0.55
5:02	47.1	0.51	25.1		1.42
	49.3	0.60			

CA: chronological age, 3:04 means three years and four months.

was unremarkable. Her bone age was one year and six months (Greulich and Pyle method). On the magnetic resonance image, mild atrophy of the anterior pituitary gland was noted. Neither transection of the pituitary stalk nor ectopic posterior lobe was detected. We did arginine and insulin tests four times (at the age of three years and nine months, and three years and 11 months) and did 24-M-GH or N-M-GH three times, with parental consent (Table 1). Three out of four GH provocative tests showed GH peaks over 10 ng/ml. All mean levels of 24-M-GH and N-M-GH were extremely low, compared with our normal values [22]. Our normal mean levels of 24-M-GH and N-H-GH during the prepubertal period (mean±SD) were 4.4 ± 1.2 (range 2.2-6.7, n=21), 5.4 ± 2.1 (range 2.4-10.0, n=21) ng/ml, respectively (22, our unpublished results).

The results of serum IGF- I and IGFBP-3 levels are also shown in Table 1. Those IGF- I and IGFBP-3 values were lower than the lower limit of age-matched controls [17-20].

At the age of three years and 11 months, we started GH therapy (0.5 U/kg/week, six times a week). Height velocity SD score [23] improved from -8.6 (pretreatment) to +1.9 (one year after GH treatment). Delta height increment (subtracting pretreatment height velocity (cm/year) from post-treatment height

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Fig 1. Growth curve of this patient and her sister on cross-sectional percentile growth curve for Japanese girls [33]. Closed and open circle indicate height of her and her sister (twins). The seven lines show 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentile.

velocity (cm/year)) was 7.9 cm, one year after starting GH therapy. This delta height increment is quite similar to that of a severe type of prepubertal GHD with the same style of GH treatment in our hospital ($n=14$, mean $\pm$ SD; 7.6 ± 2.1 cm).

At the age of five years and one month, we stopped GH treatment for two weeks and reevaluated GH secretion capacity, with parental consent (Table 1). We obtained similar results of the GH provocation test and low physiological GH levels as before.

Discussion

Five out of six GH provocation tests (insulin, arginine) showed GH peaks over 10 ng/ml. The result of the arginine test at the age of three years and 11 months was considered to be false positive if we arbitrarily decide the cutoff line of GH provocation tests is 10 ng/ml, because the other results of GH provocation tests were completely normal. It has been reported that some apparently normal short children, who were defined by the other GH provocation tests, showed false positive results [24-26]. According to our data, the false positive rate in normal short children was 23% [21].

The results in our case, namely, normal results of GH stimulation tests, low IGF-I, and low mean levels of 24-M-GH were compatible with the original concept of NSD. The therapeutic success in our case was also consistent with the original concept of NSD.

Although some reports have been in favour of the concept of NSD [9-13], some have been against the concept [27-29]. One issue against the concept is that 24-M-GH or N-M-GH do not give us reproducible results [27-28]. The other issue against the concept is that normal values of mean level of 24-M-GH overlap with those of patients with GHD [29]. The definition of NSD is not yet clearly made among researchers.

This case report suggests that a case clearly exists which has normal GH provocation

tests and a low mean level of 24-M-GH, with growth on GH therapy, quite similarly to a classical GHD. We think that it is important to make a diagnosis carefully after repeating GH provocation tests and measurements of GH during 12 or 24 hr, because there are some limitations of GH provocative tests such as reproducibility [30-32] and false positive tests [23-26] as well as those of 12 or 24 hour measurements of GH as described above.

Finally, of note is that this kind of condition, a case with "typical" NSD, is probably very rare, because in our seven years' experience (150 short children, and about 50 24-M-GH analyses), this is the only case with low IGF-I levels, normal GH provocation tests and low mean levels of 24-M-GH. We think that further study of neurosecretory dysfunction, especially how to define the concept, is needed.

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