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Case Series

Septo-Optic Dysplasia among Children in Central Brooklyn

Aditi Khokhar*, Vatcharapan Umpaichitra and Sheila Perez-Colon

Department of Pediatrics, Division of Pediatric Endocrinology, SUNY Downstate Medical Center, Kings County Hospital Center, Brooklyn, NY, USA

***Corresponding author**

Aditi Khokhar, Department of Pediatrics, SUNY Downstate Medical Center, 445 Lenox Road, Box#49, Brooklyn, NY, USA, Tel: 001-718-613-8605; Fax: 001-718-613-8548; Email: aditi.khokhar@downstate.edu

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Keywords

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- Optic nerve hypoplasia
- Pituitary dysfunction

Abstract

Background: Septo-optic dysplasia (SOD) is a rare condition characterized by midline brain abnormalities, optic nerve hypoplasia and hypothalamic-pituitary deficiencies. Both genetic and environmental factors are involved in its pathogenesis. Genetic abnormalities are identified in only one percent of patients.

Objective: To describe varied clinical spectrum of SOD among five children from different ethnicities living within the same geographical area and to review and identify common maternal and perinatal factors among them.

Method: Retrospective chart review.

Conclusion: Five patients were diagnosed with SOD over a period of fifteen months. Patients had varied clinical spectrum but shared common maternal and perinatal factors. SOD is more common in young primigravida mothers and in first-born appropriate for gestational age children. Central Brooklyn is a region with high population density. Not all patients had pituitary insufficiency at presentation. Early diagnosis of this condition should decrease the disease related morbidity and mortality.

ABBREVIATIONS

FT: Full Term; BW: Birth Weight; B/L: Bilateral; ONH: Optic Nerve Hypoplasia; GER: Gastro-Esophageal Reflux; RDS: Respiratory Distress Syndrome; Neg: Negative.

INTRODUCTION

Septo-optic dysplasia (SOD), also known as de-Morsier's syndrome [1] is a phenotypically heterogeneous condition characterized by association of midline brain abnormalities, Optic Nerve Hypoplasia (ONH) and hypothalamic-pituitary endocrine deficiencies. It is a rare condition with reported incidence of 1/10,000 live births and a male:female ratio of 1:1 [2,3]. SOD is multifactorial in nature with both genetic and gestational factors playing important role in its pathogenesis [2,4-6]. Genetic abnormalities are identified only in 1% of patients suggesting that other prenatal and perinatal factors as well as unidentified genetic mutations may be involved in the development of this condition [7,8].

Some of the key genes that have been implicated in SOD pathogenesis include *HESX1, SOX2, SOX3, OTX2, PROKR2, FGF1,* and *FGF8* [9-11]. These genes are expressed in regions that determine the formation of the forebrain and related midline structures, including hypothalamus and pituitary. Different mutations in these genes have been reported to cause varied phenotypic presentations in SOD.

Some of the prenatal and perinatal factors that have been observed in patients with SOD include young maternal age with reported mean age of 21 years [12], young paternal age with reported median age of 23.5 years [13], primigravidae mothers, gestational diabetes, viral infections, environmental teratogens and vascular or degenerative injury during pregnancy. Maternal smoking, alcohol consumption, and the use of addictive drugs during early gestation have been reported to be possible risk factors as well [10,12,14,15]. Increased first trimester bleeding was also noted in mothers of SOD patients [13]. Areas with high population density, inner city areas with high unemployment rate and high rate of teenage pregnancies are known to have higher incidence of SOD [2].

We diagnosed five patients with SOD at our institution over a period of fifteen months. We hypothesized that all five newly diagnosed SOD patients at our institution shared common maternal and perinatal factors. We did a retrospective chart review. The purpose of this case series is to describe the varied clinical phenotypes of the five patients; and to identify common maternal and perinatal factors, if any, among them. Although these patients were from different ethnicities, they all were residents of central Brooklyn.

SOD, if not identified early, can result in delay in diagnosis of various hypothalamic-pituitary abnormalities including central adrenal insufficiency, growth hormone deficiency, central

hypothyroidism, secondary hypogonadism and/or central diabetes insipidus [16]. These hormonal deficiencies can lead to growth failure, poor neurodevelopmental outcome, delayed puberty and even death, if not detected on time. With this case series, we aim to familiarize the clinicians with the varied clinical spectrum of SOD and to highlight the importance of early and periodic pituitary hormonal monitoring for patients with this condition.

CLINICAL FEATURES

SOD presents with varied clinical spectrum and is defined by the presence of at least two out of three features: Optic Nerve Hypoplasia (ONH), midline brain abnormalities and hypothalamic-pituitary endocrine deficiencies. Miller et al proposed the term 'SOD-plus' to describe SOD associated with cortical developmental malformations. The clinical findings described in this group include global developmental delay, motor deficits, seizures and/or visual signs [17]. Another term proposed by Riedl et al for patients with optic nerve hypoplasia and pituitary abnormalities with normal to near-normal septum pellucidum is 'SOD-like'[18].

Optic nerve hypoplasia (ONH) may be unilateral or bilateral, the latter being more common, and is usually the first presenting feature of the condition. Most of the patients have low visual acuity. Nystagmus, strabismus and esotropia are also known to be associated findings [19-21]. Among eye findings, esotropia is the most common.

Midline brain defects that have been classically described in SOD patients include complete or partial absence of the septum pellucidum with fused midline fornices (60% of cases) and/or corpus callosum abnormalities, such as agenesis, dysplasia, or hypoplasia [7,8,22]. Other associated anatomical brain abnormalities that have been reported include cavum septum pellucidum, cerebellar hypoplasia, schizencephaly, aplasia of the fornix, encephalocele, cortical dysplasia, gray matter heterotopia, polymicrogyria, and hippocampal malformations [17,18,23-25]. Severino et al reported hypoplasia of pons, medulla, and vermis in more than 50% of patients with SOD in their report [26]. Additional features that were observed by them include midbrain tectum enlargement and agenesis of the epithalamus.

Neurologic deficits are common in patients with SOD, ranging from developmental delay, mental retardation, cerebral palsy to focal deficits such as seizure disorder and hemiparesis [17]. SOD patients with small hindbrain on neuro imaging are more likely to present with cognitive impairment and developmental delay [26]. Recent studies reported 30-33% incidence of Autistic spectrum disorders in SOD patients [27,28]. Ectopic posterior pituitary is usually associated with pituitary hormone deficiencies, while neurodevelopmental deficits are more likely if hemispheric migration anomalies are present [28].

The extent of pituitary hormone dysfunction in SOD patients is highly variable ranging from single hormone deficiency to panhypopituitarism [16,29]. Approximately 40% of SOD patients have normal endocrine function at presentation, while hormone deficiencies can gradually evolve over the patient's lifetime [4,30]. Growth hormone deficiency is the most common hormone affected, followed by adrenocorticotrophic hormone (ACTH) and thyrotrophic hormone (TSH) deficiencies [31,32]. Varied spectrums of puberty, from precocious puberty to hypogonadotrophic hypogonadism, have been associated as well [10]. Pituitary dysfunction may even present as neonatal hypoglycemia warranting early diagnosis and treatment.

CASE PRESENTATION

We describe the clinical and radiologic findings of five pediatric patients diagnosed with SOD between July 2013 and October 2014 at SUNY Downstate Medical Center and Kings County Hospital Center, Brooklyn, NY. Single investigator retrospectively reviewed patient charts. All patients were evaluated by an ophthalmologist and had brain imaging done. Endocrine function was assessed on all patients at initial diagnosis and periodically afterwards. We received exemption from SUNY Downstate Institutional Review Board for retrospective chart review.

Clinical presentation, radiologic features and perinatal history of all the patients are shown in Table 1. Out of five patients, three were female and two were male. Three patients were African American; one was Asian and one of Hispanic descent. Two patients were diagnosed at birth while the other three were diagnosed at age 2, 3 and 7 years respectively.

PERINATAL HISTORY

All patients were firstborn children. Four of the five patients were born full term and appropriate for gestational age (AGA). The patient who was born prematurely had a complicated NICU stay due to respiratory distress syndrome, hyperbilirubinemia and meconium ileus. The rest of the patients had uncomplicated postnatal course. Four of five patients were born to young mothers in their early twenties with uneventful prenatal course. All mothers had negative prenatal laboratory results although one mother had inconsistent prenatal follow up. None of the mothers reported alcoholism, smoking or drug abuse during pregnancy.

CLINICAL FINDINGS

Case 1 presented at the age of 7 years with polyuria and polydipsia. He was diagnosed with central diabetes insipidus after performing a water deprivation test and was started on desmopressin nasal spray. He was found to be adrenal deficient with baseline morning cortisol level of 1.1 µg/dl (reference: 3.0 to 21 µg/dl) and ACTH level of 20.1 pg/ml (reference: 6 to 48 pg/ml). Given such low cortisol level, hydrocortisone was started without performing ACTH stimulation test. His thyroid function tests showed hypothyroidism with TSH of 6.77 µU/ml (reference: 0.6 to 5.5 µU/ml) and free T4 of 0.71 ng/dl (reference: 0.8 to 1.7 ng/dl). He was started on levothyroxine replacement then. He had normal IGF1 of 78 ng/ml (reference: 44 to 211 ng/ml) and normal IGFBP3 of 4.1 mg/L (reference: 2.1 to 4.2 mg/L). His height and weight were above 97th percentile for his age and sex. There was no history of reported hypoglycemic events. Initial prolactin level was 62.8 ng/ml (reference: 3 to 18ng/ml) although the repeat level was lower at 41ng/ml. He had bilateral nystagmus on physical exam. He had normal phallus length for age and bilaterally descended testes, no history of microphallus or cryptorchidism at birth. Ophthalmologic exam revealed bilateral ONH. He has global developmental delay and history of

seizure disorder, which is well controlled now. He is wheel chair bound and is verbal with poor articulation. He was found to have absent corpus callosum on CT Head done at 2 years of age.

Case 2 was referred to the ophthalmologist at 3 months of age due to astigmatism and was found to have bilateral ONH. At the age of 3 years and 8 months, she was referred to Endocrinology clinic at our institution due to failure to thrive and ONH. Her height was 87.6 cm (<3rd percentile for age and sex) and her weight was 12.16 Kg (<3rd percentile for age and sex) at presentation. Her pituitary function tests revealed central hypothyroidism with TSH of 2.27 µU/ml (reference: 0.6 to 5.5 µU/ml) which was inappropriately low for free T4 of 0.69 ng/dl (reference: 0.8 to 1.7ng/dl); and growth hormone deficiency with low IGF1 and low IGFBP3 levels [18 ng/ml (reference: 26 to 162 ng/ml) and 0.78 mg/L (reference: 0.9 to 4.1 mg/L) respectively]. She had normal prolactin level of 13 ng/ml (reference: 3 to 18ng/ml). Patient had low baseline cortisol, 8 am cortisol of 1.7 µg/dl (reference: 3.0 to 21 µg/dl) and low baseline ACTH of 10.3 pg/ml (reference: 6 to 48 pg/ml). She failed low dose (1mcg) as well as high dose (250mcg) ACTH stimulation test indicating secondary adrenal insufficiency. Cortisol values during the ACTH stimulation test were as follows:

At 0 minute -2.6 µg/dl. 1 µg cosyntropin was given

At 30 minutes- 9.3 µg/dl

At 60 minutes- 12.1 µg/dl. 250 µgcosyntropin was given

At 90 minutes- 15.2 µg/dl

Subsequently, hydrocortisone, levothyroxine and growth hormone therapy were started. Her MRI of brain was normal with normal pituitary gland.

Case 3 was born with absent eye structures and short palpebral fissures. No other facial anomaly was noted. Patient's vital signs were stable and electrolytes levels were normal at birth and on further follow up clinic visits. Her pituitary hormone levels were normal at day of life (DOL) # 3 with TSH of 10.3 µU/ml (reference at this age: 1.3 to 16 µU/ml), free T4 of 1.60 ng/dl (reference: 0.84 to 4.97 ng/dl), IGF1 of 22 ng/ml (reference: 15 to 109 ng/ml), IGFBP3 not reported, LH of 0.06 mIU/ml (reference for age 0 to 23 months females: 0.0 to 0.5 mIU/ml), FSH of 0.60 mIU/ml(reference for age 0 to 23 months females: 0.4 to 7.1 mIU/ml) and prolactin of 135.18 ng/ml (reference at this age: 30 to 495 ng/ml). Cortisol level at DOL#3 was 3.2 µg/dl (reference: 3.0 to 21 µg/dl) with ACTH level of 64 pg/ml (reference: 6 to 48 pg/ml). Repeat cortisol level at 3 months of age was normal at 36.9 µg/dl. Chromosomal microarray analysis showed deletion of *SOX2*gene. No esophageal atresia was noted. MRI of brain revealed absence of the entire optic tract along with absent septum pellucidum and normal pituitary gland (Figure 1 and 2).

Case 4 was born premature with neonatal course complicated with respiratory distress syndrome, meconium ileus and hyperbilirubinemia. He had normal phallus length and bilaterally descended testes at birth. No hypoglycemic events were reported during NICU stay. Ophthalmologic exam performed at birth due to prematurity showed bilateral ONH. His pituitary hormone levels were normal at birth: TSH of 1.5 µU/ml (reference: 1.3 to 16 µU/ml), free T4 of 1.08 ng/dl (reference: 0.84 to 4.97 ng/dl), IGF1 of 40 ng/ml (reference: 15 to 109 ng/ml), IGFBP3 of 0.8 mg/L (reference: 0.4 to 1.7 mg/L), LH of 10.59 mIU/ml (reference for age 0 to 23 months male: 0.5 to 1.9mIU/ml), FSH of 2.2 mIU/ml (reference for age 0 to 23 months males: 0.4 to 2.1 mIU/ml),

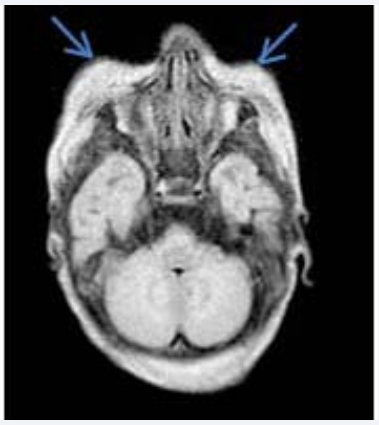

Figure 1 Case 3- MRI brain showing absent orbits.

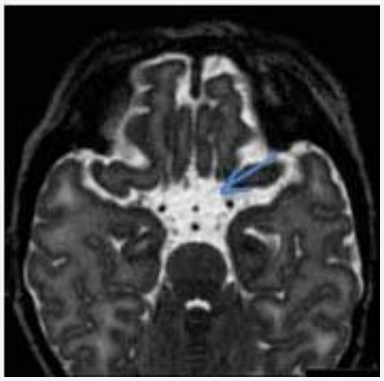

Figure 2 Case 3- MRI brain showing absent optic chiasma.

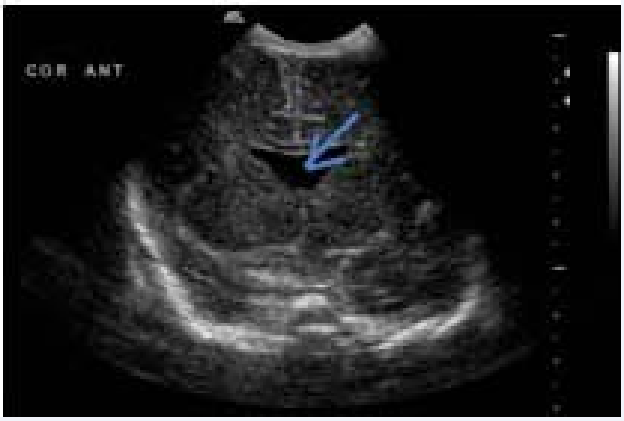

Figure 3 Case 4- Head USG showing absent septum pellucidum (vertical membrane separating the anterior horns of left and right ventricles).

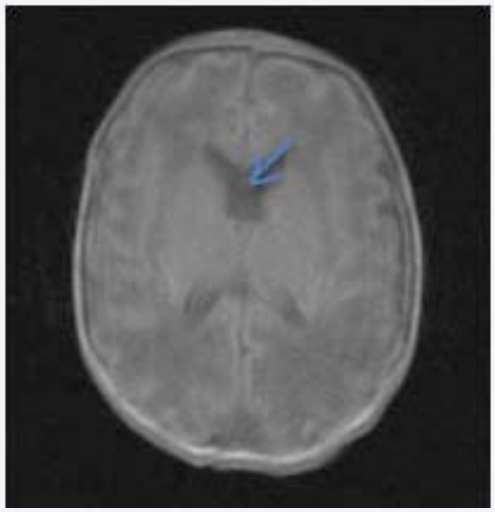

Figure 4 Case 4-MRI brain showing absent septum pellucidum.

ACTH of 55.4 pg/ml (reference: 6 to 48 pg/ml) and prolactin level of 122.8 ng/ml (reference at this age: 30 to 495 ng/ml). Baseline cortisol level was 2.9 ug/dl (reference: 3.0 to 21 µg/dl) with post-ACTH stimulation cortisol of 31.5 ug/dl. He had absent septum pellucidum on head ultrasound and MRI of the brain performed soon after birth showed normal pituitary gland (Figure 3-5).

Case 5 had right-sided esotropia and was noted to have poor vision on right eye at 2 years of age. Ophthalmologic exam showed right optic nerve atrophy. Her pituitary function tests at diagnosis were as follows: TSH of 2.26 µU/ml (reference: 0.6 to 5.5 µU/ml), freeT4 of 1.15 ng/dl (reference: 0.65 to 1.9 ng/dl), IGF1 of 98 ng/ml (reference: 20 to 141 ng/ml), IGFBP3 not reported, cortisol of 10.34 µg/dl(reference: 3.0 to 21 µg/dl) with ACTH of 13 pg/ml (reference: 6 to 48 pg/ml), LH of 0.07 mIU/ml (reference: 0.02 to 0.3 mIU/ml), FSH of 2.15 mIU/ml (reference: 1.0 to 4.2 mIU/ml) and prolactin of 4.48 ng/ml (reference: 3 to 18ng/ml). MRI of the brain done at 2 years of age showed absent septum pellucidum.

DISCUSSION

Table 1: Clinical Characteristics of SOD patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age at diagnosis	7 years	3 years	At birth	At birth	2 years
Sex	Male	Female	Female	Male	Female
Ethnicity	African American	African American	African American	Hispanic	Asian
Maternal History	20 years old, healthy, primivigravida, prenatal course normal	21 years old, healthy, primigravida, prenatal course normal	29 yr old P0020, prenatal course normal	20 yr old, healthy, primigravida, prenatal labs neg, inconsistent prenatal course	19 years old, healthy, primigravida, prenatal course normal
Birth History	FT, BW 3590g	FT, BW 2790g	FT, BW 2640g	Ex 31.7 weeker, BW 1395g	FT, BW 2854 g
Opthalmologic Findings	B/L ONH B/L nystagmus	B/L ONH, horizontal nystagmus, astigmatism	B/L micro/ anopthalmia	B/L ONH	Right Optic nerve atrophy and right sided esotropia
Endocrine Workup	Central diabetes insipidus, secondary adrenal insufficiency, hypothyroidism	Central hypothyroidism, secondary adrenal insufficiency, growth hormone deficiency	Pituitary hormone function normal	Pituitary hormone function normal	Pituitary hormone function normal
Brain Imaging	Poorly defined septum pellucidum, absent corpus callosum. Prominent B/L ventricles. Pituitary not visualized	MRI brain normal. Normal pituitary	Absent B/L globes, optic nerves, optic chiasma and optic radiations. Absent septum pellucidum. Normal Corpus callosum. Normal pituitary	Absent septum pellucidum but normal corpus callosum. Normal pituitary	Absent septum pellucidum
Genetics	Negative for *HESX1* mutation	Karyotype 46 XX	895 kb loss at 3q26.33 including *SOX2* gene	Negative for *HESX1* mutation	None
Additional findings	Global developmental delay, seizure disorder, wheel chair bound, B/L hip dislocation	Developmental delay, failure to thrive	GER	Resolved meconium ileus, intrahepatic calcifications, RDS, hyperbilirubinemia, GER	None

Abbreviations: FT: Full Term; BW: Birth Weight; B/L: Bilateral; ONH: Optic Nerve Hypoplasia; GER: Gastro-Esophageal Reflux; RDS: Respiratory Distress Syndrome; Neg: Negative.

We diagnosed five cases of SOD in fifteen months period at our institution. Our patients belong to different ethnicities but reside at similar urban setting in close proximity to each other.

As described in the literature, our case series also demonstrates that SOD is a heterogeneous condition with highly variable phenotype [8]. All patients in our study were appropriate for gestational age (AGA) first-born children with primigravidae mothers (ages ranging from 19-29 years). A larger retrospective review of thirty patients with SOD in Scotland reported patients to be of normal birth weight and gestation and born to mothers who were significantly younger than average Scottish mothers (reported median maternal age was 21 years in SOD group vs. 27.12 years median maternal age in Scotland) [12]. We observed similar findings in our series.

No significant prenatal or perinatal events were reported in any of our patients except one patient who was born premature for unknown reason. None of the mothers in our case series reported alcohol, smoking or drug use during pregnancy, which has been associated with SOD.

Patel et. al in their population-based incidence study done in Northwest England reported SOD to be more common in inner city locations with high population density and higher level of unemployment, in young mothers and in dependent children with non earning households [2]. Our institution is located in inner city with high population density, which is a similar setting as described by them.

All of our patients had eye involvement at diagnosis. One of the patients had *SOX2* gene deletion without esophageal abnormality. Two patients were tested for *HESX1* gene mutation and were negative. Genetic testing was not performed on rest of the patients.

Forty percent of our patients (two out of five) had endocrine abnormalities. Even though three of our patients did not have any endocrine abnormalities on biochemical testing, we suspect it is most likely due to their young age. We anticipate these patients might develop pituitary dysfunction later in their lifetime as has been described in SOD patients [16]. These patients need to be followed at Endocrine clinic periodically.

Even though the major limitation of our study is the small sample size, given that SOD is a rare condition, we report this case series to highlight the importance of clinicians being aware of the varied phenotype of the disease. High index of suspicion is needed for early recognition and management. Prompt diagnosis of this condition should decrease the disease related morbidity and mortality in regards to endocrinopathies by early treatment initiation.

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