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Case(s) Report

Septo-Optic Dysplasia Associated with Abnormal Pubertal Development

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Septo-optic dysplasia (SOD) is a congenital anomaly, that is characterized by a triad of optic nerve hypoplasia, structural brain defects, and hypothalamic-pituitary dysfunction. This condition is very rare and it has never been reported in a Thai population. In the present report, the authors described two SOD cases that presented with primary amenorrhea and abnormal pubertal development. Clinical features. Possible etiology of this condition was reviewed.

Keywords: *Septo-optic dysplasia (SOD), Primary amenorrhea, Blindness, Magnetic resonance imaging*

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Septo-optic dysplasia (SOD) is a rare congenital anomaly with a prevalence of about 6.3 per 100,000[1]. Males and females are equally affected. This syndrome is characterized by at least two of the following triads: 1) optic nerve hypoplasia; 2) structural brain defects such as dysgenesis of septum pellucidum or corpus callosum; and 3) hypothalamic-pituitary dysfunction[2-5].

Clinical manifestations of SOD are very variable. Patients may have an isolated pituitary hormone deficiency to pan-hypopituitarism, with mild to severe visual impairment, and various degrees of psychomotor retardation[2,4]. In the present report, the authors described two cases of SOD that were associated with abnormal pubertal development.

Case Report

Case 1

An 18 year-old female presented with primary amenorrhea. She was delivered at term by cesarean section, due to prolapse of the umbilical cord. At birth she had congenital blindness but there was no other abnormality. She had three older brothers, who were normal and healthy. She lived with her parents until the age of 11 years, when she became a boarder at a school for the blind.

In her class, she was the shortest student. Her growth and development were slightly delayed but verbal communication was normal. She had breast development at the age of 10 years, but had no axillary or pubic hair. She denied having polydipsia and polyuria.

Physical examination revealed a female with short stature, but no other stigmata of Turner syndrome. She was 122 cm tall and weighed 38 kg. Her vital signs were normal. Both eyeballs were hypoplastic. Her breast development was at Tanner stage III. She had infantile female external genitalia (Tanner stage I). Other physical examination was unremarkable. There was no abnormal neurological sign.

Her serum follicle stimulating hormone (FSH) level was normal (5.93 IU/L), while serum estradiol level was low (6 pg/mL). Serum prolactin (14.4 ng/mL) and morning serum cortisol levels (11.68 ug/dL) were within the normal ranges. Thyroid function test and adrenocorticotropic hormone (ACTH) stimulation test were normal. Insulin-like growth factor-1 (IGF-1) level was less than 25 ng/mL (normal 87-238 ng/mL) and IGF binding protein-3 (IGFBP-3) level was 0.95 ng/mL (normal 3.4-6.8 ng/mL).

A radiograph of the left hand and wrist was evaluated for bone age, according to the method of

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Greulich and Pyle, and found to be 15 years ± 11.2 months.

Magnetic resonance imaging (MRI) of the brain showed an absence of septum pellucidum and hypoplasia of the optic chiasma and optic nerves on both sides. The pituitary gland was small (2 mm in height) and the pituitary stalk was absent. Ectopic posterior bright spot was noted at the floor of the third ventricle. There was a focal absence of the posterior body of the corpus callosum, associated with eversion of bilateral cingulated gyri. The remaining portion of the corpus callosum appeared to be normal. Normal signal intensity of the brain parenchyma was seen (Fig. 1).

Case 2

A 25-year-old-woman presented with primary amenorrhea. During the prenatal period, her mother took an unknown medication to induce abortion in the first trimester. However, the attempt failed and the pregnancy went on uneventfully until term. She was delivered vaginally without any complication.

The patient had 2 elder sisters, both of whom had normal pubertal development. The patient herself had some breast development but had no axillary or pubic hair. Her mental status and learning ability were normal.

She began to have hearing deficit in early childhood. Her hearing progressively declined until she was partially deaf at the age of 15 years. The hearing impairment was more pronounced in the left than the right ear. Nevertheless, she was able to finish her college education.

One year ago, she consulted a doctor in Bangkok for primary amenorrhea. The doctor prescribed an unknown hormone tablet to be taken once a day for 21 consecutive days. After that, she had one bleeding episode. She received no further investigations or treatment, as she moved to another province soon after that.

Her general appearance was that of a normal female, except for a short stature. She had no stigmata of Turner syndrome. She was 138 cm tall and weighed 33 kg. Her vital signs were normal. Her breast and pubic hair development were at Tanner stage II and I, respectively. No other abnormality was observed.

Laboratory investigation showed normal levels of FSH (5.57 IU/L), luteinizing hormone (LH; 2.97 IU/L) and prolactin (11.64 ng/mL), but low serum estradiol level (< 5 pg/mL). Thyroid function tests were normal. Audiologic analysis revealed bilateral sensory neural hearing loss (SNHL). Brainstem auditory evoked potential suggested normal bilateral retrocochlear pathway.

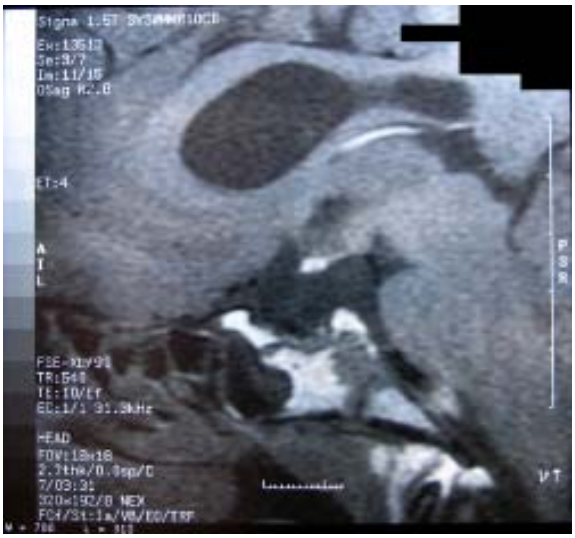

Fig. 1a Corpus callosum dysgenesis, absence of septum pellucidum and pituitary hypoplasia with ectopic posterior bright spot

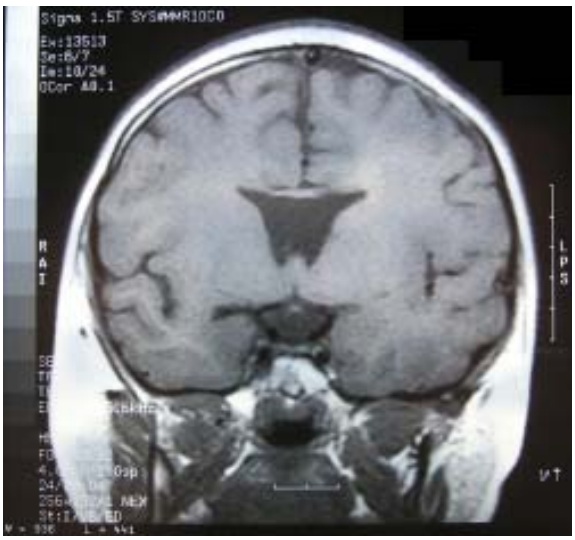

Fig. 1b Corpus callosum dysgenesis, absence of septum pellucidum and pituitary hypoplasia

MRI of the brain showed an absence of the septum pellucidum, with square-off of bilateral frontal horn. The optic chiasma and optic nerves on both sides were normal. The pituitary gland was small (4 mm in height) and the pituitary stalk was absent. Ectopic posterior bright spot was noted at the floor of the third ventricle. The corpus callosum and signal intensity of

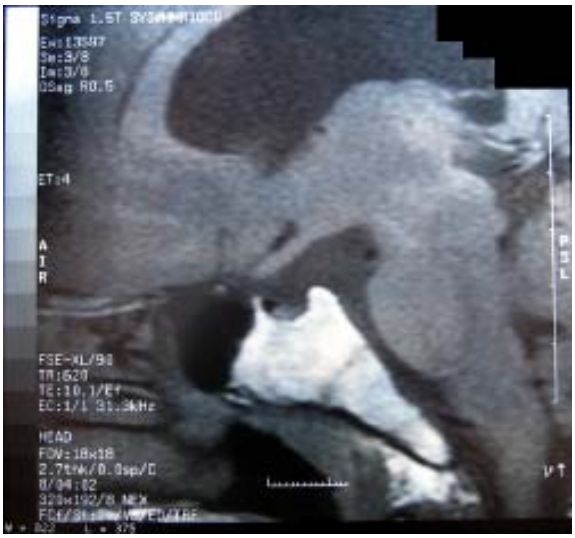

Fig. 2a Normal corpus callosum, absence of septum pellucidum and pituitary hypoplasia

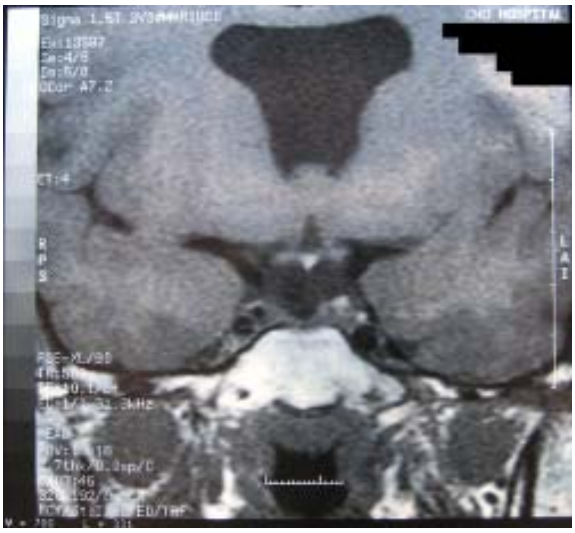

Fig. 2b Normal corpus callosum, absence of septum pellucidum and pituitary hypoplasia with posterior bright spot

the brain parenchyma appeared normal (Fig. 2).

Both cases were diagnosed as SOD with primary amenorrhea. They were treated with combined estrogen and progesterone to induce cyclic withdrawal bleeding. Calcium supplementation was given to prevent osteoporosis.

Discussion

A complete triad of optic nerve hypoplasia, structural brain defects, and hypothalamic-pituitary dysfunction is present in only 30% of SOD cases[1]. In the present report, one case had a complete triad while the other had an absence of septum pellucidum and pituitary dysfunction without optic nerve hypoplasia. A spectrum of structural brain abnormality may range from an isolated midline structural defect to multiple cerebral abnormalities. The most common finding is absent septum pellucidum, as in both of the presented cases. In a report of 8 SOD cases by Polizzi et al[4], several midline facial abnormalities were found such as frontal bossing, hypertelorism, depressed nasal bridge, synophris, microcephaly and macrocephaly.

Hypothalamic pituitary dysfunction is present in approximately 60% of SOD cases[4,5]. The dysfunction may involve a single or multiple pituitary hormone(s) and the severity is not correlated with the extent of structural brain defect[5]. Patients may have growth hormone (GH) deficiency, hypothyroidism, hypogonadotrophic hypogonadism, hyperprolactinemia, diabetes insipidus, hypocortisolism or pan-hypopituitarism. Short stature in the presented cases was probably due to a GH deficiency. However, they would not benefit from GH treatment as the first case already had fusion of her epiphyseal plate and the second case was diagnosed very late in life.

From MEDLINE search, the authors found only one case report of SOD with anosmia. Her brain MRI showed olfactory tract and bulb hypoplasia[6]. There has been no previous report of SOD in association with deafness. One patient in the present report had progressive sensory neural hearing loss, which occurred very early in life. Although brainstem auditory evoked potential was normal, a defect in brain parenchyma above the brain stem, as a part of the SOD dysplasia complex, cannot be completely ruled out. Alternatively, her hearing loss could be an incidental finding due to other acquired causes that were not related to congenital brain abnormality.

The etiology of SOD remains unknown. One possible cause is a vascular disruption of the brain, involving the proximal trunk of the anterior cerebral artery, during the 7th or 8th week of gestation, when the optic nerve, geminal matrix and septum are being formed[7,8]. Recently, a mutation of the homeobox gene, Hesx1, has been reported in association with SOD in humans and mice[9-11]. This gene plays an important role in forebrain, midbrain, Rathke's pouch and pituitary development. Studies in the mouse have shown that *Hesx1* is expressed in the anterior midline endoderm at the onset of gastrulation around embryonic

day 9. Its level diminishes by embryonic day 12 when the anterior pituitary cell types are recognizable, which corresponds to 6^{th} - 8^{th} week of gestation in humans[9,12]. Moreover, *Hesx1* is associated with the initiation of the PROP1-dependent gene program, which is necessary for pituitary development[11]. In SOD cases with variable defects, many different mutations of Hesx1 gene have been reported, such as R160C, I26T, Q6H, S170L, T181A, C509T and 306/307ins AG[10,12]. Nevertheless, Hesx1 mutation is not present in the majority of SOD cases[4]. Mutations of other transcription factors, associated with pituitary development, such as PROP-1, Pitx1/Pitx2, Lhx3/Lhx4, have not been reported in SOD cases.

A diagnosis of SOD should be ruled out when evaluating a child with delayed growth and development, in association with visual impairment. High resolution resonance imaging (MRI) is more sensitive than computerized tomography (CT) in detecting structural brain abnormality. Although SOD is a congenital abnormality, early diagnosis and appropriate management may be the best way to improve the patient's quality of life.

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รายงานผู้ป่วยที่มีกลุ่มอาการ septo-optic dysplasia (SOD)

พัชรดา อมาตยกุล, ทวิวัน พันธศรี, ธีระพร วุฒยวนิช

Septo-optic dysplasia (SOD) เป็นความผิดปกติแต่กำเนิด ลักษณะสำคัญมี 3 ประการ คือ มีการฝ่อของเส้นประสาทตา ร่วมกับความผิดปกติของสมอง และการทำงานที่ผิดปกติของฮัยโปธาลามัสและต่อมใต้สมอง ภาวะนี้พบได้น้อยมากและยังไม่เคยมีรายงานในคนไทย ในบทความนี้ ได้รายงานผู้ป่วย 2 ราย ที่มาพบแพทย์ด้วยภาวะขาดระดูชนิดปฐมภูมิ และมีพัฒนาการทางเพศล่าช้า พร้อมทั้งทบทวนวรรณกรรมเกี่ยวกับลักษณะทางคลินิกและสาเหตุของกลุ่มอาการนี้