

Testosterone priming increased growth hormone peak levels in the stimulation test and suppressed gonadotropin secretion in three Japanese adolescent boys

Takeshi Sato¹, Moe Kusakawa¹, Yosuke Ichihashi¹, Tomohiro Ishii¹, and Tomonobu Hasegawa¹

¹Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

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Introduction

The guidelines from the Pediatric Endocrine Society in 2016 recommended sex steroid priming before GH stimulation test in prepubescent boys older than 11 yr to avoid false positives owing to physiological hyposecretion of GH (1). While a previous study showed an elevation in peak GH levels in the stimulation test after testosterone priming, there have been no such reports from Asian countries, including Japan (2). Although the secretion of gonadotropins would be suppressed by the negative feedback of testosterone priming, gonadotropin levels associated with testosterone priming have not been evaluated in the guidelines (1). Here, we aimed to determine whether testosterone priming would increase peak GH levels in Japanese boys and assess the effect of testosterone priming on gonadotropin secretion.

Materials and Methods

After receiving approval from the Institutional Review Board at Keio University School of Medicine (institutional review board number 20150104) and providing opt-out statements, we retrospectively reviewed medical records of all male patients who underwent GH stimulation tests between 2017 and 2019 in the Department of Pediatrics, Keio University Hospital. We extracted data of patients meeting the following criteria: i) aged > 11 yr, ii) prepubescent status (bilateral testicular volumes < 4 mL) in two GH stimulation tests and GnRH loading test, iii) GH peak levels ≤ 6 ng/mL in two GH stimulation tests, iv) GnRH loading test with one of the two GH stimulation tests, and v) within 2 mo of the two GH stimulation tests, an

additional GH stimulation test performed 1 wk after intramuscular testosterone enanthate injection. Data on clinical and laboratory findings, including adverse effects associated with testosterone injection, were collected. Growth of patients was evaluated according to growth charts for Japanese boys (3).

Results

We reviewed medical records of 37 male patients, and three patients met the criteria. Clinical and laboratory findings of the three patients are summarized in **Table 1**. Growth charts are shown in **Fig. 1**. The patient age ranged from 13.9 yr to 14.6 yr at the two GH stimulation tests. The predicted adult height standard deviation scores (SDSs) were +0.2, -0.1, and +1.0, and the height SDS did not increase until the GH stimulation test with testosterone priming was performed. Approximately 1 yr after the GH stimulation test with testosterone priming, height velocity SDS for age increased in all the patients. The testes of all three patients increased more than 4 mL, which was consistent with pubertal development. All three patients received a 100-mg intramuscular injection of testosterone enanthate, which was the recommended dose in the guidelines (1). GH peak levels in the stimulation test with testosterone priming were elevated compared with those without testosterone priming. Serum IGF I levels were elevated after pubertal development. No patient was diagnosed as having GH deficiency, and GH therapy was not administered. While peak LH and FSH levels were elevated using the GnRH loading test, basal LH and FSH levels were suppressed by testosterone priming and were accompanied by elevated testosterone levels.

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Corresponding author: Tomonobu Hasegawa, M.D., Ph.D., Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

E-mail: thaseg@keio.jp



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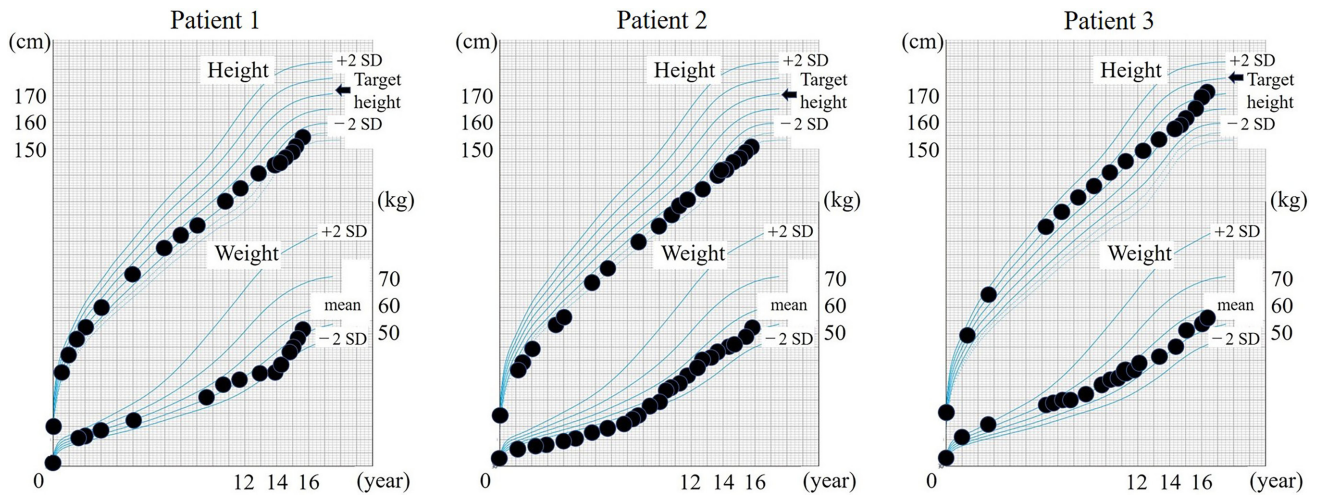


Fig. 1. Growth charts of the three boys.

Table 1. Clinical and laboratory findings of the three patients

	Patient 1					Patient 2					Patient 3				
Age (yr)	12.9	13.9	14.1	15.3	15.6	13.3	14.3	14.4	15.4	15.8	13.3	14.6	14.7	15.6	16.3
Height SDS	-1.9	-2.5	-2.8	-3.0 ^a	-2.7	-2.5	-3.3	-3.4	-3.5	-3.4	-0.7	-1.1	-1.1	-0.3	+0.3
Height velocity SDS	-3.3	-4.4	+3.8 ^a			-2.9	-3.0	+3.7			-4.0	-2.3	+6.8	+9.8	
Testicular volume right/left (mL)	2.5/2	3/3.5	6/6			2/2	2.5/2.5	6/5	8/8		3.5/3.5	4/3.5	8/9	12/12	
Reason(s) for GH stimulation tests	Short stature, low IGF-1 level					Short stature					Decreased height velocity				
GH peak (ng/mL)															
Insulin loading	2.3					3.6					4.5				
Arginine loading	4.2					1.9					5.3				
Glucagon loading	9.2 ^b					17.3 ^b					15.5 ^b				
IGF I (ng/mL)	103					175					316 ^b				
14.5	166 ^b					234					420				
LH basal/peak (mIU/mL)	2.3/14.5					0.7/20.6					1.3/19.9				
<0.1 ^b	5.9					3.0					3.1				
FSH basal/peak (mIU/mL)	4.3/7.9					5.4/17.2					4.5/10.4				
0.3 ^b	5.9					6.5					3.2				
Testosterone (ng/mL) ^c	0.24					0.2					0.22				
14.4 ^b	6.0					1.18					9.78 ^b				
6.0															

SDS, standard deviation score. ^a Patient 1 (at his personal request) received 50 mg of testosterone enanthate three times a month from the age of 14 yr 10 mo. ^b Measurements obtained 1 wk after a 100-mg intramuscular testosterone enanthate injection. ^c Local reference for male adults, 1.92–8.84 ng/mL.

Basal LH, FSH, and testosterone levels were elevated at approximately 1 yr after the GH stimulation test with testosterone priming compared with those during stimulation tests without testosterone priming. No severe adverse effects were recorded, although Patient 1 complained of pain in both arms when testosterone enanthate was intramuscularly injected.

Discussion

We found that GH peak levels in the stimulation test with testosterone priming were higher than those without testosterone priming in three Japanese boys. The degree of elevation was approximately similar to that of a previous report from Turkey, which described

that GH peak levels with and without testosterone priming were $15.4\text{--}19.3 \pm 5.1\text{--}5.9 \mu\text{g/L}$ and $4.9\text{--}5.4 \pm 2.1\text{--}3.0 \mu\text{g/L}$, respectively (2).

The peak GH levels with testosterone priming in all patients did not meet the Japanese diagnostic criteria for GH deficiency. During the observational period, height velocity SDS in all patients improved without GH therapy, accompanied by pubertal development (Table 1). A previous report did not support the usefulness of GH therapy in improving adult height in subjects with short stature and delayed puberty; furthermore, it was difficult to exclude the possibility that the patients would become taller with GH therapy than without GH therapy (4). The testosterone levels in Patients 1 and 3 at 1 wk after a 100-mg intramuscular testosterone

enanthate injection were higher than the upper limit of the normal values for male adults. We cannot deny that based on these supraphysiologic testosterone levels, GH secretion capacities were overestimated. Thus, although the different dose of testosterone enanthate may be appropriate for the Japanese, we believe that testosterone priming, according to the guidelines, enables differentiation between patients in the Japanese adolescent population who need and do not need GH therapy.

In general, for patients with delayed puberty, basal gonadotropin levels are sometimes useful to distinguish between hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, and constitutional delayed puberty. All three patients had elevated basal LH levels, implying that their delayed puberty was constitutional and that their pubertal development occurred shortly thereafter. Elevated peak LH and FSH levels in the GnRH loading test were consistent

with constitutional delayed puberty. With testosterone priming, basal gonadotropin levels were suppressed, suggesting the difficulty in distinguishing among the three aforementioned conditions. Gonadotropin secretion is difficult to evaluate when GH secretion can be assessed with testosterone priming.

In conclusion, the Japanese boys had elevated GH peak levels in the GH stimulation test with testosterone priming. Basal gonadotropin secretion should be assessed before testosterone priming.

Conflict of Interests: All authors have no financial relationships relevant to this article to disclose.

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