

## Septo-Optic Dysplasia in Saudi Arabia: Clinico-Radiological Characteristics

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### Abstract

**Background:** Septo-optic dysplasia (SOD) is rare syndrome with an estimated prevalence of ~1:10,000.

**Objective:** To describe the ophthalmological, endocrinological, and radiological characteristics of SOD.

**Methods:** This retrospective hospital-based study was conducted in children who were diagnosed with SOD. All patients underwent complete ophthalmological, radiological, and endocrinological evaluation at the Pediatric Endocrine Clinics, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia. The hormonal evaluation included growth hormone, adrenocorticotrophic hormone, thyroid stimulating hormone, gonadotropin, and anti-diuretic hormone testing.

**Result:** Six patients with a diagnosis of SOD were retrospectively reviewed. Patients were aged from 8 months to 7 years, with a mean age of 3 years 9 months. Hormonal studies indicated that five children had growth hormone deficiency, two had thyroid stimulating hormone deficiency, and three had adrenocorticotrophic hormone deficiency; gonadotropin deficiency and central diabetes insipidus were present in one patient each. Pendular nystagmus and impaired vision were the common initial signs in children with bilateral optic nerve hypoplasia. Neuroradiology findings were variable; all children had optic nerve hypoplasia, three children had an absent septum pellucidum, two had ectopic posterior pituitary, and one had absent posterior pituitary high intensity signal. All patients received appropriate hormonal replacement therapy. One male child had a micropenis which responded to testosterone therapy.

**Conclusion:** SOD is commonly associated with hypothalamic hypopituitarism, including anterior and posterior pituitary hormonal deficiencies. Early diagnosis is critical as the hormonal deficiencies can be life threatening.

**Keywords:** *Septo-Optic Dysplasia; Optic Nerve Hypoplasia; Pituitary Hormone Abnormalities; Magnetic Resonance Imaging (MRI)*

### Abbreviations

GHD: Growth Hormone Deficiency; GDD: Global Developmental Delay; ADHD: Attention-Deficit Hyperactivity Disorder; MRI: Magnetic Resonance Imaging; ONH: Optic Nerve Hypoplasia; HGh: Human Growth Hormone; GnRH: Gonadotropin Releasing Hormone

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## Introduction

Septo-optic dysplasia (SOD), also known as de Morsier syndrome, is a condition characterized by optic nerve hypoplasia and absence of the septum pellucidum; two-thirds of patients also have hypothalamic-pituitary dysfunction [1]. This syndrome was first described by de Morsier in 1956 and has an estimated prevalence of ~1:10,000 [2,3]. There is no recognized gender predilection. A number of genetic and gestational risk factors have been identified to play important roles in the pathogenesis of SOD [4]. Clinical diagnosis requires the presence of at least two characteristics and can be confirmed by ophthalmological examination, magnetic resonance imaging (MRI), and pituitary hormone analyses.

In this retrospective report, we describe our experience with six patients with SOD who were diagnosed at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, over a period of two years, from January 2017 to December 2018. The aim of this study was to describe their various clinical and neuro-radiological characteristics.

## Materials and Methods

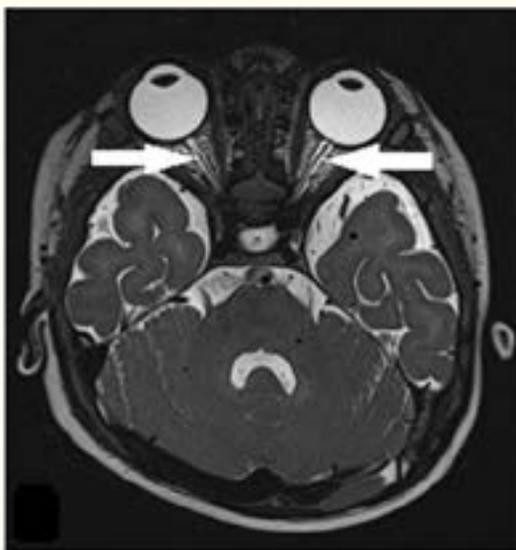
This retrospective hospital-based study was conducted in children who were diagnosed with SOD at the King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, during the period from January 2017 to December 2018. Medical records were reviewed for demographic characteristics and clinical presentation. Data from laboratory and radiological investigations were extracted. MRI with contrast was performed on each patient at the time of diagnosis. The imaging studies included views to identify midline brain defects and the appearance of the hypothalamus, pituitary gland, and optic nerves. Hypothalamic-pituitary functions were evaluated at the time of presentation. Pituitary hormone deficiencies were documented using standard tests and radioimmunoassay. Growth hormone (GH) was measured in response to arginine and clonidine stimulation tests. Adrenocorticotrophic hormone (ACTH) and plasma cortisol were evoked by the ACTH stimulation test. Thyroid stimulating hormone (TSH) and plasma free T4 (FT4) were measured randomly. Gonadotropin reserve was assessed by measuring follicular stimulating hormone (FSH) and luteinizing hormone (LH) after the GnRH stimulation test. Posterior pituitary function was ascertained by the water deprivation test, random concurrent urine/serum osmolality determinations, and with evaluation of fluid input and output records.

## Results

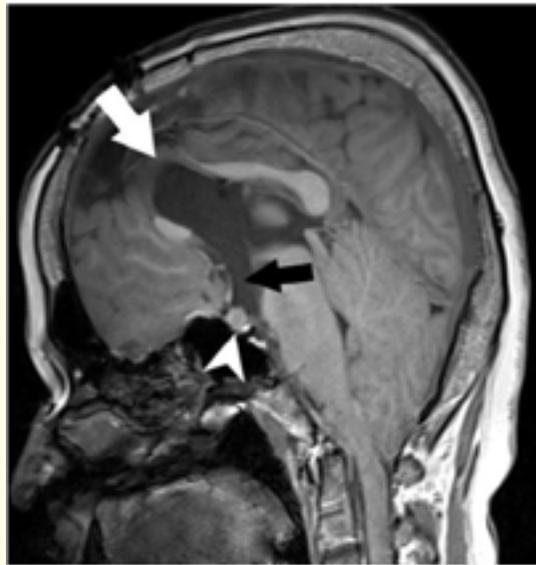
All patients in our study were appropriate for gestational age with birth weights ranging from 2.6 - 3.5 kg (mean 3 kg). The mean age was 3 years 9 months (range, 8 months to 7 years). All children had bilateral optic nerve hypoplasia; pendular nystagmus and impaired vision were present in most cases. Corpus collosum hypoplasia was found in three patients, three children presented with neonatal jaundice at birth, while hypoglycemia was documented in two patients. Delayed cognitive and psychosocial development was present in all patients. Two patients were offspring of the same family, being first degree cousins (case 4 and 5). The mean maternal age was 24 years. All children had pituitary hormone deficiencies except one patient who had normal hormonal profile. Five children had growth hormone deficiency (GHD) as part of multiple pituitary hormone deficiencies while two children had isolated GHD. Children with GHD were treated with hGH. Two children had TSH deficiency and were started on L-thyroxine replacement therapy, which kept them euthyroid. Three children had ACTH deficiency with hydrocortisone used for replacement therapy. One boy was suspected to have gonadotropin deficiency based on biochemical evidence of low gonadotropins; this was confirmed by the GnRH stimulation test and clinical observation of a micropenis (stretched penile length < 2.5 SD for age). This patient was treated with three monthly courses of intramuscular testosterone. Central diabetes insipidus was present in one child with an impaired thirst mechanism. Two children were found to have Webb-Dattani syndrome due to homozygous mutation in the ARNT2 gene, table 1.

	Case1	Case2	Case3	Case4	Case5	Case6
Maternal age/ family order	20 y/first	21 y/first	29y/ first	24y/ second	28y/third	22/third
Consanguine parent	No	Yes	No	Yes	Yes	No
Birth weight	3.5 kg	2.9 kg	2.9 kg	2.6 kg	3 kg	3.2 kg
Age at presentation	8 month	2 year	4 year	7 year	3 year	7 year
Sex	Male	Female	Female	Male	Male	Male
Ophthalmological findings	Bilateral hypoplastic optic nerve, pendular nystagmus	Bilateral optic nerve atrophy, pendular nystagmus	Bilateral nystagmus with Right eye blindness	Bilateral mild optic atrophy	Strabismus bilateral Optic Atrophy	Strabismus optic disc hypoplasia
Endocrine workup	GHD, secondary hypothyroidism, adrenal insufficiency, hypogonadism, DI	GHD, secondary adrenal insufficiency	GHD, secondary hypothyroidism and adrenal insufficiency	GHD	GHD	Normal
Additional findings	Seizure disorder	GDD	GDD	ADHD, Webb-Dattani Syndrome (homozygous mutation in the ARNT2 gene)	ADHD, Webb-Dattani Syndrome (homozygous mutation in the ARNT2 gene)	GDD

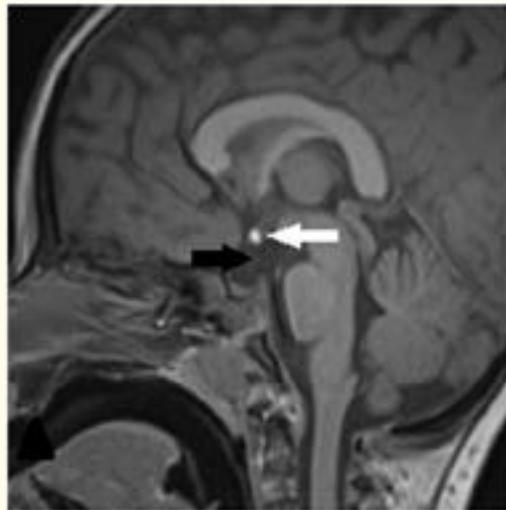
**Table 1:** Clinical presentation of SOP patients.



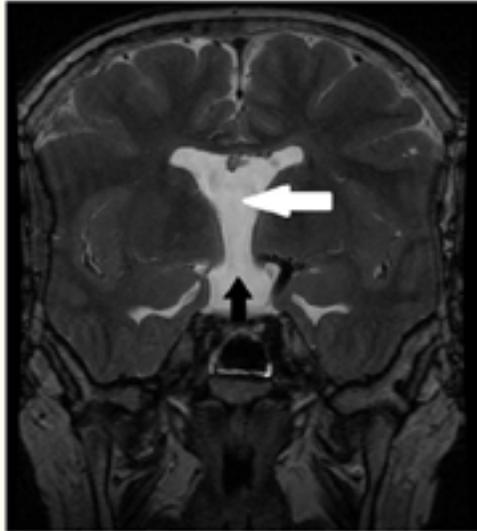
**Figure 1:** Axial T2 weighted MRI image at the optic nerve level shows severe atrophy of both optic nerves (white arrows).



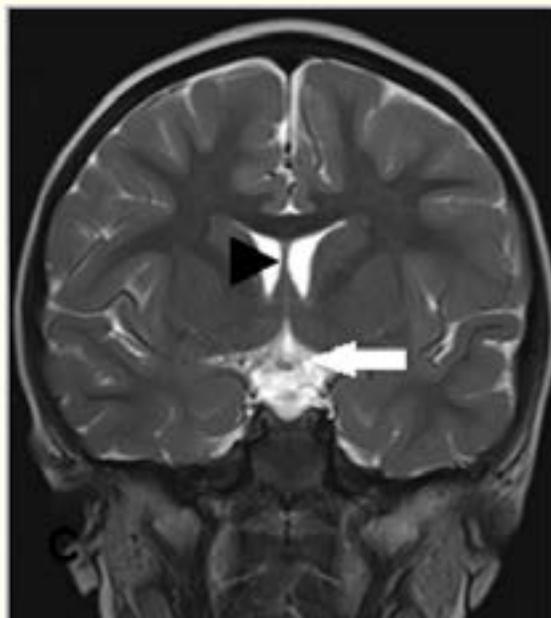
**Figure 2:** Mid-sagittal T1 weighted MRI image at the pituitary gland level shows dysgenesis of the genu and anterior body of the corpus callosum (white arrow) and absent pituitary stalk (black arrow). The pituitary gland is in a normal position (white arrowhead).



**Figure 3:** Mid-sagittal T1 weighted MRI image at the pituitary gland level shows an ectopic posterior pituitary lobe-white spot (white arrow) and an absent pituitary stalk (black arrow).



**Figure 4:** Coronal T2 weighted MRI image at the suprasellar region shows an absence of the septum pellucidum (white arrow) and an absent optic chiasm (black arrow).



**Figure 5:** Coronal T2 weighted MRI image at the suprasellar region shows atrophy of the optic chiasm (white arrow). The septum pellucidum is present (black arrowhead).

## Discussion

SOD is a rare congenital heterogeneous malformation; it was formerly known as de Morsier syndrome [2]. SOD is described as a malformation of the central nervous system characterized by absence of the septum pellucidum together with hypoplasia of the chiasm and optic nerves. We diagnosed six cases of SOD at our institution during the study period. As described in the literature, our case series also demonstrates that SOD is a heterogeneous condition with a highly variable phenotype. The cause of SOD remains uncertain; it is multifactorial in nature with both genetic and gestational factors playing an important role in its pathogenesis [4]. Genetic abnormalities are identified in only 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 [5,6]. All patients in the current study had eye involvement at diagnosis. In children with SOD, the optic nerves are abnormally small, resulting in vision problems in one or both eyes. Fundoscopic examination reveals a small optic disc encircled by a halo of hypopigmented tissue caused by hypoplasia of the retinal epithelial pigment [7]. Vision impairment may range from complete blindness to subtle impairment. Pendular nystagmus was the most common presenting sign and optic nerve hypoplasia was the most commonly associated neurological anomaly. Other midline defects that can occur because of dysembryogenesis are agenesis of the corpus callosum and septum pellucidum, holoprosencephaly and ONH [8]. Neurologic defects are common in patients with SOD, ranging from developmental delay, mental retardation, or cerebral palsy to focal deficits such as seizure disorder and hemiparesis [9]. The spectrum of endocrinological abnormalities secondary to the congenital hypothalamic-pituitary anomalies associated with SOD is variable [10]. Growth hormone was the most common pituitary hormone deficiency followed by TSH, ACTH and less commonly, anti-diuretic hormone (ADH). Multiple pituitary hormonal deficiencies occurred more commonly with bilateral optic nerve hypoplasia. One patient in our series had a pattern of progressive onset of multiple pituitary hormonal deficiencies over several months. This suggests that in patients with optic nerve hypoplasia, a thorough endocrinological assessment is indicated initially, followed by regular evaluations to detect any evolving hormonal deficiency that may be subtle and subclinical. Even though one of our patients (case 6) had no hormonal abnormalities on biochemical testing, we anticipate that this patients might develop pituitary dysfunction later in his lifetime, as has been described in SOD patients [1,11-13]. These patients need to be followed periodically at an endocrine clinic. Close endocrinological monitoring and special precautionary measures (ensuring adequate hydration, protection against hypoglycemia, increased dose of glucocorticoids during intercurrent illnesses) are essential to minimize the risk of sudden death in SOD patients with multiple pituitary hormone deficiencies. Genetic counseling may be warranted if there is any family history. 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.

## Conclusion

The SOD syndrome is commonly associated with hypothalamic hypopituitarism, including anterior and posterior pituitary hormonal deficiencies. Early diagnosis of this syndrome is critical as the hormonal deficiencies can be life threatening. A life-long multidisciplinary approach is crucial in the management of these patients in order to optimize their growth and development and help them to lead as normal a life as possible

## Acknowledgements

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## Conflict of Interests

The authors have no conflicts of interest to declare.

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