A Male Patient Presenting with Major Clinical Symptoms of Glucocorticoid Deficiency and Skeletal Dysplasia, showing a Steroid Pattern Compatible with 17 α -Hydroxylase/17,20-Lyase Deficiency, but without Obvious CYP17 Gene Mutations

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Abstract. We report the case of a 17-year-old boy with delayed puberty, who presented a complexity of clinical problems. An analysis of steroid hormones led to a diagnosis of 17 α -hydroxylase/17,20-lyase deficiency (17OHD). Unlike typical cases of 17OHD, however, the patient had pubertal development without medical intervention. In addition, he never exhibited the symptoms of mineralocorticoid excess, showing instead the symptoms of glucocorticoid deficiency, including fatigability, emaciation, and weight-loss induced by minor infection. He also had dysmorphic features, which comprised marfanoid habitus, arachnodactyly and putative craniosynostosis. The combination of these malformations substantially resembled that of Shprintzen-Goldberg syndrome. Direct sequencing of the CYP17 gene did not reveal any significant aberrations in the exons or exon-intron boundaries. We speculate that the association of partial combined 17OHD with the Shprintzen-Goldberg phenotype in the present patient may result from an aberration of a hitherto unknown gene that controls both steroid hormone synthesis and skeletal development.

Key words: 17 α -hydroxylase/17,20-lyase deficiency, Adrenal failure, Shprintzen-Goldberg syndrome, CYP17
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A SINGLE polypeptide, P450c17 α , encoded by a single copy gene (CYP17) located on chromosome 10q24–25, catalyzes both 17 α -hydroxylation and 17,20-lyase reactions in steroid biosynthesis in the gonads and the adrenal cortex [1]. Total impairment of P450c17 α function, namely, complete 17 α -hydroxylase/17,20-lyase deficiency (complete 17OHD), leads to the symptoms of mineralocorticoid (MC) excess combined with those of sex steroid deficiency [1, 2]. Overproduction of MC, particularly of 11-

deoxycorticosterone (DOC), causes hypertension and hypokalemia. Affected females (46,XX) usually present with absence of sexual development or primary amenorrhea, while affected males (46,XY) manifest either female external genitalia or ambiguous genitalia. In addition to many reports of complete 17OHD, there have been several case reports of partial 17OHD, which is characterized by modestly conserved sex steroid synthesis, along with the presence of menstruation, if not regular, in females and muscularization to some degree in males [3–5]. Hypertension and hypokalemia are cardinal features in partial 17OHD, as in the complete form. We report here a male (46,XY), whose endocrinological manifestations were those of partial combined 17OHD with spontaneous pubertal development, but who had unusual clinical manifestations, comprising

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the symptoms of glucocorticoid deficiency and generalized skeletal dysplasia. Molecular analysis of the *CYP17* gene did not reveal any mutation of the gene. The pathogenesis of this patient's unusual combination of abnormalities is discussed.

Case report

A 17-year-old Japanese boy was examined because of general fatigue, susceptibility to infection, and emaciation. He was born to healthy, non-consanguineous parents. Two younger brothers were healthy. The family history was not noteworthy. The patient was reported to be unremarkable in the perinatal period, except for bilateral cryptorchidism. He showed normal psychomotor development: he spoke a few comprehensive words at 9 months of age and walked without support at 15 months. He underwent bilateral orchidopexy at 6 years of age. At that time, he was noted to have an inconspicuous penis, which led to the first endocrinological evaluation. Neither hypertension (92/62 mmHg) nor hypokalemia (serum K=5.0 mEq/l) was evident. The serum cortisol level in the early morning was adequate (14.8 μ g/dl). Testosterone response to exogenous hCG (testosterone 32.9 ng/dl after hCG 3,000 IU/m² i.m. 3 days) was inappropriate, so that hypogonadism was diagnosed. Thereafter, a gradual decline in the patient's growth rate led to the second endocrinological study at 13 years of age. At that time, the patient's height was 142.5 cm (−1.9SD), and his weight was 27.5 kg. Blunted testosterone response to hCG (testosterone 34.0 ng/dl after hCG 3,000 IU i.m. 3 days) associated with normal gonadotropin levels (LH 3.5 IU/l, FSH 2.4 IU/l) was found. Although GH secretion was not impaired, recombinant GH therapy was attempted. After a few months of GH administration, the patient showed commencement of pubertal development and an increased growth rate. At 16 years of age, he exhibited emaciation, general fatigue, and unusual weight-loss related to episodes of minor infection. Withdrawal from GH therapy at 17 years of age did not ameliorate these symptoms. On admission, the patient's height was 163.6 cm (−1.2SD), weight 36.5 kg, head circumference 51 cm (−3.8SD), and arm span 170.0 cm. He was normotensive (122/68 mmHg), and presented normal adult external

genitalia with each testis having a volume of 12 ml (Prader's orchidometer). Pubic hair was graded as Tanner 4, whereas axillary hair was Tanner 3. Gynecomastia was absent. He showed abnormal facies (Fig. 1), along with arachnodactyly, clubfeet, contracture of bilateral toes (3rd–5th), and restricted flexion in the DIP joints of the hands. He had neither ectopia lentis nor cardiac murmur. Chromosome analysis showed a normal karyotype, 46,XY. Serum electrolyte concentrations (Na 141 mEq/l, K 3.9 mEq/l) were normal. Other routine laboratory findings were unremarkable. Endocrinological evaluation yielded the following results: first, circulating levels of 17-deoxysteroids (pregnenolone, progesterone, DOC, 18OH-DOC and corticosterone) were apparently high both before and after rapid ACTH stimulation, whereas those of cortisol, dehydroepiandrosterone (DHEA) and androstenedione were low for his age (Table); second, the cortisol level failed to respond to CRH loading despite its sufficient basal concentration, whereas ACTH showed an exaggerated response to CRH loading (Fig. 2). The

Fig. 1. A photograph of the patient at 17 years of age showing malformed, small, and low-set ear and large nose. In addition, he exhibited wide palpebral fissure and hypotelorism, which are not shown in this figure.

Table 1. Serum steroid levels before and after rapid ACTH stimulation*

	baseline value	(reference range**)	60 min. after ACTH stimulation	(reference range**)
pregnenolone (ng/ml)	2.28	(0.1–0.3)	3.87	
progesterone (ng/ml)	16.10	(0.1–0.3)	46.30	
DOC (ng/ml)	0.67	(0.05–0.14)	1.17	(0.19–0.46)
corticosterone (ng/ml)	22.2	(1.0–5.0)	69.5	(1.5–20.0)
18OH-DOC (ng/ml)	0.91	(0–0.10)	NT	
aldosterone (ng/dl)	19.0	(4–12)	NT	
17OH-pregnenolone (ng/ml)	8.91	(0.32–2.97)	10.70	(2.20–8.59)
17OHP (ng/ml)	22.2	(0.51–1.90)	39.1	(1.05–2.30)
11DOF (ng/ml)	0.98	(0.14–1.15)	1.76	(0.87–2.07)
cortisol (μ g/dl)	9.7	(5.0–15.0)	12.1	(18.0–27.0)
DHEA (ng/ml)	1.41	(1.02–4.01)	2.06	(1.93–5.09)
androstenedione (ng/ml)	0.52	(0.57–1.51)	0.73	(0.78–2.15)
testosterone (ng/dl)	298	(278–702)	NT	

* 250 μ g of ACTH (Cortrosyn) was infused intravenously at 9:00 a.m. Blood samples were drawn via an indwelling venous catheter before and 60 min. after the injection. Each steroid, except 17OHP, was measured by specific RIA with (pregnenolone, DOC, corticosterone, 18OH-DOC, 17OH-pregnenolone, 11DOF, androstenedione) or without (progesterone, aldosterone, cortisol, DHEA, testosterone) extraction. 17OHP was measured by EIA.

** The reference range was adopted from data reported by Lashansky G *et al.* (1991, *J Clin Endocrinol Metab* 73: 674–686), Peterson RE *et al.* (1985, *N Engl J Med* 313: 1182–1191) and Kater CE *et al.* (1994, *Endocrinol Metab Clin North Am* 23: 341–357)

17OHP: 17-hydroxyprogesterone; 11DOF: 11-deoxycortisol; NT: not tested

Fig. 2. ACTH and cortisol responses to CRH stimulation*

* Human CRH of 2 μ g/kg was infused intravenously at 8:00 a.m. Blood samples were drawn via indwelling venous catheter. Plasma ACTH concentration was measured by specific RIA.

** Reference value was adopted from data in children of non-endocrine short stature reported by Tanaka T *et al.* (1993, *Endocrine J* 40: 581–589) Vertical lines denote mean $\pm$ SEM.

Fig. 3. a-d: Skeletal radiographs at 17 years of age
a) arachnodactyly with mild undertubulation of the short tubular bones
b, c) Craniosynostosis was suspected because of shortening of the anterior cranial fossae and invisibility of the coronal sutures.
d) bowing of the radius and radial head deformity

diurnal variation in the cortisol level was not impaired (cortisol at 0 AM: 2.7 μ g/dl); third, LH and FSH were very high (58.3 IU/l, 62.4 IU/l, respectively) despite a lower-than-normal level of testosterone. The aldosterone level was also high, but plasma renin activity (PRA) was normal (1.7 ng/ml/hr). Urinary 17-deoxysteroid metabolites were increased (data not shown) whereas daily urinary free cortisol was lower normal (32.2 μ g/24 hr). Consequently, partial combined 17OHD was diagnosed. Radiographic examination (Fig. 3) showed generalized skeletal changes, consisting of arachnodactyly with undermodeling of the short tubular bones and joint deformities. A mild degree of craniosynostosis was highly suspected because of shortening of the skull base, although the cranial sutures were not completely obliterated. These skeletal abnormalities, together with the patient's dysmorphic features, led to a diagnosis of Shprintzen-Goldberg syndrome (marfanoid craniosynostosis syndrome).

Method

Genomic DNA was prepared from white blood cells by standard techniques. The exons and exon-intron boundaries of the *CYP17* gene were amplified by polymerase chain reaction (PCR) with oligonucleotide primers, as reported by Monno *et al.* [6]. Each PCR with a Perkin-Elmer/Cetus Thermal Cycler (Perkin-Elmer, Norwalk, CT) was performed as follows: 40 cycles of 15 seconds at 96°C, 30 seconds at 55°C and 90 seconds at 72°C. PCR products were resolved by 1.5% agarose gel electrophoresis and directly sequenced using an automated DNA sequencer (Applied Biosystems, Inc., Foster City, CA) with Taq DyeDeoxy sequencing reagents (Applied Biosystems, Inc.).

Results

No hitherto reported mutations, including nucleotide substitution, splicing mutation, small insertion and small deletion, and novel mutation, were identified in the coding regions or the exon-intron boundaries (according to the *CYP17* sequence data reported by Picado-Leonard *et al.* [7] and by Kagimoto *et al.* [8]).

Discussion

The high 17-deoxysteroid levels in the serum and urine of the present patient, with the poor cortisol response to the exogenous ACTH and CRH as well as the lower daily urinary free cortisol level, indicated that 17 α -hydroxylation reaction in his adrenal cortex was disturbed. On the other hand, the existence of androgen synthetic defect in his adrenal gland and testis was demonstrated by impaired responses of DHEA and androstenedione to the rapid ACTH test and by high gonadotropin levels, respectively. Accordingly, we diagnosed this boy as having combined 17OHD. Since his testosterone production was conserved to such an extent that he experienced spontaneous puberty, a more precise diagnosis would be partial combined 17OHD. His growth delay, which is uncommon in 17OHD, may be attributable to the accompaniment of the skeletal dysplasia discussed later.

Regarding the hormonal data described above, some unusual issues exist. First, moderately high 17-hydroxyprogesterone (17OHP) and 17OH-pregnenolone levels may be reminiscent of the report of multiple defects in steroid-biosynthesis by Peterson *et al.* [9], namely, combined deficiencies of 17 α -hydroxylase, 17,20-lyase and 21-hydroxylase. Anecdotal description of similar examples was also reported [10, 11]. These reported cases of multiple defects closely resemble those in our patient in not only basal 17OHP and 17OH-pregnenolone values but also their unexaggerated responses to ACTH. In addition, two 46,XY cases among them presented with incomplete male pseudohermaphroditism as in our patient. This particular combination may derive from a defect in the membrane-bound flavoprotein termed P450 reductase, which provides electrons to all these microsomal enzymes [12]. But since direct evidence of it is lacking, we assume that recognition of this combination as a distinct clinical entity should await deliberate discussion. On the other hand, it may be possible that at least some of the circulating 17 α -hydroxylated intermediates in such patients were produced in gonads under stimulation with high levels of gonadotropins. In fact, three months of dexamethasone administration (0.5 mg a day) to our patient had failed to suppress 17OHP (11.5 ng/ml) and 17OH-pregnenolone (2.64 ng/ml) to below the

normal range, but his ACTH level had been below the detection limit at that time. The validity of the association of 21-hydroxylase deficiency in our patient therefore needs further investigation.

The second unusual aspect in our patient is the normal basal cortisol level, despite the impaired response to ACTH and CRH. Since his circulating cortisol level declined to 2.7 $\mu\text{g/dl}$ at midnight, interference of other intermediates in the radioimmunoassay system seems unlikely, and this can also be further supported by the lower, but normal urinary free cortisol level. We infer that his basal cortisol level had been kept just at lower normal at the expense of over-secretion of ACTH, and this condition could result because the 17 α -hydroxylase defect was partial.

A feature of our patient was the conspicuous symptoms of GC deficiency instead of those of MC excess. 17OHD does not usually manifest as GC insufficiency, despite impaired cortisol synthesis. A search of the literature confirmed only 3 reported cases of 17OHD with manifestations of GC insufficiency, such as hypoglycemia and emaciation [13–15]. This paradox has been attributed to enhanced production of corticosterone (so called “back up” GC), which is mainly secreted from the zona fasciculata through increased ACTH stimulation.

In patients with 17OHD, corticosterone is usually 50- to 100-fold the normal range and is sufficient to provide adequate GC activity. However, corticosterone in our patient (22.2 ng/ml) was lower than that of previously reported cases (40–300 ng/ml) [2], which accounts for the conspicuous symptoms of GC deficiency and ultimately the paucity of “back up” GC in our patient. This lower corticosterone level must be the result of somewhat conserved 17 α -hydroxylase activity. That is to say, since the impairment of 17 α -hydroxylase is not complete, ACTH-dependent production of corticosterone in the adrenal cortex should be limited in our patient. Lower DOC (0.67 ng/ml) and higher aldosterone (19.0 ng/dl) concentrations in his serum, compared to those of reported 17OHD cases (0.3–5.0 ng/dl and 0.2–8.5 ng/dl, respectively [2]), can be explained by the same concept. Slightly high DOC yielded to the inconspicuousness of hypertension and hypokalemia, which in turn caused aldosterone not to be suppressed.

Since latent GC deficiency may deteriorate into

acute adrenal crisis under serious stress, correct diagnosis and proper management of latent GC deficiency are of vital importance. It may be advisable to exclude partial 17OHD in cases of delayed or incomplete pubertal development, even if symptoms of excess MC are absent.

The molecular basis of 17OHD has been well established. To date, 26 mutations of the *CYP17* gene have been reported in patients of different ethnic backgrounds with 17OHD, including missense mutations, nonsense mutations, small deletions, and small insertions, and 2 splice site mutations [16–21 and references therein].

In our patient, direct sequencing, covering the entire coding regions and exon-intron boundaries, did not reveal any mutation of the *CYP17* gene. All hitherto known mutations of the *CYP17* gene have been shown to be in the coding regions and splicing sites of the introns. Nevertheless, it should be emphasized that most molecular investigations of the *CYP17* gene have dealt with patients with the complete form of 17OHD, and analysis of the partial form of 17OHD is limited [5, 22]. Consequently, the presence or absence of mutation(s) in the intron or promoter/enhancer regions of the *CYP17* gene should be pursued in our patient, as well as in other patients with partial 17OHD.

It is more tempting to postulate the hypothesis that 17OHD in our patient was caused by a defect in a hitherto unknown gene, not of the *CYP17* gene, although this is highly speculative. The presumed gene aberration may impair the function of a transcription factor that binds to the regulatory sequence of the *CYP17* gene. In this regard, the skeletal malformations (the SGS phenotype) in our patient are of substantial interest because the 17OHD and the SGS phenotype in our patient may be causally related to one another.

SGS is a rare constitutional bone disease, characterized by the combination of marfanoid habitus with craniosynostosis [23–25]. SGS may be an allelic disorder of Marfan syndrome, because mutations of the fibrillin-1 gene (assigned to 15q21.1) have been recently reported in some patients with SGS [26], although it remains inconclusive whether the mutations are disease-causing [27]. To date, no association with 17OHD has been reported in either SGS or Marfan syndrome, and the concurrence of 17OHD with the SGS phenotype in our patient may be for-

tuitous. But, it is conceivable that SGS is genetically heterogeneous, and in this respect there is a suggestive report regarding a relationship between 18q deletion syndrome and 17,20-lyase deficiency [28]. The authors demonstrated the absence of 17,20-lyase activity in testicular tissue from a child with 18q deletion syndrome. They also found low DHEA-sulfate levels in other six patients with 18q deletion, and speculated that regulatory components of 17,20-lyase may be located on chromosome 18, distal to band q21. Since the clinical symptoms of 18q deletion and those of our patient overlap each other (microcephaly, ear anomalies, and arachnodactyly), it may be that our patient has a submicroscopic deletion in the 18q region.

Consequently, the unusual clinical constellation of our patient, comprising the partial form of combined 17OHD and a mild SGS phenotype, may be the result of a mutation of a novel regulator gene that controls both 17 α -hydroxylation/17,20-lyase activities and skeletal morphogenesis, which may be located in the 18q region.

Conclusion

A case of partial 17OHD is reported. The endocrinological characteristics were unusual latent GC deficiency without MC excess, as well as delayed puberty, and the patient had generalized skeletal changes. The molecular basis of this case remains unknown, and further research is needed for clarification.

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