Septo-optic dysplasia

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INITIAL PRESENTATION

Chief Complaint: Eye Shaking

History of Present Illness:

Patient is a 5-month-old male with a history of prematurity who was referred to the eye clinic for evaluation of nystagmus first noted by his parents and confirmed by his pediatrician. They have not noticed problems with him looking at faces, tracking objects, or any eye crossing or drifting. He has demonstrated normal growth and development since birth and has reached all developmental milestones appropriate for his age. No other visual concerns have been noted.

Past Ocular History:

- Negative past ocular history

Past Medical History:

- Uncomplicated spontaneous delivery at 37 weeks gestational age
- Prenatal concern for holoprosencephaly on prenatal ultrasound; in utero MRI normal

Medications:

- None

Allergies:

- No medication allergies

Family History:

- Two brothers wear glasses
- No family history of strabismus, amblyopia, or other significant ocular disease

Social History:

- Non-contributory

Review of Systems:

- Negative except for what is detailed in the history of present illness

OCULAR EXAMINATION

- **Visual Acuity at near**:
  - Right eye (OD): Central, Unsteady, Maintained fixation (CUSM)
  - Left eye (OS): CUSM
  - Both eyes (OU): Clearly able to fix and follow

- **Ocular Motility/Alignment:**

    - Horizontal motility was full with no observed strabismus
    - Readily apparent, intermittent, high-frequency horizontal nystagmus

- **Intraocular Pressure (by palpation)**:
    - OD: Soft
    - OS: Soft

- **Pupils**:
    - OD: Equal, reactive, no relative afferent pupillary defect (RAPD)
    - OS: Equal, reactive, no RAPD

- **Confrontation Visual Fields:**
    - Not reliably assessed due to age/fussiness

- **External:**
    - Within normal limits OU

- **Slit Lamp Examination (Penlight):**

	OD	**OS**
Lids/lashes	Normal	Normal
Conjunctiva/sclera	Normal	Normal
Cornea	Clear	Clear
Anterior chamber	Deep and quiet	Deep and quiet
Iris	Normal	Normal
Lens	Clear	Clear

- **Dilated Fundus Examination (DFE):**

	OD	**OS**
Vitreous	Clear	Clear
Disc	Very small, normal color, no edema	Very small, normal color, no edema
Macula	Normal	Normal
Vessels	Normal	Normal
Periphery	Normal	Normal

- **Cycloplegic Refraction:**
    - OD: +1.00 +0.50 x 090
    - OS: +1.00 +0.50 x 090

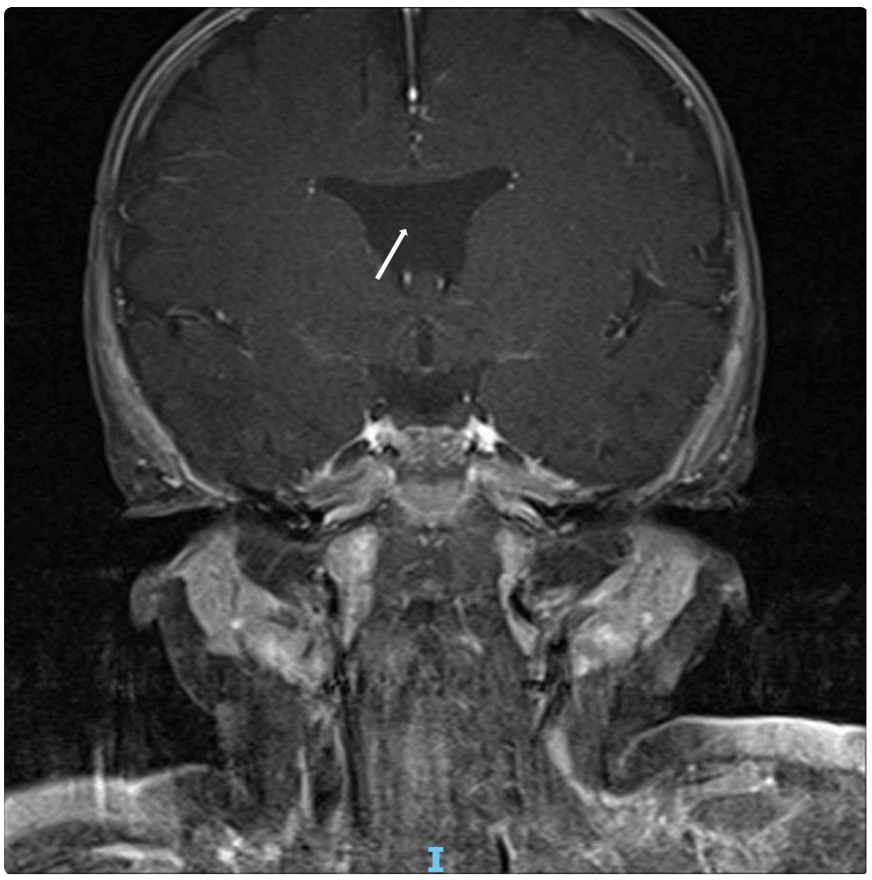
DIFFERENTIAL DIAGNOSIS:

- Optic nerve hypoplasia
- Idiopathic infantile nystagmus
- Ocular albinism

CLINICAL COURSE

At the initial presentation, pituitary function labs and neuroimaging were ordered given the association of optic nerve hypoplasia with endocrine dysfunction and midline brain abnormalities. Neuroimaging demonstrated an absent septum pellucidum (Figure 1). The patient established with endocrinology and pituitary function was normal. Given the constellation of optic nerve hypoplasia and

MRI brain result, he was diagnosed with septo-optic dysplasia.



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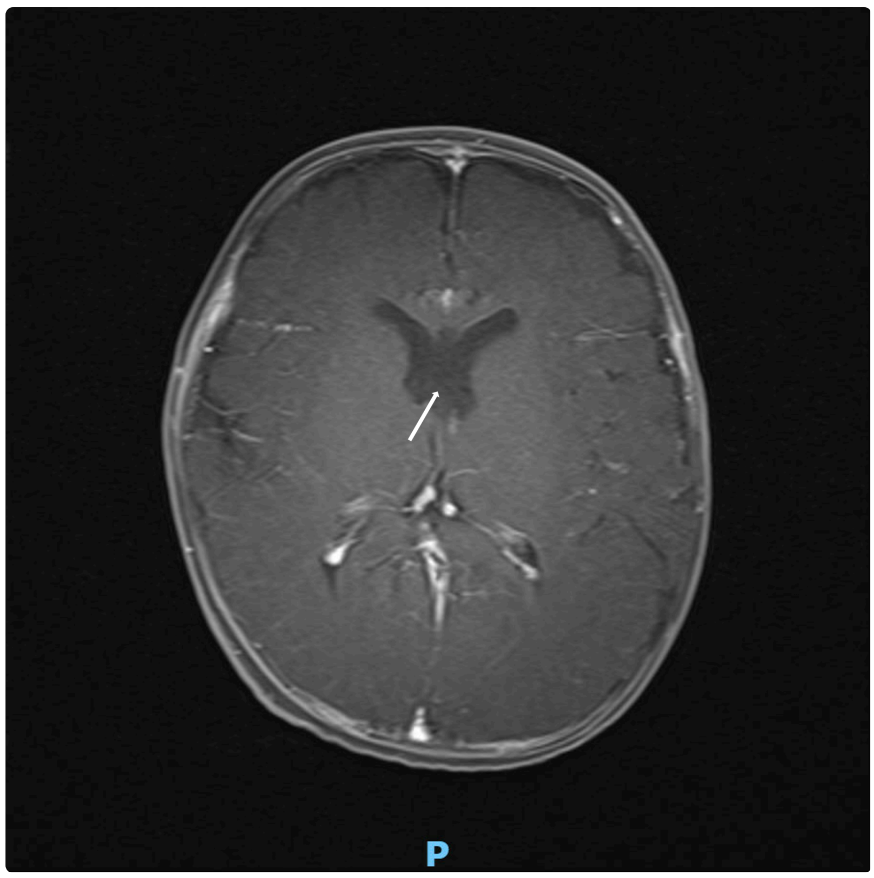

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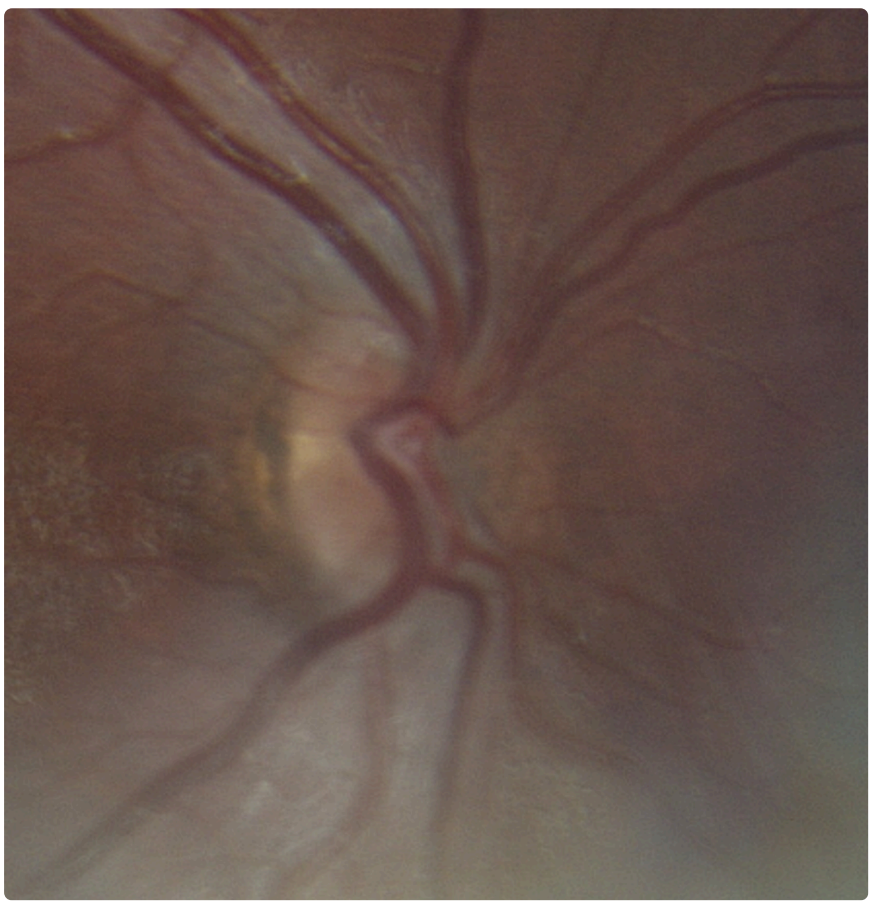
Figure 1. T1-weighted fat-suppressed (FS) post-contrast MRI demonstrating absence of the septum pellucidum (white arrow). (A) Coronal T1 FS post-contrast image. (B) Axial T1 FS post-contrast image.



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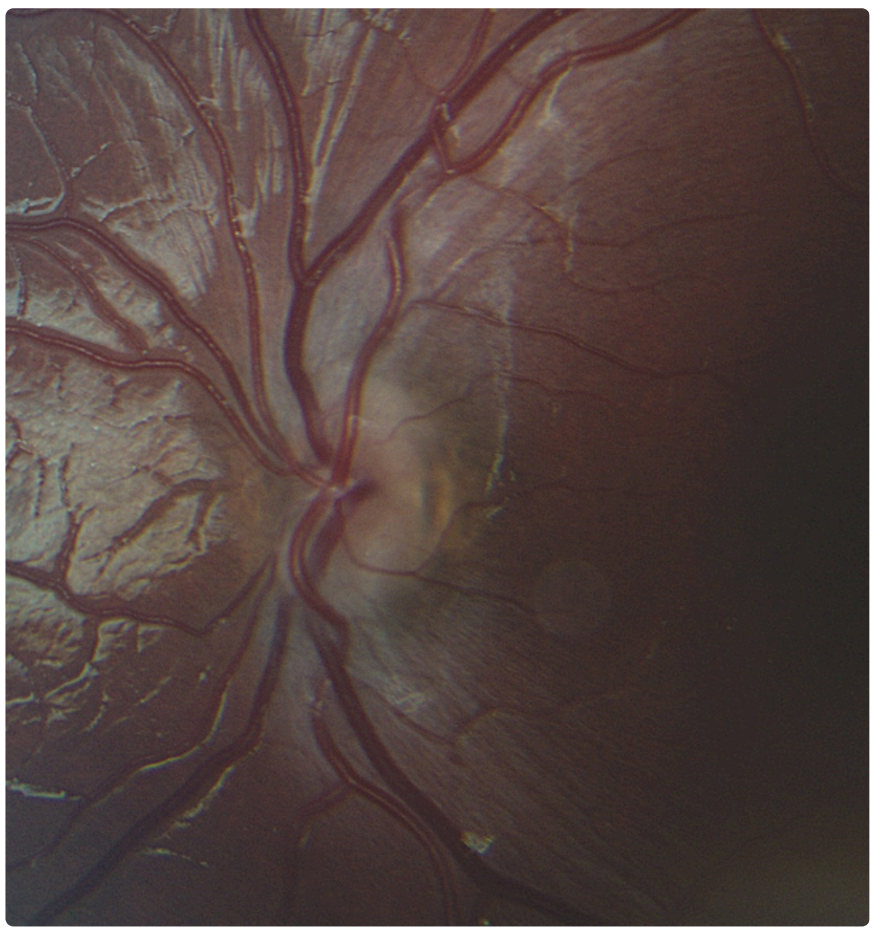

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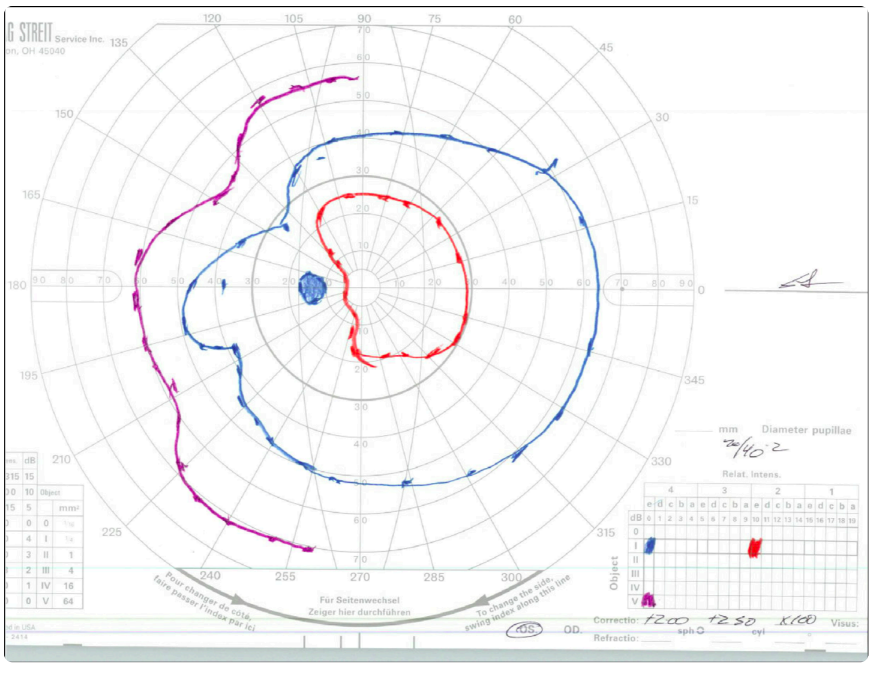
Figure 2. Fundus photograph of the patient demonstrating binasal optic nerve hypoplasia which corresponds to the temporal field defect in the Goldmann visual field. Right eye (OD, left panel) and left eye (OS, right panel).

Goldmann Visual Field (GVF) testing was obtained when the patient was old enough to participate (Figure 3).



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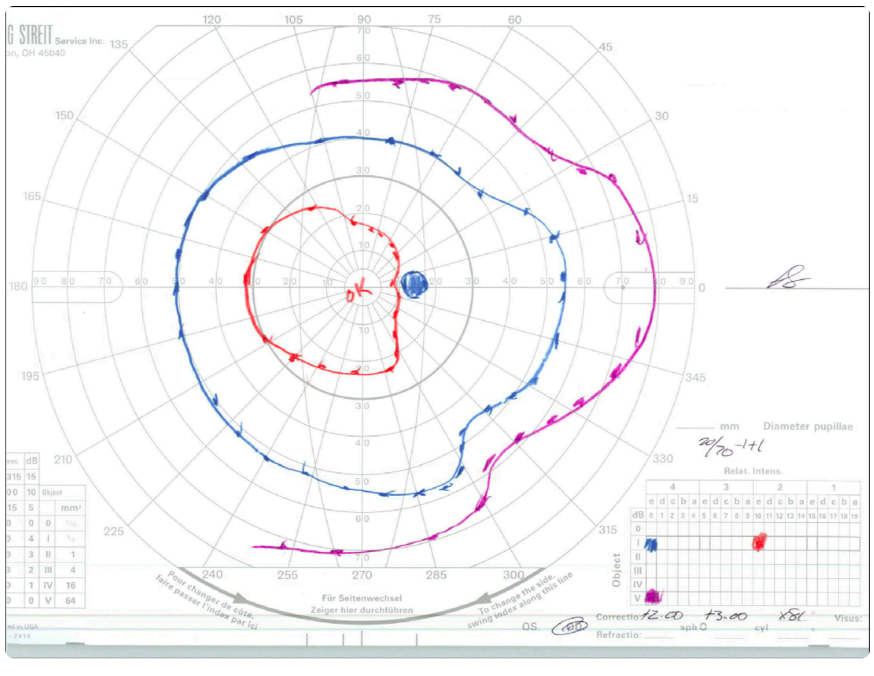

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Figure 3. Goldmann Visual Field testing demonstrating bitemporal constriction of the I2e isopter in the left eye (OS, left panel) and right eye (OD, right panel).

Over the course of multiple follow-ups, the patient has demonstrated stable vision. His most recent examination at the age of 16 years old showed:

- **Visual Acuity (Snellen) with correction**:
  - OD: 20/100 (20/80 with pinhole), Near 2.0 M
  - OS: 20/50 -1, Near 0.6 M
  - OU: 20/40 -1, Near 0.5 M

DIAGNOSIS: Septo-Optic Dysplasia

DISCUSSION

Etiology

Septo-optic dysplasia (SOD) is a heterogeneous developmental disorder defined by the classic triad: optic nerve hypoplasia (ONH), midline brain abnormalities (absent septum pellucidum ± corpus callosum agenesis) and pituitary hypoplasia. It is a multifactorial condition with contributions from both genetic and environmental factors. The key genes implicated in this disease include HESX1, SOX2, SOX3, OTX2, SHH and ARID1A (1–4), which encode transcription factors critical in the development of the optic nerve, early forebrain, and pituitary gland. Thus, mutations in these genes can disrupt normal embryogenesis and lead to the classic features of the SOD triad, with ONH being the most consistent ocular finding.

However, even in confirmed genetic cases, phenotypic variability is high, suggesting environmental factors play a vital role in the development of this condition. Reported risk factors include young maternal age, primigravida status, and maternal diabetes. Teratogen exposure and viral infections during early gestation (5, 6), coinciding with critical periods of optic nerve, forebrain, and pituitary development, are also risk factors. These genetic and environmental factors contribute to the SOD presentation in patients.

Pathophysiology and Natural History:

The first and most consistent component of SOD is the hypoplastic optic nerves. ONH is characterized by a congenital reduction in the number of retinal ganglion cell axons, leading to a small optic disc and impaired transmission of visual information from the eyes to the brain. This results from disruption of early forebrain and optic nerve development during the first trimester of gestation. The natural history is nonprogressive, but visual impairment ranges from mild to severe and may be unilateral or bilateral.

The second and third components of the SOD triad are midline brain abnormalities and pituitary hypoplasia. Midline defects include agenesis or hypoplasia of the septum pellucidum and corpus callosum, arising from the disruption of early telencephalic development. Pituitary hypoplasia results from abnormal development of Rathke's pouch and the ventral diencephalon, the embryonic precursors of the anterior and posterior pituitary (7, 8), respectively. Unlike ONH, which remains stable after birth, endocrine abnormalities may evolve over time, necessitating ongoing surveillance.

Signs/Symptoms/Findings:

The clinical manifestations of SOD are highly variable depending on which components of the triad are present. Ocular features from ONH are the most consistent and include decreased visual acuity, visual field defects, nystagmus, strabismus, and refractive error. The severity of visual acuity loss is determined by the degree of retinal ganglion cell axon loss present at birth. However, functional outcomes may improve modestly with refractive correction and amblyopia therapy. Children with bilateral ONH are at particularly high risk of legal blindness (9, 10). On physical examination, optic nerve hypoplasia is characterized by a small optic disc, often with the classic double-ring sign. The disc-macula to disc-diameter ratio is typically increased due to the underdeveloped optic nerve head (11).

In addition to the ocular features, patients may present with neurological findings in patients with midline brain abnormalities (10, 12–14), such as seizures, developmental delay, or motor deficits. Endocrine abnormalities have also been reported related to pituitary hypoplasia, including growth hormone deficiency, adrenal insufficiency, hypothyroidism, and hypogonadism. These deficits may lead to growth failure, delayed puberty, life-threatening hypoglycemia, and adrenal crises if left untreated (9, 15).

Diagnosis:

The diagnosis of SOD is established when two of the three classic features are present. In the case of our patient, two of the three features were identified, confirming the diagnosis. Diagnosis typically involves a combination of ophthalmic examination to identify optic nerve hypoplasia, neuroimaging (MRI) to evaluate for midline brain defects, and endocrine testing to assess pituitary hormone function (15).

Treatment/Management:

Because manifestations may evolve over time, patients require multidisciplinary evaluation and ongoing follow-up with ophthalmology, neurology and endocrinology. From an ophthalmic standpoint, ONH requires regular monitoring of visual acuity to track developmental progress and detect amblyopia. Refractive error should be corrected early with glasses, and amblyopia therapy initiated as appropriate. Patients with strabismus may benefit from amblyopia therapy and/or surgical correction (16, 17). While visual impairment from ONH itself is nonprogressive, early intervention with these measures can optimize functional vision and prevent secondary vision loss.

With regard to midline brain abnormalities, management may involve antiepileptic medications for seizures, as well as physical therapy, occupational therapy, and early educational interventions to address motor and developmental delays. For patients with pituitary and endocrine dysfunction, hormone replacement may be necessary for deficiencies in growth hormone, thyroid hormone, cortisol, and sex hormones. Because endocrine deficits can emerge over time, regular surveillance is recommended even in patients with normal baseline testing.

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EPIDEMIOLOGY

- **SOD incidence:** 1.41 to 8.3 per 10,000 live births.
- No strong sexual dimorphism.
- Most cases are sporadic, but familial cases are linked to the mutations noted in the article.

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ETIOLOGY

- **Genetic factors:** HESX1, SOX2, SOX3, OTX2, SHH and ARID1A.
- **Environmental factors:** young maternal age (<25 years), primigravida status, maternal diabetes, teratogen exposure, including smoking.

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SIGNS/SYMPTOMS/EVALUATION

- **Optic nerve hypoplasia:** decreased visual acuity (nonprogressive and severity fixed at birth), temporal visual field defects, nystagmus, strabismus, and refractive errors.
- **Midline brain abnormalities:** seizures, motor deficits and developmental delay.
- Fundus: localized serous detachment at macula ± serous PEDs
- **Pituitary hypoplasia:** GH deficiency, hypothyroidism, hypogonadism.
- Evaluation:
  - Ophthalmic exam: ONH with small, pale optic disc, classic double-ring sign, and increased disc-macula to disc-diameter ratio.
  - **MRI:** absent septum pellucidum, corpus callosum, and/or pituitary hypoplasia.
  - **Endocrine testing:** growth hormone, cortisol, thyroid and sex hormone deficiencies.

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DIAGNOSIS/TREATMENT

- **Diagnostic criteria:** SOD is diagnosed when 2 out of the 3 classic features are present (ONH, pituitary dysfunction, and midline brain abnormalities).
- **Treatment:**
  - **Ophthalmic care: regular monitoring of visual acuity (to track development and detect amblyopia), refractive error. correction with glasses, amblyopia therapy, strabismus treatment.**
  - **Neurologic/Developmental care: antiepileptic medications for seizures and physical therapy, occupational therapy and early educational interventions for motor and developmental delays.**
  - **Endocrine care: hormone replacement and regular endocrine surveillance, since deficits may arise over time.**

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