Current status of transition medicine for 21-hydroxylase deficiency in Japan: from the perspective of pediatric endocrinologists

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Abstract. To manage of 21-hydroxylase deficiency (21-OHD), transition medicine from pediatric to adult health care is an important process and requires individually optimized approaches. We sent cross-sectional questionnaire surveys on the current status of transition from pediatric to adult health care in 21-OHD patients to all councillors of the Japanese Society for Pediatric Endocrinology. Many pediatric departments (42.2%) experienced adult 21-OHD patients, and 115 patients (53 males, mean age of 26) in 46 institutions were identified. Whereas almost two-thirds of pediatric endocrinologists regarded the problems of counterparts and cooperation as hindrance of transition medicine, the major reason for continuing to be treated in pediatrics was the patient’s own request. The prevalence of long-term complications including obesity, osteoporosis, infertility, menstrual disorder, gender dysphoria, and testicular adrenal rest tumor were 27.5%, 8.8%, 11.1%, 26.3%, 7.1%, 12.5%, respectively, which is comparable to those of other cohorts previously reported. However, several items, especially infertility and osteoporosis were not checked well enough in adult 21-OHD patients treated in pediatrics. Though 44 of 62 female patients had genital reconstructive surgery, more than half of them were not followed up by gynecologists or pediatric urologists. Quite a few adult 21-OHD patients had been followed up in pediatrics even after coming of age; however, surveillance by pediatric endocrinologists of gynecological, reproductive, and mental problems may be insufficient. Therefore, multidisciplinary approaches should be required in transition medicine for 21-OHD and prerequisite for graduation of pediatrics. Pediatric endocrinologists will need to play a leading role in the development of transition systems.

Key words: Congenital adrenal hyperplasia, Transition medicine, 21-hydroxylase deficiency

CONGENITAL ADRENAL HYPERPLASIA (CAH) is a group of autosomal recessive disorders characterized by cortisol synthesis deficiency [1, 2]. CAH due to 21-hydroxylase deficiency (21-OHD) accounts for approximately 95% of the cases. 21-OHD is classified according to symptoms and is usually divided into two forms: the classical form, which consists of the salt wasting and simple virilising forms, and the non-classical form. Newborn screening promotes early recognition and treatment of infants with classic 21-OHD, consequently reducing morbidity and mortality [1, 3]. In Japan, newborn screening started in January 1989, and one per 18,000 to 20,000 infants are found to have 21-OHD [4-6]. CAH is a lifelong condition and requires management for each stage of life. Once growth is completed, there is a need for a shift in treatment goals from optimal growth and puberty to prevention of long-term adverse outcomes and optimization of sexual function and fertility [7]. Transition medicine from pediatric to adult health care is an important process and requires individually optimized approaches. In the Endocrine Society clinical practice guideline [1], the gradual transition of adolescents to adult care over several years is recommended and the use of joint clinics comprised of pediatric, reproductive, and
Materials and Methods

A nationwide survey was conducted following the procedure below.

The primary questionnaires were administered to determine the number of adult patients, over 20 years old, with classic 21-OHD who were treated by pediatric endocrinologist in 2019. The questionnaires were sent to all councillors of the Japanese Society for Pediatric Endocrinology (JSPE). Additionally, we questioned them about whether there are any bottlenecks to transition medicine in 21-OHD.

Secondary questionnaires were sent to the responding councillors who treated adult patients with classic 21-OHD and contained questions as below: the patients’ sociodemographic information (sex, age, marriage, whether or not to have children), medical problems (obesity, hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, cardiovascular disease, infertility, menstrual disorder, gender dysphoria, testicular adrenal rest tumor (TART)), and reasons to continue to be treated in pediatrics. Furthermore, to clarify the current status of transition by pediatric endocrinologists who treated adult 21-OHD patients, secondary questionnaires asked about whether there were any bottlenecks to transition medicine in 21-OHD.

The proportion (P) of patients with a given condition was calculated as $P(%) = n/(N - u) * 100$, where $n$ is the number of patients with the condition, $N$ is the total number of patients and $u$ (unknown) is the number of patients that were not checked for the condition. The data were analyzed using JMP® Pro version 15.1. The statistical methods used were Mann-Whitney test, chi-square test, Fisher’s exact test and one-way ANOVA with post-hoc Tukey honestly significant difference test for multiple comparison.

The study was initiated by the JSPE and approved by the Ethics Committee of the Institutional Review Board of Tokyo Medical and Dental University (approval no. M2017-352) and in adherence to the principles of the Declaration of Helsinki.

Results

The procedure of surveys is shown in Fig. 1A. We sent primary questionnaires to 190 councillors of JSPE who belong to 140 hospitals and clinics, and received responses from 109 (77.9%) hospitals and clinics. Of these, 46 (42.2%) of the pediatric departments in hospitals and clinics including 20 university hospitals, 17 general hospitals, 5 children’s hospitals, and 4 clinics, experienced adult 21-OHD patients during the study period. Secondary questionnaires were sent to these hospitals and clinics, and responses were obtained from 24 pediatrics in hospitals and clinics (12 university hospitals, 7 general hospitals, 2 children’s hospitals, and 3 clinics) (Fig. 1B).

In the primary questionnaires, 179 patients were identified. The numbers of cases in each medical institution are shown in Fig. 1C. For example, the second bar indicates that 14 institutions (30.4% of the total number of institutions) had two cases. Six of the medical institutions (indicated by the four bars on the right in Fig. 1C) treated more than ten adult 21-OHD patients, and their patients accounted for 45.3% of all the patients. In the secondary questionnaires, 115 patients (64.2%) were finally identified. In addition, 39 patients who were transferred from these medical institutions to adult health care were identified.

An opinion survey on transition medicine for 21-OHD intended for 46 attending pediatric endocrinologists treating adult 21-OHD patients is shown in Fig. 2. The greatest hindrance of transition medicine for pediatric endocrinologist was insufficient knowledge and experience of physicians involved in adult health care for 21-OHD. The lack of cooperation between pediatrics and adult health care was the second only to the problem of counterpart. Though the two items accounted for almost two-thirds, “insufficient education for patients on transition medicine” accounted for only 6%.

Table 1 summarizes the survey results for adult patients with classic 21-OHD who were treated in pediatrics and transferred to adult health care. The age of patients who were treated in pediatrics or transfer to adult care was higher in female than males (The median ages of female and male patients treated in paediatrics were 30 and 25, respectively, and those of female and male patients transferred to adult health care were 27 and 21.5, respectively). The major reason for continuing to be treated in pediatrics was the patient’s own request (57/115 = 50%), and 31% of patients continued to be treated in pediatrics due to problems of counterparts including absence of experts (15 patients) and refusal of acceptance by physicians (21 patients). Five patients transferred to adult health care returned to pediatrics. The proportion of patients that were transferred to internal

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Fig. 1 Outline of the questionnaire surveys. A: Procedure of surveys, B: Breakdown of hospitals (Hp) that participated in the study. The upper and lower graphs indicate those in primary and secondary questionnaires, respectively. C: Numbers of adult 21-OHD patients treated in each institute. For example, the second bar indicates that 14 institutions (30.4% of the total number of institutions) had two cases.

Fig. 2 Opinion survey on the biggest factor that hinders transition medicine for 21-OHD intended for 46 attending pediatric endocrinologists treating adult 21-OHD patients. The answer choices are as follows: insufficient knowledge and experience of physicians involved in adult health care for 21-OHD, lack of cooperation between pediatrics and adult health care, insufficient support system for transition, insufficient education for patients on transition medicine, and others.
medicine in the same and different hospital were 38% and 49%, respectively. Eighty-two percent of the patients were transferred to adult health care with dismissal from pediatric endocrinology. The marriage proportion of patients who were treated in pediatrics was 13%, and there was no gender difference. The proportions of having children in male and female patients who were treated in pediatrics were 14.0% and 3.4%, respectively.

Long-term complications of 21-OHD in the both groups are summarised in Table 2. The proportions of patients who were treated in pediatrics that had obesity (body mass index; BMI >25), and obesity at the time of transfer to adult health care were 27.5% and 26.3%, respectively. Osteoporosis (defined as a bone mineral density (BMD) less than 70% of the young adult mean) was identified in five patients who were treated in pediatrics; however, 58 patients (50.4%) were not assessed for the presence or absence of osteoporosis. Infertility (defined as a failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse) was identified in three patients (two females) who were treated in pediatrics; however, 88 patients (76.5%) were not checked for the presence or absence of infertility. The prevalence of TARTs was 12.5% in the both groups. The proportions of patients for which TARTs were not assessed was 24.5% in pediatric care and 50% at the transfer. Four female patients (7.1%) who were treated in pediatrics had gender dysphoria. On the whole, there was no significant difference in the prevalence of long-term complications between patients treated in pediatrics and those transferred to adult health care.

The age distribution of patients treated in pediatrics with obesity is shown in Fig. 3. The median age of patients with obesity was 31.5 years (28 years in males and 32.5 years in females). The patients with obesity

| Table 1 | Summary of the survey results for adult patients with 21-hydroxylase deficiency |
|---------|--------------------------------------------------------------------------------|
|         | Patients treated in pediatrics | Patients transferred to adult health care |
| No. patients (M:F) | 115 (53:62) | 39 (16:23) |
| Age at survey median ± IQR | 26 ± 11 | 24 ± 10 |
| Male | 25 ± 9 | |
| Female | 30 ± 12 | 27 ± 9 |
| p value | 0.0380 | 0.0235 |
| Age at transfer median ± IQR | 24 ± 10 | |
| Male | 21.5 ± 6 | 21.5 ± 6 |
| Female | 27 ± 9 | |
| p value | 0.0235 | 0.0235 |
| Reason for continuing in pediatrics (M:F) | | |
| Patient’s own request | 57 (27:30) | |
| Absence of experts | 15 (8:7) | |
| Refusal of acceptance | 21 (9:12) | |
| Others | 22 (9:13) | |
| Transferred department (M:F) | | |
| Internal medicine in the same hospital | 15 (8:7) | |
| Internal medicine in the different hospital | 19 (5:14) | |
| Others | 5 (3:2) | |
| Marriage (M:F) | | |
| Married | 14 (7:7) | 7 (3:4) |
| Unmarried | 96 (45:51) | 26 (11:15) |
| Unknown | 5 (1:4) | 6 (2:4) |
| Males that had children | 6 | 2 |
| Unknown | 10 | 4 |
| Females that had children | 2 | 3 |
| Unknown | 3 | 5 |

(M:F), (male:female); IQR, interquartile range. p values were calculated by Mann-Whitney U tests.
were significantly older than those without obesity ($p = 0.0462$); however, there was no difference between the sexes. Seven of 35 male patients (20%) and five of 30 female patients (16.7%) below 30 years of age who were treated in pediatrics had obesity. In 30 obese patients who were treated in pediatrics, 23% had comorbid hypertension, 20% had comorbid hyperlipidemia, and 10% had comorbid diabetes mellitus. In ten obese patients who were transferred to adult health care, only one patient had comorbid diabetes mellitus and hyperlipidemia, and two patients had hyperlipidemia only.

Gynecological problems in female patients are shown in Table 3. About 70% (44/62) of female patients had genital reconstructive surgery. Although 48% (21/44) of them were followed up by urologists in parallel with pediatric endocrinologists, only 4 of 18 patients transferred to adult health care after reconstructive surgery (22%) were followed up. As shown in Table 2, menstrual disorders were observed in about 30% of female patients, and as shown in Table 3, 29% of female patients (18/62) treated in pediatrics consulted gynecologists in parallel with pediatric endocrinologist. Of the 18 patients that had regular visits with a gynecologist, 10 patients had menstrual disorders, while the others had uterine fibroids, uterine adenopathy, ovarian cyst, vaginal stenosis, vaginitis or a desire to bear children.

### Table 2 Long-term complications of adult patients with 21-hydroxylase deficiency

| Disorder          | Patients treated in pediatrics | Patients transferred to adult health care |
|-------------------|-------------------------------|------------------------------------------|
|                   | M + F  | Male | Female | Un-known | P§ (%) | M + F  | Male | Female | Un-known | P§ (%) |
| Total No. patients| 115    | 53   | 62     |          |        | 39     | 16   | 23     |          |        |
| Obesity†          | 30     | 14   | 16     | 6        | 27.5   | 10     | 2    | 8      | 1        | 26.3    |
| Hypertension§     | 8      | 3    | 5      | 12       | 7.8    | 1      | 0    | 1      | 4        | 2.9     |
| Diabetes mellitus¶| 3      | 0    | 3      | 10       | 2.9    | 1      | 0    | 1      | 2        | 2.7     |
| Dyslipidemia      | 11     | 5    | 6      | 10       | 8.8    | 4      | 1    | 3      | 2        | 10.8    |
| Osteoporosis††    | 5      | 4    | 1      | 58       | 11.1   | 0      | 0    | 0      | 15       | 0.0     |
| Cardiovascular    | 0      | 0    | 0      | 11       | 7.1    | 0      | 0    | 0      | 3        | 0.0     |
| Infertility§§     | 3      | 1    | 2      | 88       | 26.3   | 4      | 1    | 3      | 18       | 14.3    |
| Menstrual         | 15     | 5    |        | 26.3     | 12.5   | 1      | 8    | 12.5   |          |        |

TART, testicular adrenal rest tumor
†: body mass index >25%, §: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, ¶: HbA1c >6.5%, ††: young adult mean of bone mineral density <70%, §§: a failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse, ¶¶: Proportion = no. patients with disorder (in bold)/(total no. patients-unknown)*100.

### Discussion

Our study consisted of two parts including an opinion survey of Japanese pediatric endocrinologists on transition medicine for 21-OHD and a fact-finding survey of 115 adult 21-OHD patients who were treated in pediatrics compared with 39 patients who were transferred to adult health care as a reference. The latter survey...
revealed that many of the adult 21-OHD patients treated in pediatrics developed long-term complications in young adulthood or were not assessed for long-term complications. Because these findings indicated that several issues need to be addressed, we will discuss the background and circumstances surrounding adult 21-OHD patients.

Although early recognition and treatment of 21-OHD by the introduction of newborn screening reduced serious morbidity and mortality in infancy and childhood [1, 6], a few large cohort studies revealed that 21-OHD is associated with excess adult mortality and morbidity risk [12, 13]. Regular surveillance for long-term complications of 21-OHD and its treatment was recommended [1]; however, failure to follow up after transition is a serious problem. Cohort studies on CAH patients in Europe revealed that less than 10% of adult CAH patients are under endocrine specialist care [14], and the successful transition to adult endocrinologists by their pediatricians is associated with regular medical follow-up and better health-related quality of life in adults with CAH [7].

The present cohort consisted of 154 adult patients with classic 21-OHD, of which 102 patients (74 patients with pediatric care) were diagnosed after starting the newborn screening. The number of adult patients with classic 21-OHD after the start of newborn screening was calculated from the annual incidence and the number of births 1989–1999, 13.3 million birth, to be 665–774; therefore, around 15% of them were estimated to be included in this cohort. Our data indicated that at least 10% of adult patients with classic 21-OHD after starting the newborn screening were treated by pediatric endocrinologists in Japan. Moreover, about half of them were concentrated in specific medical institutions, university hospitals in particular. The persistent pediatric follow-up of a part of adult 21-OHD patients without transfer to adult health care may be symbolic of the current status of transition medicine for 21-OHD in Japan.

Pediatric endocrinologists in Japan who treated adult patients with classic 21-OHD were aware of the issues of transition medicine for 21-OHD and tended to regard them as a problem of the counterpart. The presence or absence of the counterpart could be associated with differences between regions or facilities. Expanding and reinforcing collaboration among child and adult health care may be the most urgent issues to focus on. On the other hand, a half of the adult patients continuing to be treated in pediatrics wished it for their own, which may suggest the need for further education of patients on transition. It is not only required to develop systems for the gradual transition of adolescents to adult care for each region or facility but to also to make pediatric endocrinologists aware of the need and significance for such systems.

Multifaceted surveillance for long-term complications of 21-OHD and its treatment was recommended [1], whereas several items, especially infertility and osteoporosis were not checked well enough in adult 21-OHD patients treated in pediatrics or at the time of transfer to adult care. Our study revealed that more than three quarters of adult patients treated in pediatrics were not checked for infertility, even though more than 10% of adult patients checked by pediatric endocrinologists suffered from infertility. The low proportion of check may be attributed to a low proportion of marriage; however, it would be better for pediatric endocrinologists to be aware of the high rate of infertility which may be due to poor disease control.

Approximately one fourth of the patients in this cohort

| Table 3: Gynecological problems of female adult patients with 21-hydroxylase deficiency |
|---------------------------------------------|---------------------------------------------|
| Patients treated in pediatrics | Patients transferred to adult health care |
|---------------------------------|---------------------------------|
| No. female patients | 62 | 23 |
| History of genital reconstructive surgery | 44 | 18 |
| Follow-up by gynecologist or urologist who performed a surgery | 21 | 4 |
| Regular visit to a gynecologist | 18 | 4 |
| Menstrual disorder | 10 | 4 |
| Uterine fibroids | 2 | — |
| Desire to bear children | 2 | — |
| Uterine adenopathy | 1 | — |
| Ovarian cyst | 1 | — |
| Vaginal stenosis | 1 | — |
| Vaginitis | 1 | — |

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had obesity, which is comparable to previous reports [1, 15]. It was reported that 16% to 25% of children with 21-OHD have high BMIs [16, 17]. In addition, adolescents and young adults with 21-OHD have increased abdominal adiposity with a higher proportion of proinflammatory visceral adipose tissue, which is strongly associated with metabolic syndrome and cardiovascular disease [18]. Moreover, a meta-analysis of 14 studies covering 437 CAH patients (300 children/adolescents and 137 adults, aged 14 months to 63 years) found a high prevalence of cardiovascular and metabolic risk factors in the patients [19]. Indeed, in the present cohort, four female patients (2.8%) had diabetes mellitus and all of them had complications with obesity, hypertension, and dyslipidemia. The higher age of adult 21-OHD patient with obesity may indicate that the risk of obesity increases as they grow older. The present study also revealed that many of the 21-OHD patients with obesity were in their 20s. Pediatric endocrinologists should thus be aware of not only the metabolic risks of young adult 21-OHD patients but also of further tight control of treatments to prevent childhood obesity.

The ages of female patients who were either treated in pediatrics departments or transferred to adult health care were higher than those of male patients, which may be due to the difficulty of follow-up or transition of female adolescent or young adult 21-OHD patients. In Japan, early surgery for virilised females with 21-OHD to prevent adverse psychosocial consequences is the most common treatment. Therefore, most of female patients in the present study had genital reconstructive surgery in infancy or early childhood. The practice guideline [1] promotes awareness of the risk of vaginal stenosis and consequent vaginal insufficiency with dyspareunia, and suggests that physicians obtain a gynecological history and conduct an examination to ensure functional female anatomy in adolescent females with 21-OHD. Although cooperation with gynecologist, reproductive endocrinologist, or liaison psychiatry team for continuous assessment and counselling of psychosocial stigma and satisfactory sexual functioning as well as fertility is recommended, more than half of the female patients who had genital reconstructive surgery were not followed up by a gynecologist or the pediatric urologist who performed the surgery.

In addition, there are several problems including gynecological complications, infertility, and gender dysphoria, to be aware of during follow-up of adult female patients with 21-OHD. One in four adult female 21-OHD patients treated in pediatrics had menstrual disorders which may be associated with androgen excess due to poor disease control. Of the 62 female patients who were treated in pediatrics, 14 were checked for infertility. Because 2 of these 14 patients (14%) were infertile, the other 48 patients should be checked for infertility. Pediatric endocrinologists as well as obstetricians should be aware of the low fecundity in women with classic CAH, which is reported to be only about one seventh of the normal rate, despite a normal pregnancy rate [1, 20]. The proportion of gender dysphoria of adult female 21-OHD patients treated in pediatrics was 7.1% (4 out of 56), which is within the ranges reported by previous analytic/descriptive literature reviews (5.2–10.1%) [21, 22], and higher than that in the general population, whereas none of the patients transferred to adult healthcare had gender dysphoria. If gender dysphoria could obstruct transition, early counselling and seamless psychological supports regarding potential gender-identity problems may be required.

Our study revealed that periodic screening of BMD and testicular ultrasound for adult 21-OHD patients treated in pediatrics may be insufficient. The high prevalence of osteoporosis (8.8%) in adult 21-OHD patients treated in pediatrics was clarified as with two previous studies of large cohorts in UK and USA reported [14, 15]. Therefore, the low proportion of check for BMD might lead to underestimating the actual prevalence of low BMD. Because the prevalence of TARTs was reported to increase after 10 years of age, it was recommended that screening by testicular ultrasound assessments should begin in adolescence [1]. In our cohort, the prevalence of TARTs (12.5%) was lower than the rates in US and UK cohorts (69% and 44%, respectively). However, it is unclear whether the low prevalence of TARTs in our cohort was due to good disease control or underestimation by an oversight because a quarter to a half of the patients were not checked by testicular ultrasounds.

The prevalence of long-term complications did not differ significantly between patients treated in pediatrics and those transferred to adult health care, suggesting the necessity of early intervention by adult or reproductive endocrinologists, gynecologists and urologists as well as further tight control of treatment in childhood. Earlier introduction of the gradual transition accompanied by education and psychological support of patients and guardians could be effective, thus awareness of mutually complementary relationship between pediatric endocrinologists and staff of adult health care may be required. To start with, we suggest identifying and discussing on problems of collaboration among child and adult health care in each region or facility at the initiative of pediatric endocrinologists.

Our study was composed of cross-sectional questionnaire surveys to all councillors of JSPE and has two limitations. First, there was no follow-up data including treatment courses, auxological, and laboratory data, nor
genetic data which may reflect or affect disease control. A longitudinal cohort study could obtain more valuable information about the effects of transition and extended follow-ups by pediatricians. Second, we did not survey counterparts of transition such as adult or reproductive endocrinologists, gynecologists and urologists. The lack of their inputs might obscure the actual condition of transition medicine with 21-OHD patients. Indeed, it remains unclear who treated the remaining 85% of adult patients with classic 21-OHD that were detected by the newborn screening or how they were treated.

In summary, our study revealed the actual condition of transition medicine with 21-OHD patients in Japan as seen through the eyes of pediatric endocrinologists. Quite a few adult 21-OHD patients had been followed up in pediatrics even after coming of age due to an insufficient transition system or insufficient education of patients on transition. The prevalence of long-term complications of them seems to be comparable to that of other cohorts previously reported [1, 14, 15, 21]; however, surveillance of gynaecological, reproductive, and, mental problems may be insufficient. Taken together, these findings indicate that a multidisciplinary approach is needed in transition medicine for 21-OHD and prerequisite for the graduation of pediatrics to adult health care. Pediatric endocrinologists must play a leading role not only in medical care but also in developing a transition system that will meet future needs. There is a need for educational materials for both medical staff and patients. For medical staff, the material should be according to stage of patient’s growth and development as a preparatory step for gradual transition, and focus on the need for transition medicine. For adolescent and adult patients, a self-care check handbook will encourage health autonomy in an age-appropriate way. In parallel with educating patients and medical stuff on the importance of transition care, there may also be a need for accumulating clinical data on adult 21-OHD patients, possibly in the form of a nationwide, registry-based cohort study from birth to adult.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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