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Case Report

Two girls with a neonatal screening-negative 21-hydroxylase deficiency requiring treatment with hydrocortisone for virilization in late childhood

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Abstract. Herein, we report two girls with a neonatal screening (NS)-negative 21-hydroxylase deficiency (21-OHD) requiring treatment with hydrocortisone due to virilization that developed in late childhood. Patient 1 was born prematurely on the 30th gestational week with normal external genitalia at birth. She passed the NS for 21-OHD. At 6 yr of age, she was referred to a hospital for evaluation of premature pubarche and clitoromegaly. Her diagnosis was central precocious puberty, and GnRH agonist was initiated. However, her symptoms did not improve despite treatment for over 4 years. She was then referred to our hospital where she was diagnosed with 21-OHD. Although she was started on hydrocortisone therapy, her adult height reached only 140 cm (−3.4 SD). Patient 2 was delivered at 37 weeks of gestation and passed the NS for 21-OHD. She was referred to a hospital because of premature pubarche at the age of 6 yr. She was diagnosed with 21-OHD, and hydrocortisone replacement therapy was initiated. Her present height at 13 yr of age is 148 cm (−1.3 SD). These cases reminded us that the possibility of 21-OHD should be considered when patients show premature pubarche or precocious puberty, even if they passed the NS test for 21-OHD.

Key words: congenital adrenal hyperplasia, 21-hydroxylase deficiency, neonatal screening, premature birth, secondary central precocious puberty

Introduction

Congenital adrenal hyperplasia (CAH) is one of the most common inborn errors of metabolism. It results from a deficiency of enzymes or cofactor proteins required for cortisol synthesis, and 90% to 95% of patients with CAH have 21-hydroxylase deficiency (21-OHD) (1, 2). There are three clinical phenotypes of 21-OHD: salt-wasting (SW), simple virilizing (SV), and nonclassical (NC). A cardinal feature of the SW and SV forms of 21-OHD in newborn females is the masculinization of the external genitalia at birth. Missed diagnosis of the SW form leads to an increased risk of early neonatal morbidity and mortality due to a life-threatening adrenal crisis. If the SV form of 21-OHD is not recognized and treated, virilization in female patients and precocious puberty due to overproduction of androgens will become a major clinical problem (3). In contrast, patients with the NC form do not present with genital abnormalities during the newborn period (3). Therefore, it is impossible to detect the NC form based on the clinical presentation of abnormalities at birth. Patients with the NC form may

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present with premature pubarche, hirsutism, virilism, acne, and menstrual irregularities later in life, or they may be asymptomatic (4).

Neonatal screening (NS) for CAH using blood samples collected on filter papers first became available in the US in the 1970s (5, 6). In Japan, it has been performed since the 1980s, and these NS programs have many recognized benefits (7). The primary purposes of NS for CAH are to detect patients with the SW form of 21-OHD and to prevent adrenal crisis in patients with the SW form as well as gender misassignment of 46, XX female neonates with the SW and SV forms. On the other hand, NS may miss some patients with the NC and SV forms by measuring the levels of 17-hydroxyprogesterone (17-OHP) on filter paper samples (8). Herein, we report on 21-OHD that was not detected in the NS for CAH in two female neonates who required treatment with daily hydrocortisone for virilization in late childhood.

Case Report 1

The patient was the second child of Japanese non-consanguineous parents. She was born at 30 weeks of gestation as a younger dizygotic twin sister. Her birth weight and length were 890 g (−2.5 SD) and 32.0 cm (−1.8 SD), respectively. Her external genitalia were normal, and no skin pigmentation was observed at birth. The values of 17-OHP on filter paper at 5 days of life measured by both direct and extraction procedures were elevated (15.4 ng/mL in the direct assay, reference value <6.0 ng/mL; 4.2 ng/mL in the extraction assay, reference value <3.0 ng/mL). However, the level on reexamination at discharge from the hospital (103 days of life) was reported to be normal (5.3 ng/mL in the direct assay), and she passed the newborn screening. The patient had no episodes of adrenal crisis during infancy.

She was referred to the hospital because of clitoromegaly and premature pubarche when she was 6 yr and 8 mo old. On physical examination, she had Tanner stage 2 pubic hair growth but no breast development. Her height was 113 cm (−0.8 SD), and her weight was 19 kg (−0.7 SD). Her linear growth had accelerated since she was about 6 yr old (**Fig. 1**), and her bone age (BA) was greater (9 yr and 0 mo) than her chronological age (CA: 6 yr and 8 mo). In the GnRH stimulation test, peak LH was 10.4 (reference range for pubertal children: 5.70–18.50) mIU/mL, and peak LH-to-FSH ratio was 0.68 (reference range for pubertal children: 0.74–1.4). The values of serum estradiol and dehydroepiandrosterone sulfate (DHEA-S) were 11 pg/mL and 208 μg/dL, respectively. No intracranial or intraperitoneal lesions were observed on MRI. Finally, the onset of central precocious puberty (CPP) was diagnosed, and gonadal suppression therapy with GnRH agonist was performed for 4 years. The size of the clitoris did not decrease, and pubic hair growth was not stopped.

She was referred to Osaka University Hospital when she was 10 yr and 11 mo old. Her height was 139.5 cm (−0.6 SD). BA (13 yr and 0 mo) was greater than CA (10 yr and 11 mo). She had facial acne, Tanner stage 4 pubic hair but no breast development, marked clitoromegaly (width, 15 mm; length, 33 mm), and Prader stage 2 virilization. Serum testosterone, DHEA-S, and 17-OHP levels were elevated (**Table 1**). An ACTH stimulation test revealed impaired cortisol response and elevated baseline and peak 17-OHP levels (**Table 2**). A urinary steroid profile revealed increased pregnanetriolone and 11-hydroxyandrosterone levels, which were compatible with a diagnosis of 21-OHD. A genetic study of *CYP21A2* was performed by extracting DNA from whole blood, followed by PCR amplification and direct DNA sequencing. The patient was found to be compound heterozygous for the P30L and IVS2-13A/C>G mutations. Therefore, the results of these tests and her clinical history of normal external genitalia at birth led to a diagnosis of NC21-OHD. Because she presented with virilization, treatment with hydrocortisone (20 mg/day, 17 mg/m^2/day) was initiated at 10 yr and 11 mo of age with subsequent dose adjustments. The clitoris decreased in size (width, 12 mm; length, 18 mm) after 3 months of hydrocortisone treatment. Menarche occurred at 11 yr and 10 mo. However, her linear growth stopped when her height reached 140 cm (−3.4 SD).

Case Report 2

The patient was born to healthy non-consanguineous Japanese parents. Her family history was unremarkable, and her older sister was healthy. The patient was delivered at 37 weeks of gestation. Her birth weight was 2,754 g (−0.1 SD). Immediately after birth, her father was concerned about the clitoromegaly of the patient, but her mother did not notice anything unusual, and the patient did not undergo any particular examination. She passed the NS test for CAH based on the 17-OHP values on filter paper at 5 days of life. There were no episodes of adrenal crisis during infancy.

She was referred to the hospital because of pubic hair growth when she was 6 yr and 4 mo old. She had Tanner stage 3 pubic hair growth and clitoromegaly (width, 8 mm; length, 15 mm) but no breast development. Her height was 114 cm (−0.1 SD), and her weight was 20 kg (−0.1 SD). Her BA (9 yr and 3 mo) was greater than her CA (6 yr and 4 mo) (**Fig. 2**). Serum testosterone, DHEA-S, and 17-OHP levels were elevated (**Table 3**). An ACTH stimulation test revealed an impaired cortisol response and elevated baseline and peak 17-OHP levels (**Table 4**). The results of a urinary steroid profile analysis and genetic study of *CYP21A2* were compatible with the diagnosis of 21-OHD. She was compound heterozygous for the P30L mutation and 8-bp deletion in exon 3. Hydrocortisone replacement therapy was started due to virilization when she was 6 yr and 6 mo old. When she showed breast development at the age of 10 yr, a GnRH stimulation test was performed. The peak LH was 4.44 mIU/mL, and peak LH-to-FSH ratio was 0.91. Because she was considered to have entered puberty with a relatively short stature (127 cm, −1.8

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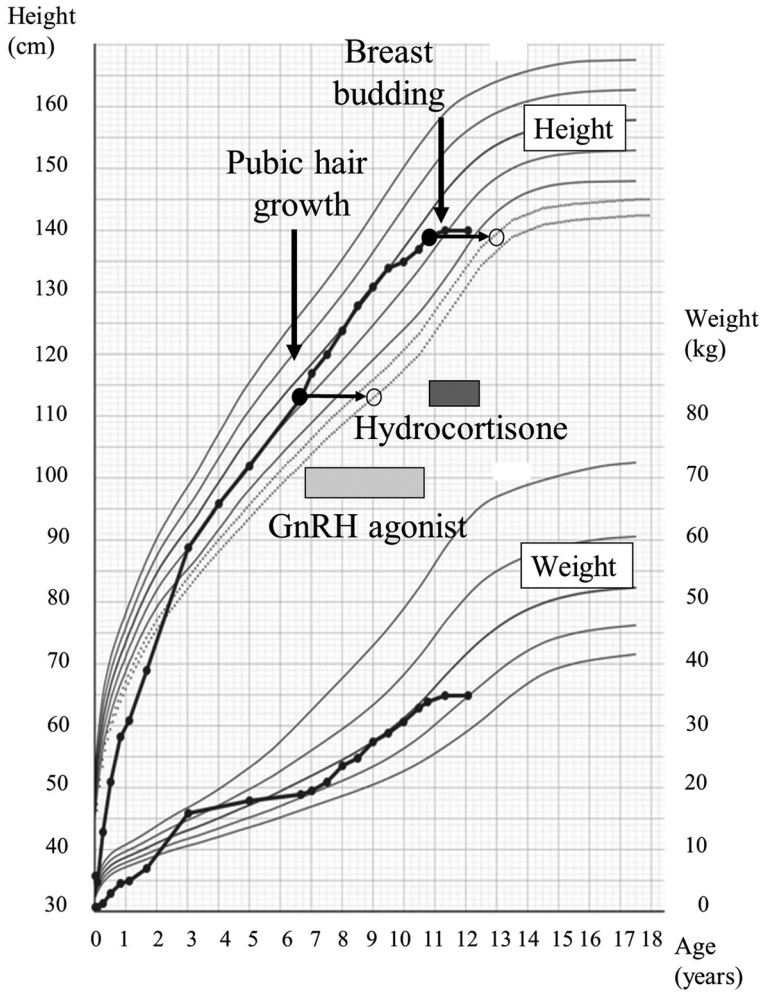

Fig. 1. Growth chart and clinical events of case 1. The patient's linear growth accelerated since about the age of 6 yr. GnRH agonist was started at 6 yr and 10 mo and was stopped at 10 yr and 8 mo. Hydrocortisone was initiated at 10 yr and 11 mo. Breast budding and menarche occurred at 11 yr and 2 mo and 11 yr and 10 mo, respectively. Her adult height was 140 cm. Open and closed circles represent bone age and chronological age, respectively.

Table 1. Laboratory data in case 1 at the age of 10 yr and 11 mo

LH	4.1 mIU/mL
FSH	6.9 mIU/mL
Estradiol	13 pg/mL
Testosterone	1.27 ng/mL
ACTH	61 pg/mL
Cortisol	8.0 mg/dL
DHEA-S	382.1 μg/dL
17-OHP*	19.2 ng/mL
PRA	4.3 ng/mL/hr
Aldosterone	142.2 pg/mL
IGF-1	399 ng/mL

DHEA-S, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; PRA, plasma renin activity. * detected in serum by ELISA.

Table 2. The result of the ACTH stimulation test in case 1

	Baseline	Peak
Cortisol (mg/dL)	7.4	7.8
17-OHP* (ng/mL)	44.3	62.4

17-OHP, 17-hydroxyprogesterone. * detected in serum by ELISA.

SD), gonadal suppression therapy with GnRH agonist was administered for 2 years to improve adult height.

She was referred to our hospital at the age of 12 yr, because she moved to Osaka. Her height was 138.9 cm (−2.1 SD), and BA was 11 yr and 1 mo (CA: 12 yr and 3 mo). Her external genitalia showed clitoromegaly (width, 10 mm; length, 20 mm). The dose of hydrocortisone has been adjusted, and she is currently supplemented with 20 mg/day (16 mg/m^2/day). Her present height is 148 cm (−1.3 SD) at the age of 13 yr.

Discussion

The SW, SV, and NC forms of 21-OHD are all caused by homozygous or compound heterozygous mutations in

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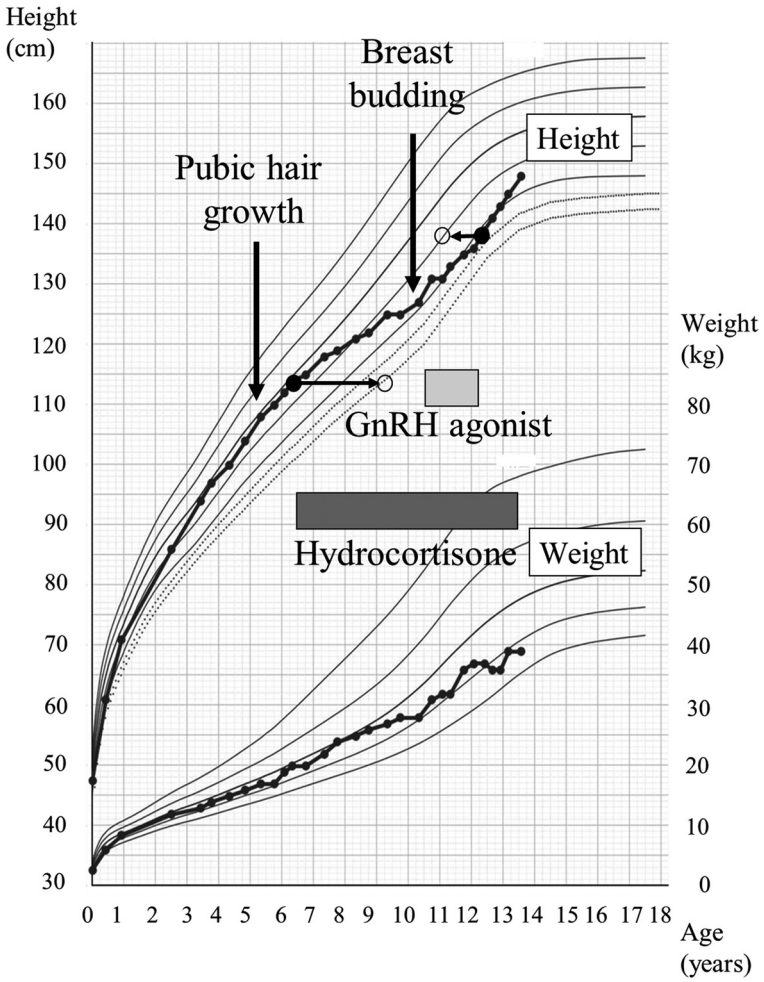

Fig. 2. Growth chart and clinical events of case 2. Hydrocortisone was initiated at 6 yr. Breast budding occurred at 10 yr. GnRH agonist was started at 10 yr and 7 mo and was stopped at 12 yr and 3 mo. Open and closed circles represent bone age and chronological age, respectively.

Table 3. Laboratory data in case 2 at the age of 6 yr and 4 mo

LH	0.09 mIU/mL
FSH	0.20 mIU/mL
Estradiol	10 pg/mL
Testosterone	1.06 ng/mL
ACTH	65.9 pg/mL
DHEA-S	93 μg/dL
17-OHP*	45.5 ng/mL
IGF-1	118 ng/mL

DHEA-S, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone. * detected in serum by ELISA

Table 4. The result of the ACTH stimulation test in case 2

	Baseline	Peak
Cortisol (mg/dL)	7.9	8.7
17-OHP* (ng/mL)	82.0	135

17-OHP, 17-hydroxyprogesterone. * detected in serum by ELISA.

the human 21-hydroxylase gene (*CYP21A2*). The clinical phenotype correlates with the less severely mutated allele and, consequently, with residual 21-hydroxylase activity (9). It has been reported that 69% of 21-OHD patients with P30L mutations had the NC form, and 23% had the SV form (10). However, in some cases, the NC and SV forms are difficult to distinguish (11). In terms of a hormonal assay, peak 17-OHP values of 10 to 100 ng/mL and more than 100 ng/mL in the ACTH stimulation test are an endocrinological criterion of the nonclassical and classical forms of 21-OHD, respectively (12).

In case 1, endocrinological and genetic findings, and clinical history in which the features of 21-OHD at birth including external genitalia abnormality were absent, were compatible with a diagnosis of the NC form. In case 2, the presence of neonatal genital abnormality was unclear because only her father was concerned about her clitoromegaly at birth. Taken together with the genetic finding of gene mutation (P30L/8-bp del), which can indicate either the NC or SV form of 21-OHD (10), the unclear presence of neonatal genital abnormality makes

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it difficult to clearly identify the form of 21-OHD in case 2, although the peak 17-OHP value in the ACTH stimulation test corresponds to the SV form. Her case was considered to straddle the classical-nonclassical boundary.

The two present cases passed the NS for CAH and were diagnosed with CAH due to virilization in late childhood. It was reported that the false-negative rate of NS for classical CAH was 2–9% in Europe, and false-negatives were more common among patients with the SV form of 21-OHD (11, 13, 14), although the false-negative rate in Japan may not be similar to that in Europe. Furthermore, the rate of NC form undetected by NS was much higher than that of classical CAH undetected by NS. In a Japanese nationwide survey, 4 of 15 patients with the NC form showed normal 17-OHP values in NS (15). Moreover, a long-term cohort study in Sweden demonstrated that the NC form was undetected in NS in 63% of patients diagnosed with the NC form (8). Therefore, we cannot exclude 21-OHD even if 17-OHP values in NS are within normal limits, especially in cases of NC or SV form, as previously reported.

In case 1, the 17-OHP value was elevated at 5 days but decreased to within the normal range at 103 days. Follow-up was discontinued because the patient had no features suggestive of CAH. A low positive predictive value (PPV), especially in preterm infants, is a major concern regarding the use of NS for CAH. According to some studies, the PPV in preterm infants was 0.4–2.0% (16–18). Therefore, it is difficult to diagnose 21-OHD using a single positive test in preterm infants. A previous study suggested that preterm infants should be screened at several time points to increase the PPV (19). In Japan, repeat testing is required for preterm infants (20). It was also reported in the Netherlands that adopting the cutoff values for 17-OHP stratified by gestational age improved the PPV of NS (21). NS-positive infants are generally regarded as normal if 17-OHP values are within normal limits on reexamination. A previous study reported that infants with transient serum hyper-17-hydroxyprogesteronemia (hyper-17-OHPemia) had no clinical signs and gene mutations of 21-OHD; thus, no further investigations seemed to be necessary for infants with transient serum hyper-17-OHPemia (22). Therefore, it is difficult to diagnose the NC form correctly by NS even if, as in case 1, 17-OHP values were elevated at the time of the first blood sampling. The detection of the NC form is not the essential purpose of NS for CAH, because patients with the NC form of 21-OHD are generally not treated until they show symptoms of androgen excess (23).

Patient 1 presented with secondary CPP due to chronic androgen excess, which is recognized in cases of undertreated 21-OHD (24). Chronic hyperandrogenemia in these patients induces hypothalamic-pituitary axis activation, leading to CPP (24). Therefore, in case 1, the possibility of 21-OHD should have been considered when CPP was diagnosed by the GnRH stimulation test and gonadal suppression therapy was initiated. A recent study reported that no single clinical characteristics or laboratory parameters were able to accurately differentiate between idiopathic CPP and CPP associated with the NC form, although basal androgens were significantly higher in the NC group (25). Further examination, including the ACTH stimulation test, should be considered in patients with CPP accompanied by hyperandrogenemia. It has also been reported that delayed diagnosis of 21-OHD leads to the advancement of BA and reduced adult height (26, 27). Patient 1 had a short adult height (140 cm, −3.4 SD), but the present height of patient 2 is 148 cm (−1.3 SD) at 13 yr. This suggests that earlier diagnosis and intervention might have contributed to the achievement of better height gain in patient 2.

Conclusion

We described the cases of two female patients with NS-negative 21-OHD who required treatment with daily hydrocortisone for virilization in late childhood. These cases reminded us that the possibility of 21-OHD should be considered when patients present with premature pubarche or precocious puberty, even if they passed the NS test for 21-OHD.

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