

Sphenoethmoidal meningoencephalocele with variable hypopituitarism: A case report and review of literature

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Abstract. Sphenoethmoidal meningoencephalocele is a rare congenital meningocele with unclear clinical course. Its clinical symptoms are diverse, and this disease is widely observed across all ages. The prognosis of this disease depends on the severity of the central nervous system complications. We reported a case of sphenoethmoidal meningoencephalocele incidentally discovered in a 2-yr-old patient, with the subsequent appearance of diabetes insipidus at school age. An endocrinological evaluation performed when the patient was nine years old using the TRH/CRH/LH-RH load test showed a low response of gonadotropins and slightly hyper-response and normal response of ACTH and TSH, respectively. GH provocative tests indicated severe GH deficiency. Desmopressin and GH treatment efficiently improved his growth rate and quality of life. His pituitary function had presumably been normal from the neonatal period to infancy, but the dysfunction gradually progressed over the next few years along with his physical growth. The symptoms were suspected to be the product of the natural course of his hypothalamus or pituitary gland degeneration, or were otherwise due to gradual damage by chronic mechanical compression or extension. These findings underscore the importance of conducting careful systemic management in the long term, specifically with respect to the endocrinological evaluation of sphenoethmoidal meningoencephalocele.

Key words: sphenoethmoidal meningoencephalocele, hypothalamus, pituitary, diabetes insipidus, growth hormone deficiency

Introduction

Meningoencephalocele is a rare congenital malformation characterized by herniation of the brain tissue through a defect in the skull bone. A cranial meningocele comprises a cerebrospinal fluid-filled meningeal sac only, whereas a cranial encephalocele contains a sac plus cerebral cortex, cerebellum, or portions of the brain stem (1). Depending on the anatomical location, meningoencephalocele is classified as trans-ethmoidal, spheno-ethmoidal, spheno-orbital, spheno-maxillary, or trans-sphenoidal type (2). Some frontal lesions are associated with a cleft lip and palate. Congenital malformations associated with sphenoidal meningoencephalocele manifest as particular clinical features, including (i) characteristic malformation of the face and head and functional abnormalities of the (ii) optic nerve, (iii) central nervous system, and (iv) hypothalamus and pituitary gland. The symptoms vary

considerably depending on the size and location of the meningoencephalocele. The age of appearance of the symptoms also varies broadly, from the early neonatal period to adulthood (3). Sphenoidal meningoencephalocele is likely to cause various complications, including a dysmorphological face and head and abnormalities of the central nervous system, optic nerve, pituitary, and hypothalamus, depending on the size and location of the lesion and the involvement of brain tissues (4, 5). Regarding hypothalamic and pituitary dysfunction, insufficient secretion of hormones from the anterior and posterior lobe of the pituitary gland is relatively variable (3).

We herein report a boy with sphenoidal meningoencephalocele incidentally discovered when he was 2 yr old in whom the clinical symptoms of hypopituitarism became clinically apparent during childhood.

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Case Report

A Japanese boy was born via vaginal delivery at 41 weeks' gestation. His birth weight and height were 3,556 g (+ 0.9 standard deviation [SD]) and 50.8 cm (+ 0.5 SD), respectively. Cleft lip was detected at birth, and he was referred to the department of dental and oral surgery at Oita University Hospital. At that time, he also visited the pediatric department, and a small (2 mm in diameter) mass in the right medial canthus was also detected. When he was 3 mo old, he subsequently underwent cheiloplasty to repair the unilateral cleft lip, and testicular fixation was performed on the right moving testis when he was 2 yr old. Head magnetic resonance imaging (MRI) was performed to evaluate the patient's benign mass at the right eye, and a defect of the corpus callosum and sphenoidal meningoencephalocele were incidentally detected (**Fig. 1**).

The brain abnormalities seemed asymptomatic; hence, the patient was followed up at the outpatient clinic of the pediatric department. At four years old, he underwent an operation to remove the right eye mass. At 8 yr old, he consulted our hospital again with complaints of polydipsia, polyuria, and growth retardation (height, -2.0 SD). A physical examination revealed minor anomalies, such as saddle nose, blepharophimosis, and a small penis. Brain MRI demonstrated a defect in the corpus callosum and ampulla with sphenoidal meningoencephalocele but did not clearly reveal the pituitary gland (**Fig. 2**).

He was hospitalized for an endocrinological evaluation when he was 9 yr old. He had polyuria (daily urine volume $\geq 3,000$ ml) with diluted urine (urine osmotic pressure ≤ 300 mOsm/kg). Thus, water restriction and antidiuretic hormone (ADH) load tests were performed. We diagnosed the patient with diabetes insipidus because his maximum urine osmotic pressure was less than 360, his minute water restriction was 326 mOsm/kg, and the ADH load increased the urine osmotic pressure to 561 mOsm/kg. A TRH/CRH/LH-RH load test showed a low response of gonadotropins and slightly hyper-response of ACTH with a normal TSH response (**Table 1**). The serum levels of free T3 and T4 were 4.3 pg/mL and 1.1 ng/dL, respectively, indicating a normal thyroid function. Arginine and GH-releasing peptide (GHRP)-2 provocative tests indicated severe GH deficiency based on the GH peak values of 0.37 and 2.2 ng/dL, respectively, with a low IGF-1 level (26 ng/mL; normal range, 84–350). Oral desmopressin treatment for central diabetes insipidus was relatively effective in managing his polydipsia and polyuria and normalizing his sleep rhythm. GH treatment has efficiently improved his growth rate (**Fig. 3**). No pubertal development was observed by 10 yr and 6 mo.

We performed whole-exome sequencing for the case-parent trio but did not detect any pathogenic variants in the candidate genes, including the *ARTN2* gene, a mutation of which may have caused congenital pituitary hormone deficiency and diabetes insipidus (data not shown).

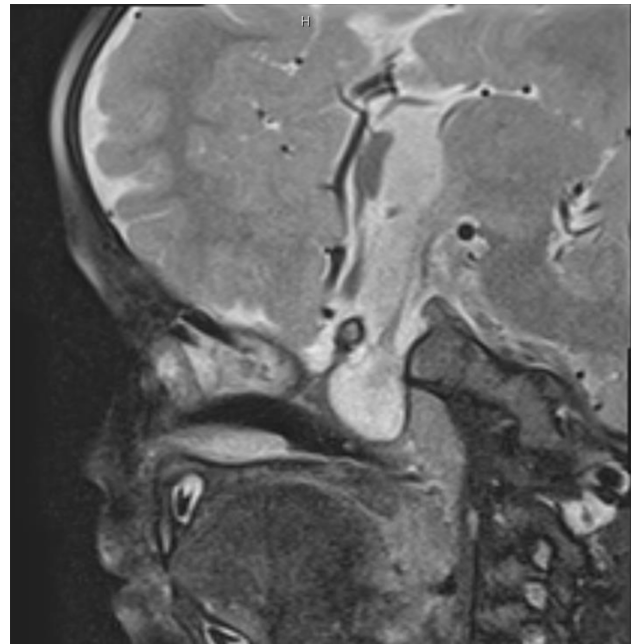


Fig. 1. T2-weighted magnetic resonance imaging at 2 yr old. A sphenoidal meningoencephalocele was incidentally detected.



Fig. 2. Magnetic resonance imaging at 9 yr old. T1-weighted imaging did not clearly reveal the pituitary gland with a thin pituitary stalk (arrow). No major anomalies of the cerebrum, cerebellum, or brain stem were observed, except for a defect in the corpus callosum.

Discussion

Meningoencephalocele is etiologically classified as congenital, idiopathic, or secondary to traumatic damage (1). Congenital meningoencephalocele is an inborn malformation with a frequency of 1 in 3,000–

Table 1. TRH/CRH/LH-RH test

	0 min	30 min	60 min	90 min	120 min
TSH (μIU/min)	1.6	9.8	7.1	5.7	4.2
PRL (ng/mL)	22.6	51.8	41.6	29.9	23.6
ACTH (pg/mL)	30.8	105.5	70.8	39.4	32.9
Cortisol (μg/dL)	13.2	23.6	23.6	21.1	18.6
LH (mIU/mL)	0.1	0.66	0.80	0.80	0.76
FSH (mIU/mL)	0.42	1.49	1.98	2.32	2.47

Normal ranges of peak values: TSH, 5–30; PRL, higher than twice of the basic level at 30 min; ACTH, 28–130.6; cortisol, 10.6–26.9; LH, 0.4–6.0 (prepuberty); FSH, 6.3–15.6 (prepuberty).

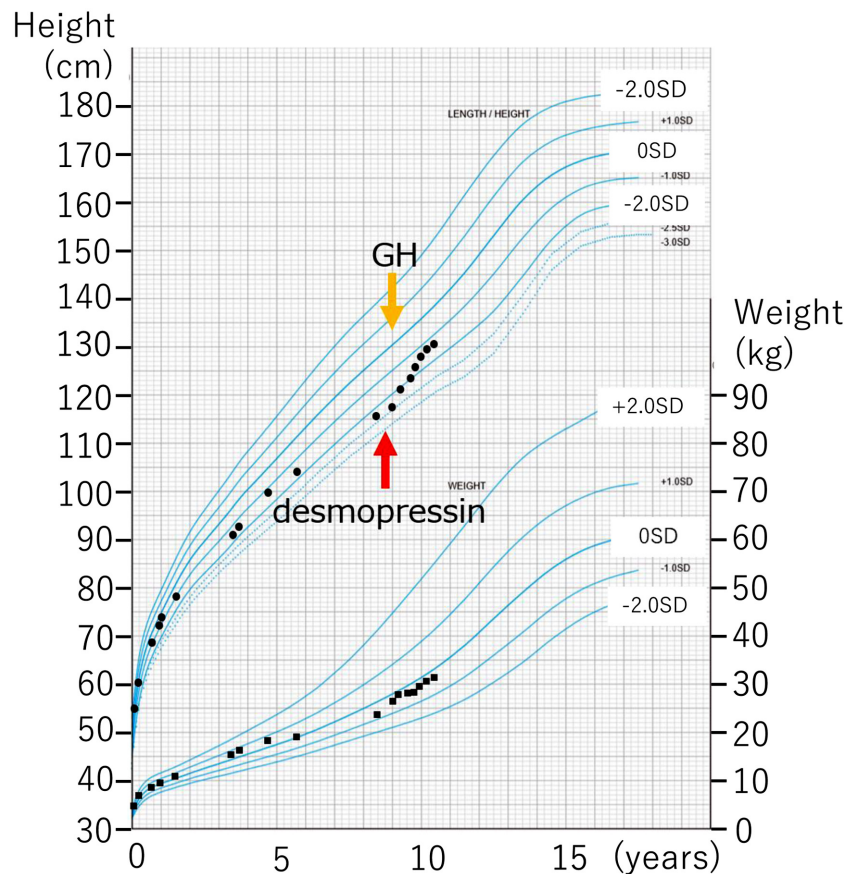


Fig. 3. Growth chart of the patient. The arrows indicated the starting points of desmopressin and GH treatment.

5,000 live births, and the sphenoidal type is as rare as approximately 5% of all basal meningoencephaloceles, with a frequency of 1 in 700,000 live births (6, 7). Sphenoidal meningoencephalocele is derived from the persistent cricopharyngeal canal at 50 d of embryonic developmental age, caused by the incomplete ossification of the sphenoidal bone (2). The third ventricle drops down to the hypopharynx, and brain tissues, such as the hypothalamus or optic chiasm, are displaced downward, thus causing neuroendocrinological symptoms.

The clinical characteristics at diagnosis are essentially dependent on the patient’s age. We briefly summarized the clinical findings of the reported cases of sphenoidal meningoencephaloceles with pituitary hormone deficiencies (Table 2). In the early neonatal

period, external malformations of the face and head are characteristics of sphenoidal meningoencephalocele, such as hypertelorism, a cleft lip and palate, and a high palate, all of which are caused by developmental midline craniofacial defects (8). Meningoencephalocele may be discovered incidentally on head computed tomography or MRI for the evaluation of external anomalies, as in the present case. Respiratory distress is clinically important for infants and is caused by obstruction due to prolapse of the encephalocele into the oral and nasal cavity. Hypothalamic dysfunction and hypopituitarism are clinically not observed in most cases during the neonatal period (3, 4).

However, clinical symptoms of sphenoidal meningoencephalocele discovered during adolescence and

Table 2. Clinical findings of the reported cases of sphenothmoidal meningoencephaloceles with pituitary hormone deficiencies

Reference (First author)	No.	Age (yr)	Sex	Disturbed hormones	Malformations	Hormonal replacements
(3) Spacca B	1	1/12	F	GH	Callosal agenesis (septo-optic dysplasia)	GH (for 8 years)
(11) Ogiwara H	2	2	M	ACTH, TSH	Orbital hypoplasia, Chiari malformation	N/D (stable after surgery)
(3) Spacca B	3	5	M	Hypopituitarism, GH	None	N/D (panhypopituitarism)
(8) Koral K	4	6	F	GH, TSH, ACTH	Mid-face hypoplasia, anophthalmia, microphthalmia, cleft palate, agenesis of the corpus callosum	L-T4, HDC
(15) Morioka M.	5	8	F	GH, ADH	Morning glory syndrome (eye)	GH
Present case	6	8	M	GH, AVP, LH, FSH	Cleft lip, agenesis of the corpus callosum and ampulla, saddle nose, blepharophimosis, moving testis, small penis	GH, AVP
(16) Holanda MMA	7	9	F	GH	Cleft lip and palate, hypertelorism (low height/weight development and normal intellectual development)	GH (clonidine)
(3) Spacca B	8	12	M	LH, FSH, TSH	None	No hormone replacement (after surgery)
(11) Ogiwara H	9	13	M	ACTH, TSH	Cleft lip and palate, agenesis of the corpus callosum	N/D (after surgery)
(3) Spacca B	10	14	M	Panhypopituitarism	Callosal agenesis (septo-optic dysplasia)	No hormone replacement (after surgery)
(8) Koral K	11	15	M	fT4, cortisol, GH	None (normal intelligence and neurological development)	GH, L-T4, HDC
(17) Sanjari R	12	17	M	GH, ACTH, LH	Hypertelorism, cleft lip, high-arched palate	N/D
(3) Spacca B	13	18	M	Panhypopituitarism	Morning glory syndrome (eye)	Improvement in hormone functions (after surgery)
(4) Abe T	14	26	F	PRL (high), ADH	Hypertelorism, morning glory syndrome	HDC (after surgery), AVP
(10) Maric A	15	31	F	GH, PRL (high), ADH, LH (slightly low)	None (no facial anomaly)	L-T4

N/D, not described; L-T4, levothyroxine; HDC, hydrocortisone; AVP, arginine vasopressin.

adulthood are mainly associated with hypopituitarism, such as delayed puberty, short stature, and primary amenorrhea (3, 9). Additionally, nonspecific symptoms of the brain, such as a headache, visual disturbance due to meningitis, and/or cerebrospinal fluid leakage, are sometimes observed (10). It is suspected that pituitary dysfunction gradually occurs due to degenerative changes in the hypothalamus or pituitary glands induced by chronic mechanical compression or repeated meningitis (11).

The present case showed clinical symptoms characteristic of both neonatal and adult cases. The presence of micropenis and migratory testis may suggest

latent gonadotrophic dysfunction during the fetal stage. The pituitary function otherwise was presumably normal from the neonatal period to infancy, with the dysfunction gradually progressing over the next few years. We were unable to determine the exact age of onset because of the lack of a clinical checkup in patients aged 4 to 9 yr. Ideally, the pituitary function of the patient would have been carefully followed up over the years, as an underlying hypothalamic hypo-adrenal function might cause dysfunction in the future.

Septo-optic dysplasia (SOD)/de Morsier's syndrome is a congenital malformation syndrome overlapping

with sphenoidal meningoencephalocele. This syndrome is characterized by optic nerve hypoplasia, pituitary endocrine dysfunction, and midline brain abnormalities, such as agenesis of the septum pellucidum or corpus callosum, although only 30% of patients present all three major symptoms of the brain, eyes, and pituitary gland. Pituitary dysfunction is observed in 44 to 81% of these patients, most of whom are suspected of having hypothalamic hypopituitarism (12–14). These findings of endocrinological dysfunction overlap with those associated with sphenoidal meningoencephalocele, suggesting that the same pathogenesis underlies both of these congenital disorders. The cause of SOD remains unknown in most cases, and a combination of genetic and environmental factors may play a role in its development. The same might hold true for sphenoidal meningoencephalocele as well. We performed whole-exome sequencing for the case-parent trio but did not detect any candidate genes. Further clinical and basic studies will be required to clarify the pathogenesis of sphenoidal meningoencephalocele.

Conclusion

Sphenoidal meningoencephalocele is a rare congenital malformation of unknown pathogenesis and presents with various symptoms. Our findings underscore the importance of conducting careful systemic management in the long term, specifically with respect to the endocrinological evaluation of patients with sphenoidal meningoencephalocele.

Conflict of interest: The authors declare no conflicts of interest in association with the present study.

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