Longitudinal analysis of growth and body composition of Japanese 21-OHD patients in childhood

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Abstract. Substitution therapy of glucocorticoid is a major part of the treatment for 21-OHD (21-hydroxylase deficiency). However, the therapy causes two major adverse effects, impairment of linear growth and obesity, so that collecting precise growth data is essential for optimizing the therapy. We longitudinally evaluated the linear growth and the body composition of Japanese 21-OHD patients during childhood. For the present study, we chose 16 patients (eight of each sex) who were diagnosed during the newborn period, and continuously observed them in our institute until they were at least 15 years old. All patients were treated according to the guidelines from The Japanese Society for Pediatric Endocrinology. The final height standard deviation score (Ht-SDS) of all the patients was -1.18 ± 0.85 SD, and no significant differences were observed between males and females or between the simple virilizing form and the salt wasting form. As previously reported, in spite of nearly normal height at the onset of puberty, the pubertal height gains were severely impaired, resulting in reduced final heights. Body composition of the patients was evaluated with BMI-SDS. Our longitudinal data showed that BMI was increased up to +1.23 SD in males and up to +1.75 SD in females, and that adiposity rebound was precipitated. Our study should alert physicians to the risk of metabolic syndrome and provide a framework for further studies of metabolic syndrome in 21-OHD patients.

Key words: 21-OHD, Metabolic syndrome, Adiposity rebound, BMI, Short stature

21-HYDROXYLASE DEFICIENCY (21-OHD) is the most common type of congenital adrenal hyperplasia (CAH) that is caused by the loss or severe decrease in activity of steroidogenic enzymes involved in cortisol biosynthesis. The disease is classified into two types, classical and non-classical, according to the clinical phenotypes. In the classical type, there are two forms, the salt wasting (SW) form and the simple virilizing (SV) form. In the SV form, the clinical phenotype is virilization of external genitalia in newborn females and precocious puberty due to overproduction of androgens from the adrenal cortex. In the SW form, aldosterone deficiency causes additional phenotypes, such as hyponatremia, hyperkalemia, and hypovolemic shock. The worldwide incidence of classical 21-OHD is approximately 1 in 14,000 births [1, 2].

One of the major goals of 21-OHD therapy is to minimize the suppression of linear growth in order to achieve a final height similar to the genetic potential height, although, optimizing the therapy for 21-OHD patients has been challenging. Substitution therapy of glucocorticoid is a major part of the treatment for 21-OHD, and the therapy reduces the excessive production of androgen and its metabolites by the adrenal gland. Undertreatment causes androgen excess that would result in maturation of bone age and precocious puberty, leading to a decreased final height, while overtreatment suppresses linear growth by glucocorticoid itself, and has an additional side effect, iatrogenic Cushing’s syndrome [3-5].

Obesity is another great concern in 21-OHD patients. Glucocorticoid administration, even in substitution doses, may cause obesity [6]. Body mass index (BMI) is elevated in most 21-OHD patients [7-12]. Furthermore, recent studies showed that adult CAH patients also tend to have metabolic syndrome [13].
While there have been many studies on the linear growth of CAH patients during childhood, there are few precise reports of body composition of CAH patients during childhood. One of the major reasons is a lack of reference BMI-SDS values that are applicable to patients of a given race or ethnicity. Recently, BMI reference values (mean and SD) for Japanese children were reported [14], allowing the BMI of Japanese children to be evaluated precisely.

In this study, we report the longitudinal growth and BMI profile of Japanese 21-OHD patients during childhood who were treated from the newborn period. As previously reported, our data showed impaired linear growth during the pubertal period, resulting in a decreased final height. Furthermore, our data showed increased BMI and precipitated adiposity rebound during childhood. These data should provide clues to better managing 21-OHD patients.

Materials and Methods

Since the introduction of newborn screening for CAH in Japan [15, 16], 16 patients (8 males, 8 females) were diagnosed with classical form of the 21-OHD in neonatal period and followed up continuously to an age of at least 15 years. All the patients were picked up by the newborn screening and the diagnosis of CAH was based on both clinical symptoms and on hormonal analysis with confirmation by genotyping. For all patients, treatment was started in the neonatal period (Table 1).

We analysed the data retrospectively from all patients between 1989 and 2008. Eleven patients had salt-wasting (SW) 21-OHD which showed plasma sodium <130 mEq/L and/or potassium >6mEq/L at diagnosis, whereas 5 patients had the simple virilizing (SV) form. Patients with nonclassical forms of CAH were not included in this study. All patients were continuously cared for in our hospital, with follow-up appointments every month during infancy and every 2-3 months in childhood.

Seven male and five female patients had received hydrocortisone (HDC) three times daily for glucocorticoid replacement until the age of 15 years. The treatment was performed according to the clinical guidelines for 21-OHD in Japan [17]. The dose of medicine was adjusted based on auxological and hormonal data.

The height standard deviation score (Ht-SDS) at each age were obtained by using Japanese standard data [18]. The BMI including L, M, S reference values were previously reported [14], and the BMI-SDS were calculated by the formula previously reported [19]. Bone age was assessed annually by X-ray of the left hand using the Japanese standard TW2 method (RUS method) [20]. The start of puberty was defined as testicular volume greater than 3 mL in boys, and the second Tanner stage in girls.

### Results

#### Growth pattern and final heights

The final Ht-SDS of all the patients was -1.18 ± 0.85 SD, and a significant difference between male and female patients was not observed [males (n=8): 163.6 ± 2.5 cm (-1.24 ± 0.43 SD), females (n =8): 152.0 ± 5.7 cm (-1.15 ± 1.08 SD)] (Table 1, Fig. 1A). We also did not find significant difference of heights between the SW and SV forms [SW (n=11): -1.40 ± 0.75 SD], SV (n=5): -0.73 ± 0.73 SD] (Fig. 1B). The ages of pubertal onset in both sexes were almost the same as those of normal Japanese children (males: 11.4 ± 1.34 years old, females: 9.7 ± 0.76 years old) (Fig. 1 C, D). In both male and female patients, the transition of Ht-SDS had a similar pattern, i.e., the Ht-SDS decreased to -1SD or less during the infantile period, subsequently catching up at around 2-3 years of age. A significant difference of Ht-SDS between males and females was not observed until the onset of puberty. At the onset of puberty, the Ht-SDS were almost in the normal range, although, the pubertal height gain was significantly less than that of normal Japanese children, resulting in

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Growth profile of 21-OHD patients

In male patients, throughout the observation period, the BMI average exceeded that of age-matched healthy Japanese boys. The mean BMI-SDS increased from 0.42 to 1.23 between ages 2 and 7 years (Fig. 2A). Between the ages of 8 and 11 years, BMI-SDS decreased from +1.21 SD to +0.24 SD, and from 11-12 years old, i.e., the onset of puberty, BMI continued to increase until 15 years old.

Except for the infantile period, the BMI of female patients exceeded that of aged-matched healthy Japanese girls. From infancy until 7 years old, i.e., around the onset of puberty, the BMI-SDS increased rapidly up to +1.75 SD (Fig. 2A). After 9 years old, the BMI-SDS decreased until 15 years old (Fig. 2A). To determine whether the disease severity contributes to the BMI value, we compared the longitudinal BMI data of the SW and the SV forms, and found that the SV impaired final heights (Fig. 1C, D). The growth pattern and final Ht-SDS observed in this study were similar to those in previous reports [1, 5]. Bone age was delayed during the infantile period, however, it started to accelerate, exceeding chronological age at school age.

Body Mass Index during growth in Japanese classical 21-OHD patients

Because of the sufficient outcome of linear growth, we considered the patients in this study are representative of Japanese 21-OHD patients, allowing us to evaluate BMI of those patients. The BMI data of normal Japanese children is available, and we plotted the longitudinal BMI-SDS of the classical 21-OHD patients. In both sexes, the age of the nadir of BMI during childhood, which marks the start of adiposity rebound, was 4.5 ± 1.6 years in males, and 3.0 ± 1.6 years in females, earlier than those in healthy Japanese children (Table 1).

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Fig. 1 Longitudinal data of linear growth in the 21-OHD patients
A: Ht-SDS transitions in male and female patients. Closed squares and grey circles indicate male and female patients respectively. B: Ht-SDS transitions in SV and SW patients. Closed lozenges and grey triangles indicate SV and SW patients respectively. C and D: Transition of HDC treatment and difference between bone age and chronological age (BA-CA) in the male (C) and female (D) patients. Bar graphs, grey triangles show the HDC dosage and (BA-CA) respectively. The closed squares (C) and the closed circles (D) show Ht-SDS of male and female respectively. Gray circles and horizontal error bars indicate the mean value of onset of puberty and SD, respectively. “F” shows the final height-SDS. Error bars: +/- SD.
form tended to have lower BMI throughout the observation period (Fig. 2B), although the difference was not significant.

Based on the BMI data of the SW and the SV patients, we hypothesized that the dosage of the HDC treatment could contribute to the difference of BMI. We classified our patients into two groups, obese and non-obese. The obese group was defined to have a history exceeding +2SD of BMI during the observed period. We excluded patients who received glucocorticoid other than HDC, such as DXM. Eight non-obese patients and four obese patients were eligible for the analysis, and there was no significant difference of HDC dosage between the obese and non-obese groups (Fig. 2C).

**Discussion**

21-OHD is mainly treated with glucocorticoid supplementation, and one of the major goals of the treatment is preventing short stature caused by androgen excess. However, to suppress adrenal androgen satisfactorily, a supraphysiological dose of glucocorticoid is necessary, leading to iatrogenic Cushing’s syndrome with obesity and short stature. Indeed, it is well documented that patients with classic 21-OHD have significantly higher BMI than the general population [11, 13]. Thus, collecting precise clinical profile including auxological data is essential for optimizing the glucocorticoid therapy for 21-OHD.

To collect precise data of the linear growth and BMI, our study had two advantages, the homogeneity of the eligible patients and conducting longitudinal analysis. For accurate evaluation of the auxological data, especially obesity, it is important to secure the homogeneity of the eligible patients. All the patients in our study were Asian (Japanese) that were discovered by newborn screening and most of them were continuously treated in one institute. The normal range of BMI during childhood depends on race and ethnicity [21-25], and fortunately, precise statistical data of BMI in Japanese children is available, allowing us to calculate SDS values of BMI at every point during childhood.

Second, in order to evaluate the auxological data precisely, we conducted longitudinal analyses of the patients. Longitudinal data is obtained by repeated observation at the individual level, so that the differences observed in those people are less likely to be the result of cultural or habitual differences across

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**Fig. 2** Longitudinal data of BMI in the 21-OHD patients

A: BMI-SDS transitions in male and female patients. Closed squares and grey circles indicate male and female patients respectively. B: BMI-SDS transitions in SW and SV patients. Closed lozenges and grey triangles indicate SW and SV patients respectively. C: Transition of HDC treatment and BMI-SDS of obese and non-obese group patients. Grey and open bar graphs show the HDC dosage of obese and non-obese group respectively. Open circles and closed triangles indicate BMI-SDS of obese and non-obese patients respectively. Error bars: +/- SD.
generations. This is the first report to evaluate the longitudinal BMI-SDS from two years of age to adolescence in 21-OHD patients.

In terms of linear growth, the SDS values of final heights and growth patterns were consistent with data previously reported, i.e., Ht-SDS stayed within the normal male and female ranges before the pubertal stage, and the gain of heights during the pubertal period was remarkably reduced, resulting in decreased final heights, -1.18SD, although the final heights were still favorable in comparison with previous reports (5). Taken together, our results suggest that the therapy regimen used in this study had achieved satisfactory results, and the patients were representative of Japanese 21-OHD patients.

Consistent with previous reports [11], the BMIs of our 21-OHD patients were higher than those of healthy Japanese children. Especially the peak BMI-SDS reached more than +1.0SD in both sexes before the onset of puberty. Furthermore, the adiposity rebound that generally takes place around the age of 6 years [26], is occurred earlier in our patients. Adiposity rebound is the point at which BMI increases after its nadir, and an early adiposity rebound is associated with higher BMI in adolescence and young adulthood, substantially increasing the risk of adult obesity [27, 28]. A cross-sectional analysis has suggested that the adiposity rebound occurs earlier in 21-OHD patients [11], and our longitudinal data also documented the precipitated adiposity rebound.

In our study, including HDC dosage, we could not identify the factors that increased BMI and caused early adiposity rebound. We are planning to identify the factors that affect the start of adiposity rebound by increasing the number of the patients. The linear growth of our patients was not impaired before the onset of puberty, suggesting that increased BMI-SDS before the onset of puberty and the early adiposity rebound were caused by body weight gain rather than by a delay in linear growth.

The present study has some limitations. It is a retrospective study and is based on a small number of patients. In addition, the observation period was not long enough to observe the long-term prognosis of the patients. In spite of these limitations, our data suggest that besides improving final height, preventing severe obesity might be another major goal of the treatment for 21-OHD patients. For establishing the optimized treatment regimen for 21-OHD, further study is necessary to observe the long-term metabolic situation in 21-OHD patients by longitudinal analysis.

In summary, we carried out a retrospective longitudinal analysis of 21-OHD patients whose HDC treatment was initiated during the neonatal period. The linear growth of these patients was impaired during the pubertal period, as reported previously. Our longitudinal data support a previous cross-sectional study that showed increased BMI and early adiposity rebound in 21-OHD patients [11]. Our study should alert physicians to the risk of metabolic syndrome and should provide a framework for further studies of metabolic syndrome in 21-OHD patients. There remains the substantial clinical problem of designing a treatment regimen 21-OHD patients during early infancy and childhood.

References

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