Original Article

Septo-Optic Dysplasia [SOD] and Endocrine Abnormalities in Khon Kaen, Thailand

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Background: Septo-optic dysplasia [SOD], is a rare congenital syndrome being defined by the association of 2 of 3 features: optic nerve hypoplasia [ONH], midline brain abnormalities, and hypothalamic-pituitary endocrine deficiencies.

Objective: Our aim was to describe the clinical manifestations and type of hypothalamic-pituitary dysfunction in SOD patients seen at Srinagarind Hospital, Khon Kaen, Thailand.

Materials and Methods: A retrospective cross-sectional study was performed. The medical records of SOD patients between 0 to 15 years of age followed-up at the Pediatric Endocrinology Clinic, Srinagarind Hospital, between January 2013 and April 2017 were included. Clinical manifestations and endocrine abnormalities were reviewed.

Results: A total of 60 SOD patients, 31 boys (51.7%) and 29 girls (48.3%) were included. The median age at presentation was 8.5 (IQR: 4.8 to 14.2) months. The most common initial manifestation was abnormal eye movement (58.3%). Three-fifhts (61.7%) of patients had developmental delays. Structural brain abnormalities were documented in all of patients. The most common endocrine abnormality was hypothyroidism (45.0%). Other hypothalamic-pituitary disorders were secondary adrenal insufficiency (16.7%), central diabetes insipidus (11.7%), growth hormone deficiency, (11.7%), and hypogonadism (3.3%). Twenty-five patients (41.7%) had no abnormal hypothalamic pituitary hormones. Appropriate hormonal replacement and rehabilitation were given to all patients with disorders.

Conclusion: There are variations of the clinical manifestations of SOD which need to be investigated systemically. Early detection of abnormalities and endocrine dysfunctions lead to timely treatment with good neurodevelopmental outcomes.

Keywords: Septo-optic dysplasia, De Morsier syndrome, Endocrinopathies, Hypopituitarism, Khon Kaen

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Septo-optic dysplasia [SOD] or De Morsier syndrome is a rare congenital condition, first described by Reeves in 1941[1]. The SOD phenotype is highly heterogeneous, being defined by the association of 2 of 3 features: optic nerve hypoplasia [ONH], midline neuroradiological abnormalities (i.e., agenesis of the corpus callosum and absence of the septum pellucidum) and hypothalamic-pituitary endocrine deficiencies. Only 30% of patients presented all three features[2]. The incidence of SOD is 1 in 10,000 live births with the prevalence between male and female being equal[3]. The main reported clinical finding is hypopituitarism (62 to 80%)[4]. SOD used to be rare in Thailand and most cases were referred by ophthalmologists. There has, however, been an increase in the number of cases at pediatric referral centers including Srinagarind Hospital, Khon Kaen University. The current study thus aimed to characterize the clinical presentations and endocrine abnormalities among children with SOD at a tertiary referral hospital in the northeastern Thailand with hopes of improving early detection and management.

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Materials and Methods

A retrospective cross-sectional study was performed. Medical records were included of SOD patients between 0 and 15 years followed-up at the Pediatric Endocrinology Clinic, Srinagarind Hospital between January 2013 and April 2017. Clinical

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manifestations and endocrine abnormalities were reviewed. The study was approved by the Ethics Committee of the faculty of Medicine, Khon Kaen University.

The diagnosis of SOD was based on the presence of at least 2 of 3 features (a) optic nerve hypoplasia [ONH], (b) midline brain abnormalities especially of absence or hypoplasia of septum pellucidum and/or corpus callosum from brain magnetic resonance image [MRI], and/or (c) hypothalamic-pituitary endocrine dysfunction. ONH was documented by ophthalmologists at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. Clinical manifestations of hypothalamic-pituitary hormone deficiencies were recorded. Screening of pituitary hormones included IGF-1 and IGFBP3. In addition, the 1 μg ACTH test, thyroid function tests, urinalysis and serum electrolyte were performed in all SOD patients. Further hormonal tests were performed in patients with abnormal screening tests[5]. Plasma gonadotropins and sex hormones were determined in girls and boys over 13 and 14 years of age, respectively.

Growth hormone deficiency [GHD]

Two growth hormone stimulation tests (insulin tolerance and clonidine tests) were performed in all patients of short stature; with low screening IGF-1, IGFBP3 levels for age and sex specific reference ranges. The cut-off level for GHD is the peak GH level below 7.0 ng/mL for both 2 tests.

Adrenocorticotropin [ACTH] deficiency

The low dose (1 μg) ACTH test was done in all patients. ACTH deficiency was documented in patients who had peak cortisol levels below 18 μg/dL.

Antidiuretic hormone [ADH] deficiency or central diabetes insipidus [DI]

The vasopressin challenge test was performed in patients with symptoms of polyuria, polydipsia, urine specific gravity [sp.gr] below 1.010, being under 3 years of age, and hypernatremia. The water deprivation test was done among those who had a normal sodium level but who had polyuria, and/or polydipsia with low urinary specific gravity.

Statistical analysis

SPSS and Microsoft Excel were used to calculate the descriptive statistics, (viz., average percentages, medians, means and standard deviations [SD]).

Results

Sixty SOD patients, 31 boys (51.7%) and 29 girls (48.3%) were included. The median age at presentation was 8.5 (IQR; 4.8 to 14.2) months. Most patients had a normal gestational age (73.3%) and normal birth weight. The demographic characteristics are presented in Table 1. The most common initial manifestation was abnormal eye movement (i.e.; nystagmus), which was found in 35 patients (58.3%). Based on the eye examination, 48 patients (80.0%) had optic nerve hypoplasia [ONH]. MRI of the brain revealed structural brain abnormalities in all patients, absence of the septum pellucidum was found in 43 patients (71.7%) (Table 2); endocrine abnormalities were documented in 35 (58.3%); and hypothyroidism in 27patients (45.0%) (Table 3). Hormone replacement therapy was given to all patients who had any hormonal deficiency.

Discussion

Septo-optic dysplasia [SOD] has a wide variation in clinical manifestations, as well as associated neurodevelopment, and endocrine dysfunction[6,7]. Prenatal diagnosis of SOD is suspected in fetuses presenting with absence of septum pellucidum during the ultrasound examination[8]. Likewise, during the neonatal period, a diagnosis of SOD should be suspected in newborns with hypoglycemia, jaundice, micropenis with or without undescended testes, nystagmus, and abnormal eye presentation with or without associated midline abnormalities such as cleft palate. In these infants, baseline endocrine tests should be performed.

MRI brain images in conjunction with dynamic studies of pituitary function can be used to confirm the diagnosis. Optic nerve hypoplasia [ONH] is generally the first manifestation of the syndrome[9]; it can be uni- or bilateral, manifest as nystagmus, and present a smaller than usual optic disc. The degree of visual impairment is variable, ranging from normal vision to complete blindness. Four-fifths (80%) of the patients in the current study had ONH, and abnormal eye movement was the most common presentation in more than half of the patients (58.3%). The latter was related to a poor prognosis vision.

The most common brain malformation was absence of the septum pellucidum (71.7%). A high prevalence of developmental delay had been reported[10,11] and three-fifths (61.7%) of cases in the current study had developmental delay, ranging from isolated focal defects to global delay. Endocrinopathies

Table 1. Demographic characteristics of 60 SOD patients

Characteristics	n
Age at presentation (months) median (IQR)	8.5 (4.8 to 14.2)
Sex	
Male (%)	31 (51.7)
Female (%)	29 (48.3)
Birth weight (g) mean ± SD	2,867.5±608.1
Gestational age	
Term (%)	44 (73.3)
Preterm (%)	8 (13.3)
Post-term (%)	2 (3.3)
Unknown (%)	6 (10.0)
Abnormal neonatal history	
Seizure	2 (3.3)
Hypoglycemia	7 (11.7)
Jaundice	8 (13.3)
Sepsis	2 (3.3)
Teratogenicity	2 (3.3)
Others (respiratory distress syndrome, persistent pulmonary hypertension of the newborn, hypoxic ischemic encephalopathy, dislocation of the hip, arthrogryposis)	4 (6.7)

Table 2. Clinical manifestations of 60 SOD patients

Manifestations	n (%)
Eye presentation	
Abnormal eye movement	35 (58.3)
Poor vision/Blindness	20 (33.3)
Eye examination	
Optic nerve hypoplasia [ONH]	48 (80.0)
Unilateral ONH	8 (13.3)
Bilateral ONH	40 (66.7)
Microphthalmia	6 (10.0)
Others e.g. strabismus, amblyopia, cloudy cornea, microcornia	13 (21.7)
Brain malformation	
Absence of septum pellucidum	43 (71.7)
Abnormal of corpus callosum	19 (31.7)
Pituitary hypoplasia	4 (6.7)
Schizencephaly	19 (31.7)
Holoprocencephaly	4 (6.7)
Other malformations e.g. ectopic pituitary bright spot, frontal lobe atrophy/agenesis, porencephaly, colpocephaly, hydrocephalus, polygyria	10 (16.7)
Boys	
Undescended testis	1 (3.3)
Micropenis	3 (9.7)
Short stature	10 (16.7)
Abnormal head size	7 (11.7)
Macrocephaly	2 (3.3)
Microcephaly	5 (8.3)
Delayed development	37 (61.7)

Table 3. Endocrine abnormalities in 60 SOD patients

Endocrine abnormalities	n (%)
Growth hormone deficiency	7 (11.7)
Hypothyroidism	27 (45.0)
Adrenal insufficiency	10 (16.7)
Diabetes insipidus	7 (11.7)
Hypogonadism	2 (3.3)
Combined pituitary hormone deficiency	24 (40.0)
No endocrine abnormalities	25 (41.7)

may not be evident at the first visit; some patients developed endocrine abnormalities by the follow-up visit. Brain malformation may manifest as variable endocrine disorders ranging from isolated GH deficiency to deficiency of both anterior and posterior pituitary hormones. The most common endocrine dysfunction was hypothyroidism (45.0%). Hypothyroidism (35%) was also the most common endocrinopathy in a multicenter ASEAN study[12]. Two-fifths (41.7%) in the current study had no endocrine involvement. Normal pituitary function at the initial evaluation does not preclude development of endocrinopathy in the future in children with SOD[13]. It has been suggested that abnormalities of the septum pellucidum and hypothalamic-pituitary axis on neuroimaging can predict the severity of endocrine dysfunction[14].

Neurological deficit is common, ranging from global retardation to focal deficits such as epilepsy or hemiparesis. Three-fifths (61.7%) of patients had developmental delay. Most instances of SOD are sporadic and several etiologies including young maternal age[15], and drug and alcohol abuse have been suggested to account for the pathogenesis. The use of valproate during pregnancy has been implicated as a possible etiology of SOD[16] but the association of SOD with low maternal age is mooted[3,15]. The precise etiology of the condition remains unknown and is most likely to be multifactorial, with a combination of genetic and environmental factors[17].

Reports of screening patients with sporadic SOD have yielded 6 novel heterozygous mutations within HESX1. In an initial series of 228 patients with hypopituitarism, of whom 105 had SOD, 3 heterozygous mutations were initially identified: Q6H, S170L, and T181A[18]. A number of familial cases have been described with an increasing number of mutations in developmental transcription factors including HESX1, SOX2, SOX3, PAX6 and OTX2 being implicated in its etiology[19,20]. Variations in the PROKR2 gene mutation are also associated with hypopituitarism in SOD patients[21]. These factors are essential for normal forebrain and pituitary development. Disruptions to these genes could account for the features observed in SOD and other midline disorders. In most cases, SOD is a sporadic birth defect of unknown cause and does not recur with subsequent pregnancies, as genetic abnormalities are identified in <1% of the patients[4]. The variable phenotypes in this condition are most likely due to the varying contributions of genetic and environmental factors.

Ophthalmologists and neurologists should be concerned at the identification of any of these features in such patients and forward them early to a pediatric endocrinologist. Though not all patients have hypothalamic-pituitary dysfunction at diagnosis, endocrine abnormalities may evolve over time, necessitating long-term evaluation and follow-up for both clinical and hormonal assessments. Early hormonal replacement and rehabilitation can help such patients reach full developmental potential.

Conclusion

Although rare, SOD is one of the most common causes of congenital hypopituitarism in children with midline brain defects. The prevalence of endocrine abnormalities in SOD patients is high and it can evolve overtime. Early detection of abnormalities and endocrine dysfunctions can lead to early treatment with good neurodevelopmental outcomes.

What is already known on this topic?

SOD is one of the causes of congenital hypopituitarism.

What this study adds?

There is a high prevalence of endocrine abnormalities in SOD patients and it can evolve overtime.

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Potential conflicts of interest

The authors no declare conflicts of interest.

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