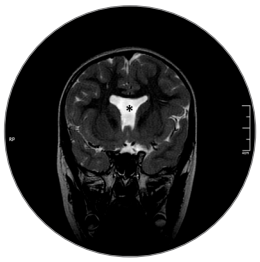

Septo-Optic Dysplasia: Imaging Findings and Review of the Literature

Displasia septo-óptica: hallazgos imagenológicos y revisión de tema

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Summary

Septo-optic dysplasia, also known as De-Morsier syndrome, is a congenital disease that presents a variable combination of defects in its clinical and imaging presentation. All patients with optic nerve hypoplasia must be studied by imaging, especially with magnetic resonance imaging, with the aim of detecting abnormalities in the development of the midline structures of the central nervous system. A review of the literature and subsequently a retrospective evaluation of the patients of our institution was carried out in order to illustrate the main neuroradiological findings of this syndrome.

Resumen

La displasia septo-óptica, también conocida como síndrome de De Morsier, es una enfermedad congénita que consiste en una combinación variable de defectos en su presentación clínica e imagenológica. Todos los pacientes con hipoplasia del nervio óptico deben ser estudiados imagenológicamente, en especial con resonancia magnética, con el objetivo de detectar anomalías en el desarrollo de las estructuras de la línea media del sistema nervioso central. Se realizó una revisión de la literatura y una evaluación retrospectiva de los pacientes de nuestra institución, con el fin de ilustrar los principales hallazgos neurorradiológicos de este síndrome.

1. Introduction

Septo-optic dysplasia (SOD), also known as De-Morsier syndrome, is a congenital disease that encompasses a variable combination of defects including: hypoplasia or absence of the septum pellucidum or corpus callosum, optic nerve dysplasia/hypoplasia, and hypothalamic-pituitary dysfunction (Figures 1-3). It can manifest as disruption of a single pituitary hormonal pathway to panhypopituitarism (1, 2). It is a rare, heterogeneous condition and may occur with additional brain abnormalities (3), such as schizencephaly, cortical dysplasia, polymicrogyria, among others (4) (Figures 4-6). An approximate incidence of 1 per 10,000 live births has been described (5) and a 1:1 ratio between males and females (6).

An explanation for the etiology of OSD has not yet been found. Despite this, it has been proposed that it is the result of genetic abnormalities or in utero lesions caused by a sequence of vascular disruption, especially by an anomaly in the anterior cerebral artery (7, 8); it has also been related to viral infections and maternal exposure to valproic acid (2, 9); it has also been related to viral infections and maternal exposure to valproic acid (2, 9).

Most cases occur sporadically; however, rare cases have been described in which a family history of mutation has been identified in genes encoding essential transcription factors involved in forebrain and pituitary development, such as HESX1, SOX2 and SOX3 (10). More recent studies have identified the FLNA gene mutation in OSD development (11).

The main objective of this article is to review the literature and to illustrate the main neuroradiological findings of this syndrome.

2. Methods

Images of patients of different ages, attending the authors' institution, who were diagnosed with OSD by tomographic or MRI study, were analyzed. The most representative images of this entity were included in the present review and a review of the literature was made based on the incidence by age, most frequent manifestations and additional characteristics that may be present.

3. Etiology

Multiple etiologies have been postulated to explain the sporadic occurrence of OSD, such as viral infections, different types of teratogens, vascular or degenerative damage (12, 13). However, the precise etiology of this syndrome is still unknown, so a mul-

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tifactorial component including genetic and environmental factors has been proposed (10).

Currently, it is believed that the genetic factor affects cortical development (14, 15); however, familial cases of OSD are rare and genetic diagnosis is made in less than 1% of patients (9), of which most are associated with an autosomal recessive inheritance pattern, although cases of autosomal dominant inheritance have also been described (16-18). The main genes encoding transcription factors essential for forebrain and pituitary development that are mutated are HESX1, SOX2 and SOX3. Recently, an association has been found with the FLNA gene (10, 11). Among the environmental factors, drug use during pregnancy, gestational diabetes, cytomegalovirus infection, use of drugs such as quinidine and antiepileptic drugs, maternal age under 22 years, and primigestational mothers have been documented (19, 20). It has also been found that OSD cases seem to cluster in places with high population density and in inner city areas where there is a high unemployment rate (9). Other hypotheses propose that OSD is the result of lesions produced by a sequence of vascular disruption in utero (7), this being the same etiology of multiple congenital defects, such as hydranencephaly, gastroschisis, small bowel atresia, and Poland syndrome (21).

3.1 Clinical manifestations

The clinical presentation of OSD varies phenotypically according to the associated abnormalities. Most cases are detected in childhood; however, in patients without severe involvement of the involved structures it can be detected in adolescence and even in adulthood (Figures 6a and 6b). Among the main clinical manifestations are visual pathway abnormalities and hypothalamo-hypophyseal dysfunction, which can be expressed clinically with short stature, visual impairment, nystagmus and endocrine dysfunction (22, 23); however, approximately 40% of patients may have a normal endocrinological profile (24). In patients with endocrine disturbances it has been shown that these differ between cases, as diabetes insipidus, hypothermia, hypoglycemia, TSH, GH and ACTH deficiencies have been found (25, 26). Even so, the degree of pituitary dysfunction in these patients is very variable, in some phenotypes it can evolve throughout life from an isolated deficiency of a hormonal line to a panhypopituitarism (27, 28). Usually, the first thing that is detected in these patients is optic nerve hypoplasia and it has been described that, generally, it is bilateral (Figure 7) in most patients, unlike the case of Figure 2 where it is unilateral (6). Some studies have shown that 31% of patients with OSD were diagnosed with autism spectrum disorder. These patients may also manifest neurological deficits, such as global developmental delay, focal insufficiencies, epilepsy, hemiparesis, including behavioral and communication difficulties (4, 29, 30).

3.2 Radiological manifestations

OSD can be suspected in the prenatal period by ultrasound and MRI studies in the fetus. On ultrasonography the cavity of the septum pellucidum should be easily visualized at 18 to 20 weeks as a triangular (hypoechogenic) space in the anterior portion of the midline, which develops between the two laminae of the septum pellucidum (hyperechogenic line). In its absence the frontal horns in axial section are visualized as square in shape (31, 32).

The absence of the pellucid septum is neither necessary nor specific for this syndrome. This finding can occur in isolation without other anomalies, in the context of holoprosencephaly, agenesis of the corpus callosum, Chiari II malformation, obstructive hydrocephalus or encephaloclastic processes (hydranencephaly, porencephaly) (33).

Brain ultrasound has some limitations, because it only allows visualization of the absence of septum pellucidum, which can be confused with a variant of the cyst-like abnormality of the septum pellucidum. CT is not usually useful for defining abnormalities associated with neuronal migration or alterations in cortical organization (32, 34, 35).

Magnetic resonance imaging (MRI) provides evidence of optic nerve hypoplasia (unilateral or bilateral) (36) and optic chiasm, as well as agenesis of the septum pellucidum (37-39) (Figure 8) and abnormalities of the corpus callosum and hypothalamic-pituitary axis (40); however, imaging findings among patients vary (28).

There are indirect neuroimaging signs related to optic nerve hypoplasia, such as bullous dilatation of the anterior recess of the third ventricle and enlargement of the prechiasmatic cistern. Other anomalies include pituitary ectopia, pituitary stalk anomalies, porencephaly, schizencephaly, polymicrogyria, periventricular heterotopias, focal cortical dysplasia and hydrocephalus (41). Additionally, atrophy of cerebral hemispheres and brain stem can be found (42); and cases associated with arachnoid cysts have been described (43-45).

4. Diagnosis

OSD, since its manifestation is so heterogeneous and variable among patients, requires the intervention of an interdisciplinary team to make an adequate diagnosis, which will have an impact on the patient's evolution. Early diagnosis can be prenatal or neonatal by means of trans-fontanelar ultrasound (Figure 9) (46). In patients who are not diagnosed early, clinical manifestations of OSD may be observed later, including growth retardation and visual abnormalities such as strabismus or nystagmus (47, 48).

Clinically, the diagnosis should be suspected when a neonate has hypoglycemia, jaundice, microcephaly, cryptorchidism, and midline defects such as cleft palate. In these patients, MR brain imaging and dynamic pituitary function studies, along with appropriate ophthalmologic assessment, should be performed to confirm the diagnosis. Among the pituitary function tests, thyroid function should be studied with a TSH to rule out secondary hypothyroidism and cortisol levels should be evaluated by random cortisol testing. In patients with confirmed hypoglycemia, IGF-1 should be measured in the same manner as IGFBP-3. In patients older than one year with growth retardation GH should be measured with stimulation testing (49). In adolescent patients OSD may be associated with precocious puberty or hypogonadotrophic hypogonadism secondary to LH or FSH deficiency, so it is important to measure this hormonal pathway (6). Likewise, it is important to evaluate sleep disorders in these patients because of their relationship with the defect in melatonin production (50).

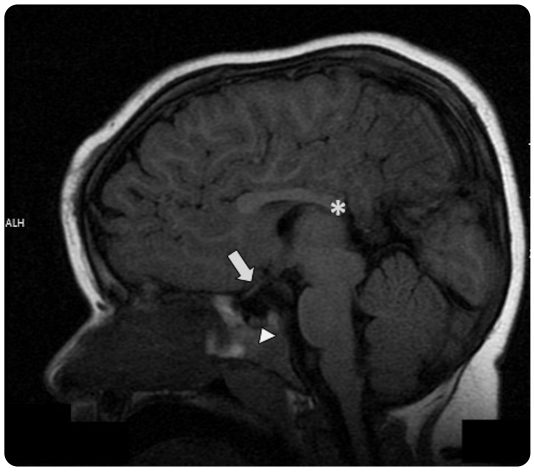

Figure 1. 3-year-old male patient with a diagnosis of psychomotor disorder. Sagittal MRI T1 FLAIR: corpus callosum dysgenesis (*), optic nerve hypoplasia (arrow) and pituitary hypoplasia (arrowhead). Hyperintense signal of neurohypophysis present.

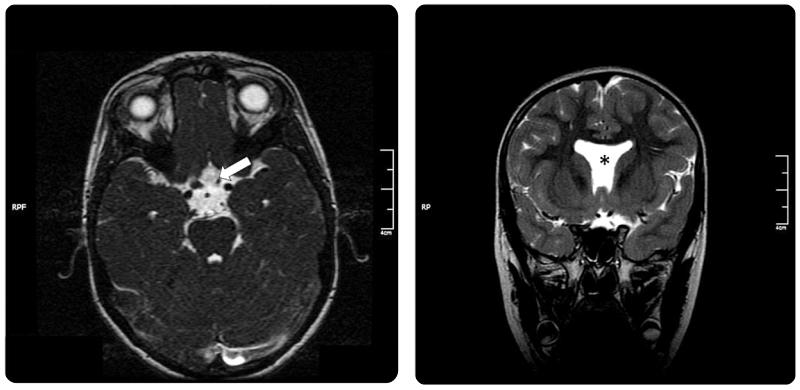

Figure 2. a and b) 6 months old male patient with diagnosis of convulsive syndrome. MRI axial slice 3D FIESTA-C: left optic nerve hypoplasia (arrow). MR coronal reconstruction T2 frFSE: agenesis of pellucid septum (*).

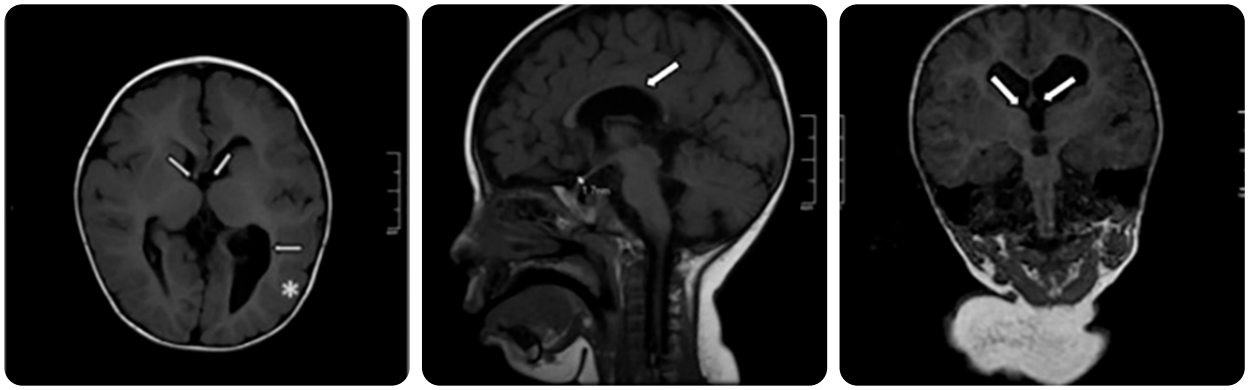

Figure 3. 14-month-old patient with prenatal diagnosis of mild ventriculomegaly. MRI axial slice T2 FLAIR*. a) Axial plane: absence of bilateral fornix (upper arrows), colpocephaly (horizontal arrow), continuity of interhemispheric fissure with the ventricular system and ventriculomegaly of left predominance. b) Sagittal plane: dysgenesis of the corpus callosum. c) Coronal plane: bilateral absence of fornix.

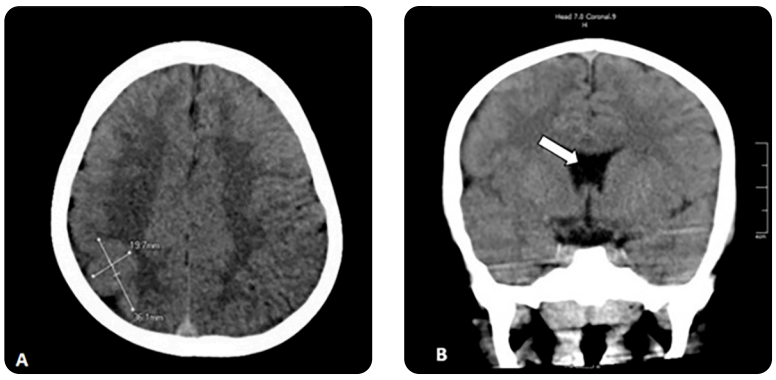

Figure 4. 3-year-old male patient with a diagnosis of unspecified seizure syndrome. a) Axial view: focal thickening of the cortical gray matter is identified in the right frontoparietal junction, extending approximately 3.6 cm in its longitudinal axis by 2 cm thick, with prominence of the adjacent sulci, without evidence of white matter involvement, compatible with cortical dysplasia. b) Coronal view: absence of pellucid septum.

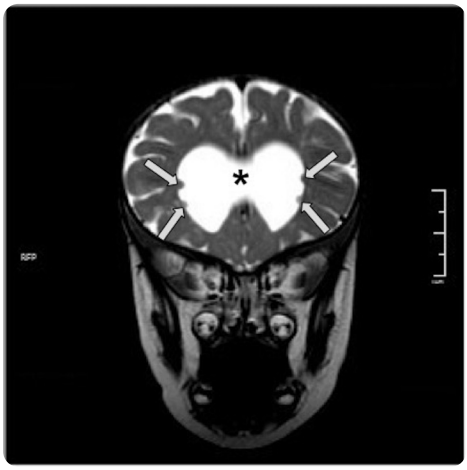

Figure 5. 11-month-old male patient with diagnosis of unspecified seizure syndrome. Coronal MRI T2 frFSE: areas of heterotopia of the subependymal gray matter (arrows) and agenesis of the pellucid septum (*).

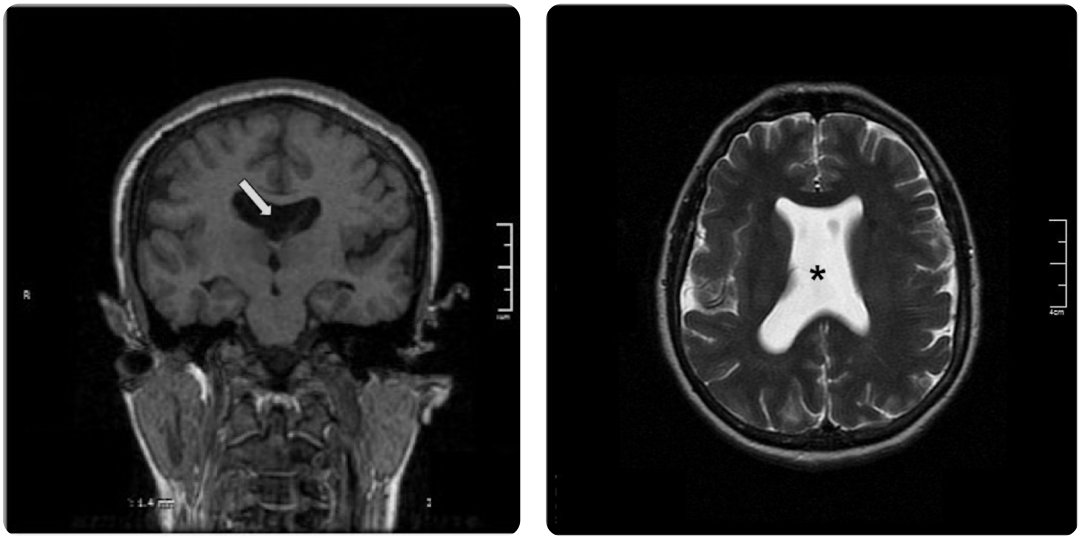

Figure 6. 43-year-old female patient. Study for epilepsy control. a) Coronal MRI T1 3D SPGR: agenesis of septum pellucidum (arrow). b) Axial MRI T2 slice: agenesis of septum pellucidum (*).

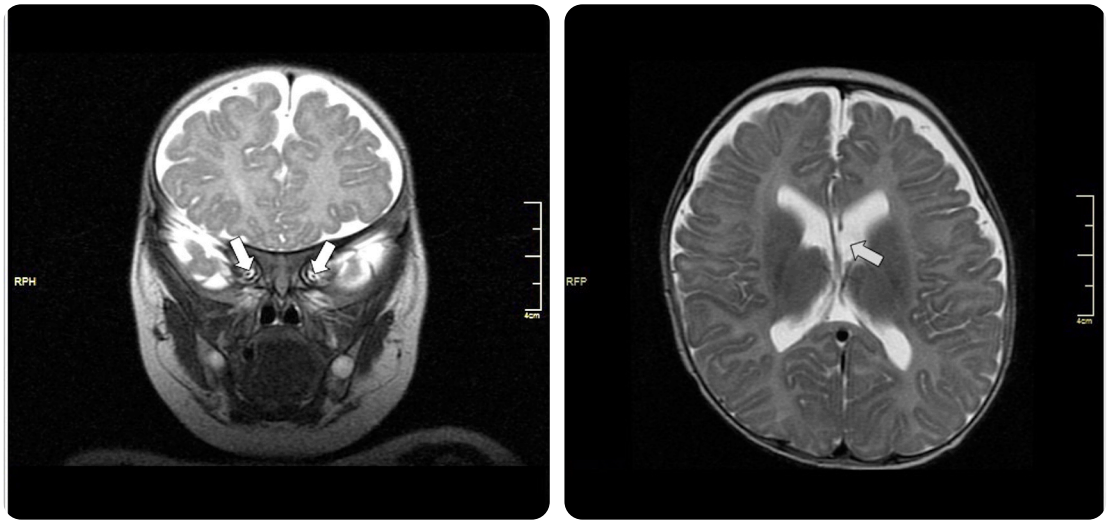

Figure 7. 9 months old male patient with diagnosis of unspecified convulsive syndrome. a) T2 frFSE coronal MRI: bilateral hypoplasia of the optic nerve (arrows). b) Ventricular system, hypoplasia of left fornix.

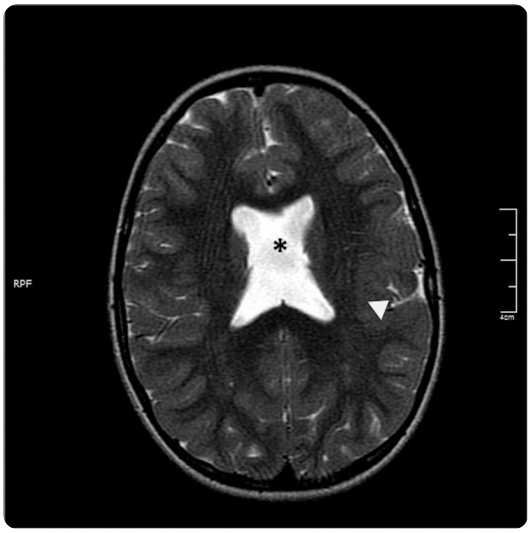

Figure 8. 6-year-old male patient with diagnosis of unspecified seizure syndrome. MRI axial slice T2 frFSE: agenesis of the septum pellucidum (*) and cortical dysplasia (arrowhead).

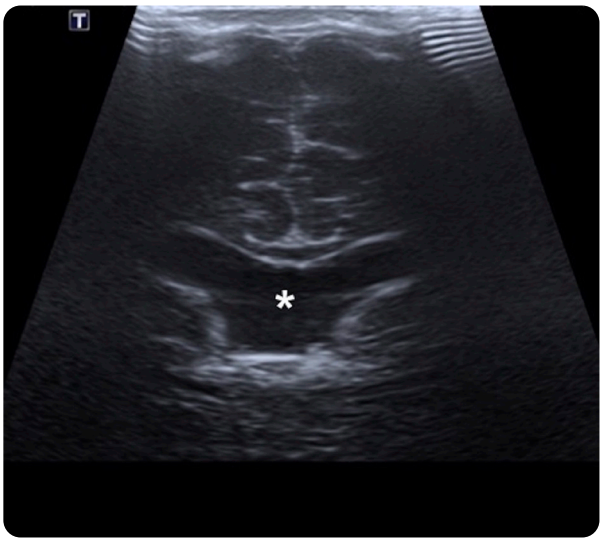

Figure 9. 2-month-old male patient with a diagnosis of unspecified seizure syndrome. Coronal transfontanelar ultrasonography: absence of the pellucid septum.

5. Conclusions

OSD is a congenital disease with a variable presentation of defects, among which the triad composed of corpus callosum hypoplasia, optic nerve hypoplasia and hypothalamic-pituitary dysfunction stands out; these may be associated with other manifestations in the central nervous system. The diagnosis is mainly radiological, so it is important for the radiologist to present the diagnostic suspicion when encountering these manifestations. MR imaging, CT and transfontanellar ultrasound have a very important role in the diagnostic approach to this entity. In this way it is possible to provide early interdisciplinary management and improve the quality of life of this group of patients.

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