48,XXYY Syndrome Associated with Acromegaloidism

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We report a case of double male syndrome, a type of Klinefelter's syndrome with 48,XXYY chromosome, associated with acromegaloidism. Although the patient presented acromegalic appearance, he did not show hypersecretion of growth hormone (GH). GH provocation tests revealed a rather low GH responses or no responses. After testosterone therapy, the GH responses were normalized except to Insulin tolerance test (ITT). On the other hand, the plasma corticotropin (ACTH) and cortisol levels were decreased paradoxically after hypoglycemia. Testosterone therapy did not restore this ACTH response. It was speculated that these abnormal GH and ACTH responses to hypoglycemia might indicate another congenital anomaly. (Internal Medicine 32: 160–165, 1993)

Key words: low GH response, ITT, paradoxical ACTH and cortisol response, hypogonadism

Introduction

The double male syndrome, 48,XXYY karyotype, is a variant type of Klinefelter's syndrome and its phenotype is male. Since the first report by Muldal and Ockey (1) in 1960, some studies have described these patients with unusual tallness, severe mental retardation, behavioral problems and skeletal abnormalities (2–6). There have been no thorough endocrinological examinations of this syndrome. We have recently treated a case of 48,XXYY karyotype and examined his pituitary function to clarify the diagnosis of acromegaly, based on the accompanying acromegalic appearance and tall stature. The GH provocation tests revealed a low GH response rather than hypersecretion.

Some problems have been revealed regarding the evaluation of GH provocation tests. For example, some discrepancies among GH provocation tests with low GH responses were found especially in cases of obesity or hypogonadism (7). On the other hand, acromegaloidism is recognized as a syndrome with acromegalic symptoms without GH hypersecretion or high serum somatomedin (8). The occurrence of acromegaloidism and its mechanism is not well clarified yet. No case of associated acromegaloidism has yet been reported in a patient of 48,XXYY syndrome. The GH provocation tests were compared before and after testosterone therapy; we discuss the relation between the GH response and

48,XXYY.

Case Report

A 24-year-old male was referred to Nara Medical University Hospital on July 1991 for an evaluation of acromegaly-like appearance (Fig. 1). He had been in generally good health and had no history of serious illness until his acromegalic appearance and tall stature were pointed out on the occasion of his visiting a local hospital for enterocolitis. He was born after a difficult labor at full term and had moderate neonatal jaundice. According to his mother's recollections, his mental development and motor ability were delayed, but his height growth was well developed compared with boys the same age. He graduated from a Japanese junior high school. He had showed some signs of sexual development such as acne and voice change between the ages of 17 and 18. After graduation from a special educational course for the handicapped, he had been working in an industrial company as a manual laborer. His behavior was gentle rather than rebellious. Neither his parent nor his grandparent has consanguineous marriages. His parents and his brother were normal in mentality and appearance. The heights of his father, mother and brother were 165 cm, 155 cm and 170 cm, respectively.

He was 184 cm (mean + 2.5 SD) in height and 77 kg in weight. His general appearance, and all of his extremities

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Fig. 1. Pictures of the patient on admission.

presented acromegaly; his heel pad was 23 mm in size. No gynecomastia was found. No visual field defect was found and his sense of smell was normal. Axillar hair was found and pubic hair was observed as Tanner stage 4 to 5. Each testis was 4 ml in volume and of soft consistency in the scrotum.

Urinalysis, peripheral blood cell counts, routine blood chemistries, electrocardiogram and chest X-ray examination were normal. The bone age had reached adult stage. No cauliflower-like findings of the finger bones were shown in X-ray films. The heel pad thickness was 23 mm (Fig. 2). No sellar enlargement, destruction nor tumor was found in skull X-ray, brain CT and MRI.

As shown in Table 1, the baseline of serum GH was normal and the serum somatomedin-C was in the low normal range. GH secretion in urine showed normal levels (3.1 pg/mg creatinine). Basal plasma gonadotropins were elevated, with LH level of 23.6 and FSH level of 42.3 mIU/ml. The plasma testosterone level was 1.0–2.0 ng/ml in the basal state (normal adult male, 2.7–10.7 ng/ml). Basal prolactin level was normal. In GH provocation tests (Fig. 3A,B,C,D), GH responses were low in the arginine test (0.1 ng/ml → 2.5 ng/ml), GRF test (0.1 ng/ml → 9.2 ng/ml) and Insulin tolerance test (ITT) (0.2 ng/ml → 0.2 ng/ml) [Arginine test, 30.0 g i.v., GRF test, 100 g i.v., ITT, 5 U i.v.]. In the LH-RH test (100 µg i.v.), LH (22.2 mIU/ml → 84.1 mIU/ml) and

Fig. 2. X-ray films of the hands and right foot.

FSH (47.1 mIU/ml → 65.9 mIU/ml) showed high basal levels with a normal response (Table 2A). The serum testosterone response (1.4 ng/ml → 2.1 ng/ml) was low to human chorionic gonadotropin (HCG) administration (5,000 U × 3 days i.m.). In the TRH test (500 µg i.v.), TSH response to TRH was normal (Table 2B). No paradoxical responses of GH to LH-RH and TRH tests were found (Table 2A,B). Plasma ACTH and serum cortisol were low to ITT despite marked hypoglycemia (Fig. 3C,D). Chromosomal study revealed a karyotype of nonmosaic 48,XXYY and No. 9 inv. (p11,q13) (Fig.

4). His parents' and brother's chromosomal study showed no abnormality in sex chromosome but the same anomaly in No. 9 chromosome was found in his mother.

The diagnosis was 48,XXYY syndrome with hypogonadism; testosterone therapy (testosterone enantate, 125 mg/2 weeks, s.c.i.) was started as is usually done in Klinefelter's syndrome. After one year of the therapy, he seemed to have developed socially and could work normally due to improved muscle power.

We performed the same GH and ACTH provocation

Table 1. Basal Hormone Levels

Plasma hormone		Normal range/values	
ACTH	(pg/ml)	41.3	4.4–48.0
Cortisol	(µg/dl)	4.5	2.7–15.5
GH	(ng/ml)	1.2	<0.5
Somatomedin-C	(U/ml)	1.16	0.36–2.00
FSH	(mIU/ml)	42.3	2.9–8.2
LH	(mIU/ml)	23.6	1.8–5.2
Testosterone	(ng/ml)	1.4	2.7–10.7
E ₂	(pg/ml)	<25	<85
TSH	(µU/ml)	1.1	0.24–3.70
T ₃	(ng/dl)	152.9	70–210
T ₄	(µg/dl)	9.1	4.5–12.3
free T ₄	(ng/dl)	1.0	0.8–2.1
PRL	(ng/ml)	15.5	<10
U-17KS	(mg/day)	3.6	5.8–21.3
U-17OHCS	(mg/day)	3.1	2.7–9.8
GH in Urine	(pg/mg CRE)	3.1	1.7–8.5

Table 2. The Results of LH-RH Test and TRH Test

A. LH-RH test

	Time (min.)				
	0	30	60	90	120
LH (mIU/ml)	22.2	81.8	84.1	67.5	53.2
FSH (mIU/ml)	47.1	60.7	62.2	65.9	59.2
GH (ng/ml)	0.1	0.2	0.1	0.1	0.1

B. TRH test

	Time (min.)					
	0	15	30	60	90	120
TSH (µU/ml)	3.0	15.5	16.3	12.5	8.8	6.5
PRL (ng/ml)	31.3	70.3	55.0	43.4	32.2	31.3
GH (ng/ml)	0.2	0.8	0.8	0.2	0.5	0.9

Fig. 3. GH and ACTH provocation tests. ○—○, △—△ shows before testosterone therapy and ●—●, ▲—▲ shows after therapy.

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Fig. 4. Giemsa-banded karyotype of leukocyte. The 48,XXYY pattern was consistently found, and No. 9 abnormality was present.

tests after the testosterone therapy to clarify the etiology of their abnormal responses. As shown in Fig. 3, the GH responses to arginine (0.4 ng/ml → 11.8 ng/ml) and GRF (0.2 ng/ml → 30.7 ng/ml) were normalized, but that to ITT still gave no response after 6 months of treatment. ACTH and cortisol responses to ITT revealed the same decreasing response as before treatment (Fig. 3D). The basal levels of ACTH and cortisol were normal and urinary 17-OHCS and 17-KS to the methylapone test revealed a normal response. These ITT studies were

performed twice at a six month interval with no change in the abnormal responses of GH, ACTH or cortisol.

Recently, we treated another case of 48,XXYY syndrome, a 15-year-old male associated with tall stature and slight mental retardation. We present a summary of the endocrinological data for comparison with the former patient.

This case showed Tanner 3 sexual development with a +3 SD height of matched age. Bone age was 15-years, equal to chronological age. Although his appearance

Table 3. Basal Hormone Levels of Another 48,XXYY Syndrome Patient at the Age of 12 and 15 Years

Plasma hormone	12 y	15 y	Normal range/value
ACTH (pg/ml)	<4.0	17.2	4.4–48.0
Cortisol (μg/dl)	4.6	7.6	2.7–15.5
GH (ng/ml)	0.9	0.1	<0.5
Somatomedin-C (U/ml)	9.52	—	0.44–2.18
(ng/ml)	—	476.0	156–1,094
FSH (mIU/ml)	27.6	40.5	2.9–8.2
LH (mIU/ml)	8.6	10.9	1.8–5.2
Testosterone (ng/ml)	2.6	1.0	2.7–10.7
E ₂ (pg/ml)	—	62.0	<85
TSH (μU/ml)	0.6	0.7	0.24–3.70
T ₃ (ng/dl)	165.1	195.2	70–210
T ₄ (μg/dl)	7.7	8.0	4.5–12.3
PRL (ng/ml)	3.0	—	<10

Table 4. GH, ACTH and Cortisol Responses to Arginine Test and ITT of Another 48,XXYY Syndrome Patient at the Age of 15 Years

A. Arginine test

	Time (min.)				
	0	30	60	90	120
GH (ng/ml)	0.8	0.2	0.1	0.4	12.8

B. ITT

	Time (min.)				
	0	10	20	30	35
ACTH (pg/ml)	19.2	—	—	18.9	27.4
Cortisol (μ g/dl)	9.3	7.5	6.9	6.3	19.4
GH (ng/ml)	0.1	0.1	0.1	0.1	7.8
Glucose (mg/dl)	94	65	35	28	74

was not acromagalic, his jaw and forehead were prominent. Table 3 shows the basal hormone levels of this case at the ages of 12 and 15 years. The ACTH, cortisol, GH levels and thyroid function were normal at both 12 and 15 years. The somatomedin-C level at 12 years was high (9.52 U/ml: RIA by the non-extraction method), and that at 15 years normal (476.0 ng/ml: RIA by the extraction method). FSH and LH levels were more elevated at 15 years than at 12 years. Testosterone level was lowered from 2.6 ng/ml at 12 years to 1.0 ng/ml at 15 years. These data indicate that hypogonadism had started by 15 years. The GH response to the arginine test was normal but that to ITT was low (Table 4). ACTH and cortisol responses to ITT were found. We will follow this case from the viewpoint of the relation between the GH or ACTH response to ITT and his growth.

Discussion

These cases showing 48,XXYY karyotype are the so-called double male syndrome, and are recognized as a variant type of classical Klinefelter's syndrome. Race and Sanger (9) speculated that the most probable etiological mechanism of 48,XXYY chromosomal constitutions would be successive meiotic nondisjunctional events during spermatogenesis, resulting in an XYY sperm. The present case had another chromosomal anomaly on No. 9 chromosome which was also found in his mother. This anomaly on No. 9 was regarded as a normal variant with no pathological significance. The 48,XXYY syndrome generally shows physical findings similar to those in 47,XXY syndrome, such as hypogonadism, gynecomastia, small testes, as well as unusual tallness, mental retardation, behavioral problems and

skeletal anomalies (2–5). Borgaonkar et al suggested that the phenotype of the 48,XXYY male results from a combination of 47,XXY and 47XYY features (3).

The present case presented hypogonadism, tall stature, acromegalic appearance and slight mental retardation. Furthermore, this case also showed abnormal responses of GH and ACTH to ITT. Therefore, it is necessary to consider acromegaloidism and the relationship between these abnormal responses and hypogonadism. The acromegalic appearance and tall stature observed in this case were sufficient findings to suspect acromagaly or gigantism, but the serum GH and somatomedin-C levels were not high. No paradoxical response of GH to TRH and LH-RH typically seen in acromagaly was observed. No sellar ballooning nor pituitary tumor were detected on image diagnosis. These findings should be recognized as a form of acromegaloidism, a condition which resembles acromegaly by its clinical manifestation without excess secretion of GH and somatomedins (8). No case of 48,XXYY associated with acromegaloidism has yet been reported. It is well known that the height of the 48,XXYY patients is greater than that of normal males or 47,XXY patients (3). The tall stature associated with this syndrome is observed early in childhood before puberty. 48,XXYY cases show hypogonadism after the age of about 16 years old with progressing testicular hyaline degeneration (3). The present case showed secondary sexual characteristics at 17, and was already tall for his age. The etiology of his tall stature may be due to the chromosomal abnormality rather than the delay of epiphyseal closure accompanied by hypogonadism. The other case of 48,XXYY described above showed tall stature and a high somatomedin-C level, but a normal GH. This case may provide a insight into about the tall stature of 48,XXYY syndrome as we follow his growth.

The GH response was interesting; GH provocation tests revealed rather low GH responses or no responses, and the GH responses were normalized except to ITT after testosterone therapy. GH secretion is controlled by GRF and somatotropin release inhibiting factor (SRIF). These GH secretory mechanisms are enhanced by the development of puberty, particularly by the increasing serum testosterone (10) and estradiol (11) levels.

We have treated 4 cases of hypogonadotropic hypogonadism with low GH responses to ITT, which were restored after normalization of serum testosterone levels by gonadotropin therapy (7). We speculate that the mechanism of hypoglycemia-induced GH secretion may require the effect of testosterone for maturation and maintenance. The other case of 48,XXYY syndrome presented showed a normal GH response to arginine and a low response to ITT. ACTH and cortisol response to ITT were normal. In the present case, the GH response to ITT was not restored after testosterone therapy. Furthermore, the lowered responses of ACTH and

cortisol to ITT also remained the same as before treatment. These results indicated the possibility that the hypoglycemia-induced GH and ACTH secretion route could be a congenital defect but is not specific to 48,XXYY syndrome. In spite of this defect, the present case did not show either GH or ACTH deficiency, because the other GH and ACTH stimulation routes were not impaired.

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