

Original Article

Endocrine status of patients with septo-optic dysplasia: fourteen Japanese cases

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Abstract. A clinical diagnosis of septo-optic dysplasia (SOD) is made when two or more of the classical triad of optic nerve hypoplasia, pituitary hormone abnormalities or midline brain defects. To date, a clinical study of SOD, regarding its endocrinological features in particular, has not been undertaken in Japan. We retrospectively evaluated 14 SOD patients at our institution. Hormonal dysfunction was present in 78% of cases: ten cases presented combined hypopituitarism and one case presented precocious puberty. GHD and hypothyroidism were the most common endocrinopathies. A thin pituitary stalk and a gradual decrease in hormone secretion were the main characteristics. SOD patients usually visited ophthalmologists during early infancy because of eye problems; however, the medical examination did not always lead to endocrine assessments being made. Consequently, children who have eye problems with optic nerve hypoplasia should undergo head MRI imaging. If diagnosed with SOD, it is very important to evaluate pituitary functions. Their endocrinological status should be followed for a long time, even if they do not exhibit any endocrinological problems at evaluation.

Key words: septo-optic dysplasia, optic nerve hypoplasia, growth hormone deficiency, hypopituitarism, midline brain defects

Introduction

A clinical diagnosis of septo-optic dysplasia (SOD), also known as de Morsier syndrome, is made when two or more of the classical triad of optic nerve hypoplasia, pituitary hormone abnormalities or midline brain defects, including agenesis of the septum pellucidum and/or corpus callosum, are present. SOD is a rare congenital anomaly, with an incidence of 1 in 10,000 live births, and affects males and females equally (1).

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In 1941, Reeves was the first to describe septo-optic dysplasia, noting an absence of the septum pellucidum in association with optic nerve abnormalities (2). In 1956, de Morsier observed an association between optic nerve hypoplasia and an absent septum pellucidum. Subsequently, an association with pituitary dysfunction was described (3, 4).

Approximately 30% of SOD patients have all three components of the syndrome (5), with the main reported clinical finding of hypopituitarism (62~80%). The most common hormone deficiency is GHD, followed by central hypothyroidism. Visual impairment and developmental delay are often also found. Seizures, developmental delay and cerebral palsy are the most frequent neurological associations. Sleep disturbance, precocious puberty, obesity, anosmia, sensorineural hearing loss and cardiac anomalies are also reported as SOD-associated features. SOD demonstrates a wide variation in the severity of its distinctive clinical features (6).

Some SOD patients exhibit abnormalities of the pituitary (ectopic, or absent posterior pituitary, truncated or absent pituitary stalk and hypoplastic pituitary) on head MRI imaging (6). The relationship between midline central nervous system on MRI and hypopituitarism is argued in optic nerve hypoplasia patients (7, 8); however, the relationship between pituitary abnormalities and hormonal abnormalities is not clear in SOD patients.

To date, an observational study on the clinical features of Japanese SOD patients, regarding endocrinological characteristics in particular, has never been performed.

Accordingly, the purpose of this study was to characterize the endocrinological characteristics of Japanese SOD patients.

Subjects and Methods

Subjects

Fourteen patients (seven males, seven females) were evaluated at Osaka Medical Center

and Research Institute for Maternal and Child Health between November 1981 and May 2015. SOD was diagnosed when a patient had two or more features of the classical triad of optic nerve hypoplasia, pituitary hormone abnormalities or midline brain defects.

Methods

We collected the following data from medical records retrospectively: perinatal and neonatal characteristics (mode of delivery, gestational age, birth weight, symptoms related to hypopituitarism: hypoglycemia, neonatal respiratory problems, prolonged jaundice, microphallus and cryptorchidism), endocrinological findings (endocrine evaluation, development of puberty, the height standard deviation scores [SDS] change of normal Japanese children across ages, thyroid-stimulating hormone [TSH] response to thyrotropin-releasing hormone [TRH] stimulation, peak cortisol on insulin tolerance test [ITT]), and head image findings (anterior pituitary size, posterior pituitary location and shape, and the presence of a septum pellucidum).

GH deficiency (GHD) diagnosis was based on a peak GH level by secretion stimulation tests. We defined GHD as the peak GH level of < 10 ng/mL before 2004 and < 6 ng/mL after 2004 using arginine, insulin, clonidine. We defined GHD as the peak GH level of < 9 ng/mL using growth hormone releasing peptide 2 (GHRP2). We converted laboratory data, which were measured by radioimmunoassay, to immunoradiometric assay data using a reduction formula. Central hypothyroidism and central hypoadrenalism were determined based on provocation tests and history of hormonal treatment. Diabetes insipidus was diagnosed by water deprivation test and desmopressin test.

Case 1 and 3 underwent GH secretion stimulation test more than once. We discontinued GH replacement therapy before the second and the third GH secretion stimulation test.

Midline brain defects, such as an absent

septum pellucidum or callosal agenesis, were diagnosed by a pediatric radiologist using head computed tomography (CT) or head magnetic resonance imaging (MRI). MRI images were taken with 3 mm thickness, except in Case 10. The maximal height of the pituitary gland was measured on midline T1-weighted sagittal images using an electronic display caliper by an experienced radiologist. The diameters of the pituitary stalk and basilar artery were measured on axial images on the same plane in the middle of the pituitary stalk. To evaluate the size of the pituitary stalk, the pituitary stalk/basilar artery ratio was calculated (9). We defined a thin pituitary stalk as below -2 SDS of normal children.

Optic nerve hypoplasia was diagnosed on funduscopy by ophthalmologists.

We also checked the chief complaints on their first visit to our institution in order to find diagnostic clues. Genetic analysis (*HESX-1*) was performed in Cases 10 and 12.

This study was approved by the Ethical Review Board of Osaka Medical Center and Research Institute for Maternal and Child Health (approval No. 911).

Results

Table 1 lists the clinical features of subjects. Table 2 is a summary of the classical triad displayed by subjects. Two (14%) patients displayed all three characteristics of the triad. Optic nerve hypoplasia was the most common characteristic of the triad (92%). Bilateral optic nerve hypoplasia was found in seven out of 13 patients. Unilateral optic nerve hypoplasia was found in six (five for the right side and one for the left side) patients. Pituitary hormone abnormalities were found in 11 patients (78%). Six patients (43%) presented with midline brain defects.

Perinatal and neonatal characteristics

All 14 SOD patients were delivered

vaginally, and a complicated delivery, such as breech presentation or vacuum extraction, was not noted. Eleven were full-term births, one (Case 3) was 6 wk premature and two (Cases 9 and 13) were post-term deliveries. Although most patients ($n = 12$, 85%) were born at appropriate-for-gestational age, Case 3 was born at small-for-gestational age, and Case 13 was born at large-for-gestational age. Half of the patients demonstrated prolonged jaundice during the neonatal period. Males did not exhibit a microphallus and/or cryptorchidism.

Chief complaints and the ages of visit to endocrinological department

Endocrinologists examined 12 SOD patients. All except Case 4 had optic nerve hypoplasia and visited ophthalmologists when they were 5 mo old (3~35 mo). They visited our department when they were 36 mo old (5~119 mo). The chief complaints on the first visit to our department were abnormal head MRI findings (five cases), short stature (two cases), precocious puberty (one case), obesity (one case) and hypoglycemia (one case). Those who visited pediatric ophthalmologists came to our department after an average of 3 mo with the chief complaint of abnormal head MRI findings. However, those who visited general ophthalmologists delayed visiting our department, taking an average of 34 mo.

Endocrinological findings

Hormonal dysfunction was present in 78% of cases: ten cases presented combined hypopituitarism and one case presented precocious puberty. GHD and hypothyroidism were the most common endocrinopathies, observed in 10 out of 14 (71%) cases. Nine cases (64%) presented adrenal insufficiency. Diabetes insipidus, hypogonadotropic hypogonadism and precocious puberty were observed in 1 case each.

Figure 1 shows the longitudinal data of a GH secretion stimulation test for Cases 1 and 3 performed twice and third for each patient

Table 1 Clinical features and MRI images

	Age (yr)	Sex	GH deficiency	Hypo-thyroidism	Adrenal insufficiency	Hypogonadism	Diabetes insipidus	Pituitary stalk (PS/BA*)
Case 1	33	F	Yes	Yes	Yes	Yes	No	N/D
Case 2	20	M	N/D***	No	No	No	No	very thin (0.28)
Case 3	17	F	Yes	Yes	No	secondary amenorrhea	Yes	very thin (0.28)
Case 4	13	F	Yes	Yes	Yes	No menarche yet	Yes	very thin (0.44)
Case 5	12	F	Yes	Yes	Yes	No menarche yet	No	very thin (0.33)
Case 6	12	F	No	No	No	No (precocious puberty)	No	very thin (0.37)
Case 7	10	M	N/D***	No	No	N/D*****	No	N/D
Case 8	8	F	Yes	Yes	Yes	N/D*****	No	very thin (0.33)
Case 9	6	M	Yes	Yes	Yes	N/D****	No	N/D
Case 10	5	F	Yes	Yes	Yes	N/D*****	No	very thin (0.36)
Case 11	5	M	N/D***	No	No	N/D*****	No	very thin (0.31)
Case 12	2	M	Yes	Yes	Yes	N/D*****	No	very thin (0.31)
Case 13	2	M	Yes	Yes	Yes	N/D*****	No	N/D
Case 14	1	M	Yes	Yes	Yes	N/D*****	No	very thin (0.28)

	Pituitary height** (mm) (age)	Pituitary height SDS	Posterior pituitary lobe	Septum pellucidum	Optic nerve hypoplasia	Other clinical symptoms	SGA or AGA or LGA
Case 1	N/D	N/D	N/D	normal	Bilateral	Unilateral cleft lip	AGA
Case 2	6.2 (18 yr)	-2.11	small	agenesis	Unilateral (l)	No	AGA
Case 3	3.3 (14 yr)	-1.79	small	agenesis	Bilateral	No	SGA
Case 4	3.3 (6 yr)	-1.48	ectopic	agenesis	No	Obesity, Thermoregulatory dysfunction, Sleep disturbance	AGA
Case 5	1.7 (12 yr)	-2.15	ectopic	normal	Unilateral (r)	No	AGA
Case 6	6.0 (10 yr)	1.46	ectopic	normal	Unilateral (r)	No	AGA
Case 7	N/D	N/D	N/D	agenesis	Unilateral (r)	Obesity, Hyperlipidemia	AGA
Case 8	3.3 (1.9 yr)	-0.94	ectopic	normal	Unilateral (r)	No	AGA
Case 9	N/D	N/D	N/D	agenesis	Bilateral	No	AGA
Case 10	4.6 (3.8 yr)	0.12	no signal*****	normal	Bilateral	Obesity, Thermoregulatory dysfunction	AGA
Case 11	4.7 (3 yr)	0.66	normal	agenesis	Unilateral (r)	Seizure	AGA
Case 12	1.5 (6 mo)	-3.38	normal	normal	Bilateral	No	AGA
Case 13	N/D	N/D	N/D	normal	Bilateral	No	LGA
Case 14	2.3 (1.6 yr)	-3.83	ectopic	normal	Bilateral	No	AGA

F: female, M: male. N/D: not determined. l: left, r: right. SDS: standard deviation score. SGA: small for gestational age, AGA: appropriate for gestational age, LGA: large for gestational age. PS: pituitary stalk, BA: basilar artery. * The diameters of the pituitary stalk and basilar artery were measured on axial images on the same plane in the middle of the pituitary stalk. To evaluate the size of the pituitary stalk, the pituitary stalk/basilar artery ratio was calculated (9). ** Maximal height of the pituitary gland was measured on the midline T1-weighted sagittal images by an experienced radiologist using an electronic display caliper. *** No endocrinological symptoms; patients were not evaluated by provocation tests. **** The slice of head MRI was 8 mm. ***** Prepubertal age (male < 11 yr old, female < 9 yr old).

Table 2 Classical triad for participants

Optic nerve hypoplasia	No	Yes	Yes	Yes	13/14 (92%)
Pituitary hormone abnormalities	Yes	No	Yes	Yes	11/14 (78%)
Midline brain defects	Yes	Yes	No	Yes	6/14 (43%)
	1/14 (7%)	3/14 (21%)	8/14 (57%)	2/14 (14%)	

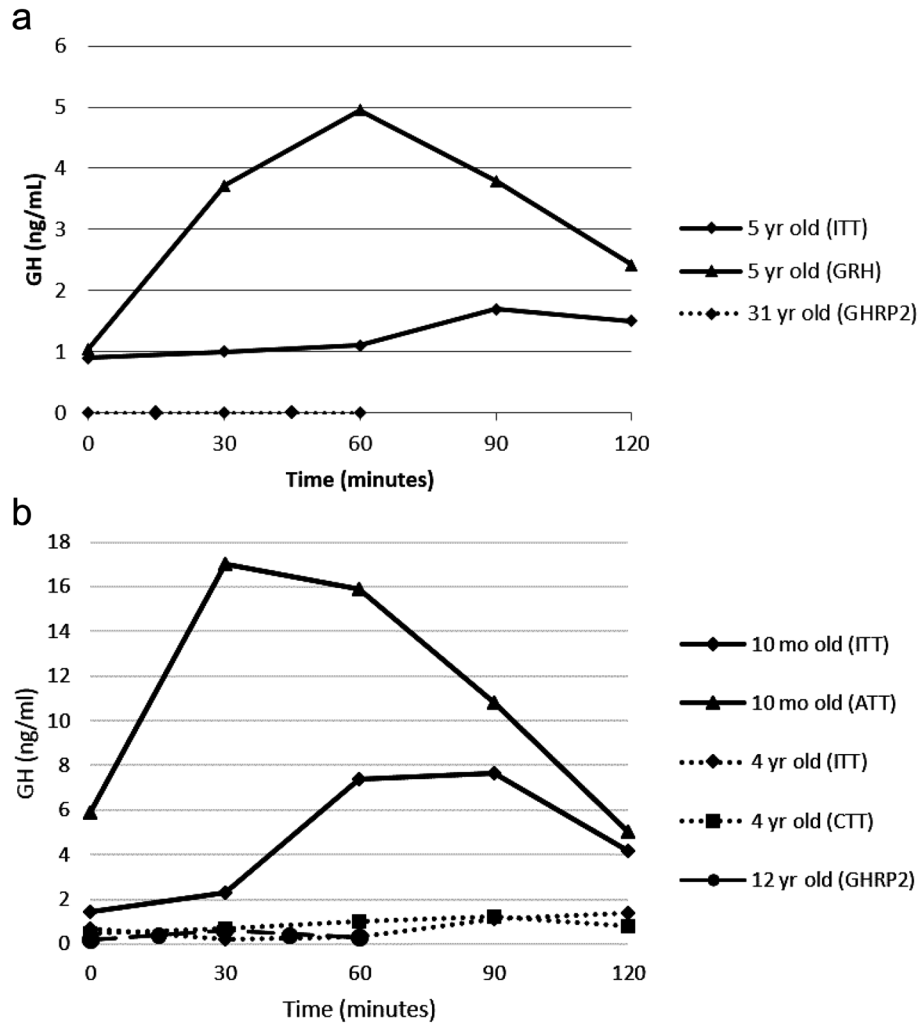


Fig. 1. a) Longitudinal data for a GH stimulation test (Case 1). Insulin tolerance test (ITT) and GH-releasing hormone (GHRH) tests were performed when the patient was 5 yr old. GH releasing peptide 2 (GHRP2) test was performed, and GH secretion was not found when the patient was 31 yr old. b) Longitudinal data for a GH stimulation test (Case 3). ITT and ATT tests were performed when the patient was 10 mo old. ITT and clonidine tolerance tests (CTT) were performed when the patient was 4 yr old. GHRP2 test was performed when the patient was 12 yr old. The peak GH level decreased markedly during the second and the third test.

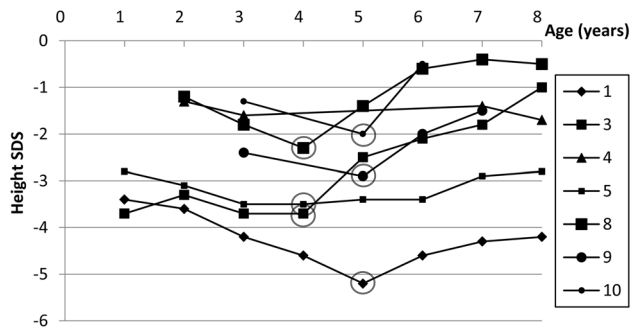


Fig. 2. Shift in height standard deviation scores with severe GH deficiency. The height SDS declined over time, but rose after all patients commenced GH replacement therapy. GH replacement therapy was very effective in increasing growth, except for two cases: Case 1 who underwent treatment twice a week, which was the standard practice more than 25 years ago, and Case 5 who complied poorly with treatment. ○: The start of GH replacement therapy.

with an interval of several years. The peak GH level fell to a low at the second test, even when factoring in all age-related secretory patterns of growth hormones. Figure 2 shows a shift in the height SDS with GHD in patients from 1 to 8 yr of age. The height SDS declined over time, and all patients subsequently commenced GH replacement therapy at a mean age of 5.2 ± 2.4 yr (mean \pm SD). Case 4 exhibited “growth without GH”, although she was severely GH-deficient. GH replacement therapy was very effective in all treated patients except for two cases: Case 1 underwent twice-a-week treatment when this was the standard practice more than 25 yr ago, and Case 5 was poorly compliant with the treatment.

Figure 3 shows the results of a TRH stimulation test in seven patients who underwent the test before commencing levothyroxine. Three patients (Cases 5, 9, 10) showed normal free T3 and free T4 levels, and normal TSH responses. The serum basal TSH levels were elevated subsequently in all three patients and levothyroxine was commenced. Four patients (Cases 1, 3, 4, 12) with normal and low-normal

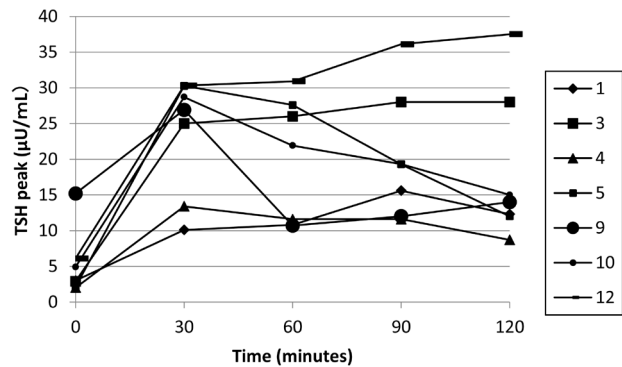


Fig. 3. Thyrotropin-releasing hormone tests. Seven patients who were levothyroxine-naïve underwent thyrotropin-releasing hormone (TRH) tests in our department. Three patients (Cases 5, 9, 10) showed normal free T3 and free T4 levels, and normal TSH responses. The serum basal TSH levels were elevated subsequently in all three patients and levothyroxine was commenced. Four patients (Cases 1, 3, 4, 12) with normal and low-normal free T4 levels had delayed or prolonged responses.

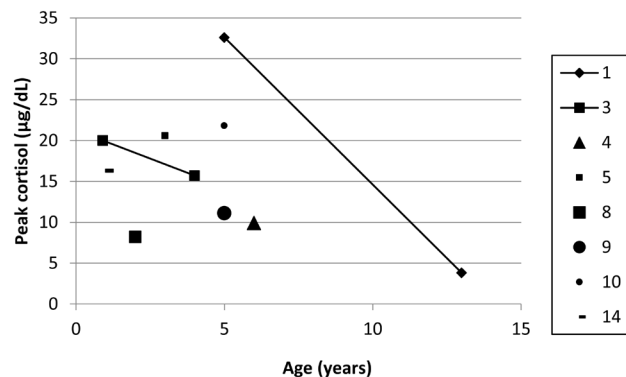


Fig. 4. Cortisol peak levels of insulin-induced hypoglycemia tests. Eight patients underwent an insulin tolerance test (ITT). The peak cortisol level was under 20 µg/dL in four patients. Cases 1 and 3 underwent the ITT test twice: peak cortisol level declined over time for both.

free T4 levels had delayed or prolonged responses.

Figure 4 shows peak cortisol levels, as revealed by ITT, in eight patients. The peak cortisol levels were under 20 µg/dL in four

patients. The peak cortisol concentrations declined over time in Cases 1 and 3.

Head MRI findings

Ten patients underwent a head MRI at our hospital (Table 1). All patients presented a very thin pituitary stalk. Six out of ten had a small anterior pituitary lobe (8) and five had an ectopic posterior lobe.

Other clinical symptoms

Obesity was found in three patients (body mass index [BMI] = 33~45). Thermoregulatory dysfunction was observed in two patients and sleep disturbance in one patient. These symptoms were thought to be due to an abnormal hypothalamus. Hyperlipidemia, a unilateral cleft lip, a tic disorder and ventricular septal defects were also observed. Seizures was exhibited in one patient. *HESX1* was not detected in Cases 10 and 12.

Case Presentation

Case 1 (progressively decreasing endocrine function)

She is now a 33-yr-old woman. She was born after 39 gestational weeks, with a birth weight of 2980 g. No medical episodes related to hypopituitarism were demonstrated in the neonatal period. She was born with a unilateral cleft lip and palate. She visited an ophthalmologist with a chief complaint of strabismus when she was 22 mo old. She did not undergo head MRI at the time. She visited our institution when she was 5 yr old with a chief complaint of short stature. She exhibited a height of -5.3 SDS and presented GHD with a GHRH test and ITT. She had bilateral optic nerve hypoplasia and was diagnosed with SOD. A septum pellucidum was detected by head MRI. She started GH replacement therapy and levothyroxine hormone replacement therapy from 5 yr of age. The peak cortisol level on the ITT at 13 yr of age was lower than at 5 yr of age (Fig. 4), therefore she was

started on oral hydrocortisone. She underwent GnRH test twice. The peak levels of LH and FSH declined at the second test. She started hormone replacement therapy for hypogonadotropic hypogonadism when she was 17 yr old. GHRP2 test was performed, and GH secretion was not found when the patient was 31 yr old (Fig. 1a). She did not have diabetes insipidus.

Case 4 (Growth without GH)

She is now a 13-yr-old girl. She was born at 32 gestational weeks, with a birth weight of 2162 g because of premature membrane rupture. She presented mild neonatal hypoglycemia and mild respiratory problems in the neonatal period. She visited our institution because of short stature when she was 5 yr old. An ATT and a CTT revealed that she had GHD. At that time, she did not exhibit hypothyroidism or adrenal insufficiency. Her septum pellucidum was absent on head MRI and she was diagnosed with SOD. She did not have optic nerve hypoplasia. Despite GHD, her height SDS was above -2 SDS. She presented growth without GH as her height remained above -2 SDS until 11 yr of age. Subsequently, GH replacement therapy was commenced. She was obese, and exhibited thermoregulatory dysfunction and sleep disturbance as well.

Case 6 (precocious puberty)

She is now a 12-yr-old girl. She was born at 39 gestational weeks, with a birth weight of 2914 g. She was diagnosed with bilateral optic nerve hypoplasia when she was 3 mo old. Mammary development started at 6 yr of age. She was diagnosed with precocious puberty based on GnRH testing when she was 9 yr old. She was subsequently started on a GnRH agonist. Head MRI demonstrated a very thin pituitary stalk and ectopic posterior lobe. The patient did not exhibit agenesis of the septum pellucidum or hypoplasia of the pituitary anterior lobe. Normal pituitary hormone secretion was noted except for in the hypothalamus-pituitary-gonadal axis.

Discussion

In this study, seventy-eight percent of SOD patients were found to have endocrinological abnormalities; GHD and central hypothyroidism were the most common disorders. The prevalence of endocrinopathies in SOD patients in Europe is 62~80%, with GHD being the most common (6). Thirteen out of 14 patients were born at an appropriate/large body size for their gestational age. Compared with congenital GHD children without optic nerve hypoplasia, SOD patients presented with a greater birth height and weight (10). A significantly short stature during the fetal period is uncommon in SOD patients.

A thin pituitary stalk was apparent in all our patients. The existence of an invisible or thin stalk led to a slow decline in hormone secretion (11, 12). Cases 1 and 3 exhibited a gradual decrease in hormone secretion. On follow-up, SOD patients notably demonstrated a progressive worsening of hormone secretion because of a characteristically thin pituitary stalk. We should note that there may be a gradual decrease in hormone secretion even if pituitary hypoplasia is not apparent, as in Case 10.

Growth without GH was observed in Case 4. Growth without GH is commonly associated with the postsurgical resection of suprasellar/hypothalamic tumors and leads to metabolic abnormalities. It is related to the presence of growth-promoting factors, which are independent of GH, and also with the excessive secretion of insulin (7, 13). We did not evaluate insulin resistance in this case, but the patient's obesity seemed to be related. Thermoregulatory dysfunction and sleep disturbance may also be related to a damaged part of the hypothalamic pituitary system. An abnormal body composition, metabolic abnormalities and a low quality of life are the typical signs of severe GHD. GH replacement therapy improved these symptoms in adult GHD (14). In children, serum lipid profiles, lean body mass and bone mineral content were improved by one or two years of GH

replacement therapy (15, 16). We postulate GH replacement therapy is effective for metabolic abnormalities caused by GHD; however, the efficacy of GH replacement therapy for metabolic abnormalities in those who exhibit growth in the absence of GH needs to be demonstrated.

Although SOD patients frequently demonstrate delayed puberty as a characteristic symptom of hormone deficiency, Case 6 showed precocious puberty. Several SOD patients with precocious puberty have previously been described (8, 17–21). GH replacement therapy and arachnoid cysts are said to be related to precocious puberty (17), but the definitive mechanism responsible for this is unknown. Most SOD patients with precocious puberty have a normal pituitary structure with agenesis of the septum pellucidum (8); several disorders which control the onset of puberty above the hypothalamus seem to be associated with this characteristic. Recently, gonadotropin-releasing hormone-regulating factors, such as kisspeptin, reelin and tachykinin 3, have been found (22). We hope to investigate mechanisms relating to precocious puberty in SOD patients in the future.

Diabetes insipidus was observed in Case 3. A normotopic, poorly-formed pituitary lobe causes diabetes insipidus, which will not occur with a well-formed pituitary lobe (23). We should note the presence of diabetes insipidus when the posterior lobe is hypoplastic. We should be also careful about diabetes insipidus when an ectopic posterior lobe is detected. An ectopic posterior lobe refers to a newly formed pituitary posterior lobe on the proximal portion of the dissected pituitary stalk. It has an accumulation of secretory granules containing posterior pituitary hormones, which normally migrate to the posterior pituitary lobe from the eminentia mediana. Ectopic posterior lobe suggests dissection of the pituitary stalk for some reason (24).

Our study revealed that it took approximately 22 mo to evaluate pituitary function, although most patients visited ophthalmologists in early infancy. SOD patients are associated with a high

incidence of pituitary hormone abnormalities. Therefore, an immediate endocrinological evaluation is needed after each diagnosis of SOD. The delay in evaluation of pituitary function may be because most general ophthalmologists are not very familiar with the clinical features of SOD. Sudden death in SOD patients related to adrenal insufficiency has also been reported (25). Fortunately, our patients did not present with severe signs of hypopituitarism during infancy. Those involved in children's health care need to be better educated on the characteristic features of SOD.

As this study was a retrospective study in a single center, it may have an unintended selection bias. As a result, a multicenter prospective study of SOD is required in the future.

Conclusion

We herein report on the endocrinological features of Japanese SOD patients. All of our SOD patients presented with a thin pituitary stalk, and 78% displayed endocrinological problems. Each case exhibited diverse hormonal abnormalities, with severe GHD and central hypothyroidism being the most common symptoms. A gradual decrease of hormone secretion was an important characteristic. Their endocrinological status should be followed for a long time, even if they do not exhibit any endocrinological problems at evaluation. Precocious puberty was sometimes observed in SOD patients, although hormone deficiencies were more common features. SOD patients usually visited a doctor during early infancy because of eye problems; however, the medical examination did not always lead to endocrine assessments being made. Consequently, children who have eye problems with optic nerve hypoplasia should undertake head MRI imaging. If diagnosed with SOD, it is very important to evaluate pituitary functions and follow them longitudinally.

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