MEDDOCS Open Access Publisher

ISSN: 2637-885X

Journal of Radiology and Medical Imaging

Open Access | Case Report

Septo-Optic Dysplasia A Case Presentation for Revisiting this Intriguing and Uncommon Condition

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Received: Mar 10, 2021

Accepted: Mar 25, 2021

Published Online: Mar 29, 2021

Journal: Journal of Radiology and Medical Imaging

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Septo-optic displasia; Septum pellucidum; Optic nerve hipoplasia; Corpus callosum; Cerebral cortex.

Abbreviations: SOD: Septo-Optic Dysplasia; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; CSF: Cerebrospinal Fluid.

Abstract

Septo - Optic Dysplasia (SOD) also known as De Morsier Syndrome, is an uncommon medical condition which is characterized by a triad, agenesis of the septum pellucidum and/or corpus callosum, optic nerve hypoplasia and hormonal dysfunction. Although this entity has been widely recognized, some aspects of the disease remain poorly understood. SOD has the particularity of being highly heterogeneous, both genetically and clinically, with a wide range of radiological findings. In contrast with other neurological conditions, SOD can be seen in several clinical contexts, and, noticeably, SOD may be associated with other brain developmental abnormalities, therefore, the term SOD - Plus has been coined for these cases, which are surprisingly, more frequent than the SOD alone. According to this, radiologists should be aware of these potential associations, since it is likely to find schizencephaly, cortical dysplasia or other neuronal disorders in patients with SOD. The case presented in this review, is a good example of those cases where SOD is joined by cortical abnormal development. In this article, are presented in addition to the case, basic concepts about the etiology, clinical symptoms, diagnostic clues, including measurements of the optic nerves on MRI and an algorithm to achieve easily a more accurate diagnosis.

Background

Septo-Optic Dysplasia (SOD) is a rare neurological condition also known as de Morsier Syndrome [1,2]. This disorder has been characterized by abnormal development of midline structures (septum pellucidum and/or corpus callosum) and hypoplasia of the optic nerves, as its name indicates. However, there is another important clinical criterion linked to the disease, namely, hypothalamic-pituitary dysfunction with endocrine manifestations [3,4,5]. As a result, there are three key elements setting a triad, dysgenesis of the septum pellucidum or corpus callosum, optic nerve hypoplasia, and endocrine disbalance secondary to hypothalamic-pituitary axis dysfunction. At least two out of three must be present for making the diagnosis [1,2,3,4,5].

Although, there is a general consensus on how to make the diagnosis and which are the radiological and clinical manifestations of SOD. This disorder has a wide spectrum of clinical manifestations and is considered to be highly heterogeneous with significant variability of severity and neurological symptoms. Thus, some studies have reported that only, from 30% to 47% of diagnosed patients have all the three typical manifestations of the triad [5,6]. Similarly, of all SOD´s sufferers, 62% present with complications of hypopituitarism, 60% lack of septum pellucidum and about 70% have optic nerve hypoplasia being this, segmental or partial, and even, unilateral or bilateral [6].

Cite this article: Lobo AR, Ocampo M. Septo-Optic Dysplasia A Case Presentation for Revisiting this Intriguing and Uncommon Condition. J Radiol Med Imaging. 2021: 4(1); 1044.

Despite SOD was initially described more than six decades ago [1], and there are many articles about it, the exact prevalence of this disorder worldwide, perhaps is unknown. Some studies have reported a prevalence of 1 in 10000 live births [6,7], however, other studies substantially differ from this value. For instance, a population-based study carried out in Europe, found a lower prevalence of 1.9-2.5 per 100.000 live births [8]. Another study from Canada did find a prevalence from 53.3 per 100000 live births to 113.3 per 100000 live births, with an increasing rate over time [9]. Overall, there is no gender preference with very similar affection to males and females. The main clinical symptoms related to the disease are developmental delay, visual impairment or blindness, seizures, obesity, anosmia, cerebral palsy and hypopituitarism with growth hormone deficiency, being the most frequent endocrine manifestation [6].

Case Presentation

A 21-year-old male patient was referred to the Neurology institute of our hospital due to epilepsy which had worsened in the last months.

A detailed clinical history was obtained during the appointment. The patient was product of a fourth pregnancy. The delivery was normal with no complications and the birth weight was also normal. Our patient did not have a background of developmental delay or malnutrition. There were no remarkable findings in the physical examination. The patient was managed with Valproic Acid, and a series of exams were ordered, among them, a Brain MRI.

The images showed several interesting findings, that were not expected given the age of the patient and the fact that he has not been studied before. The first one was the lack of the Septum pellucidum (Figure 1), typical feature observed in SOD and an important clue for making the diagnosis. The optic chiasm had a reduced size (Figure 2), with an area of 22.05 mm2 and the right optic nerve was hypoplastic, with these two findings the diagnosis of SOD was confirmed. Additionally, in the right frontal lobe it was present a focal zone with abnormal brain cortex, thickened and irregular, representing an area of polymicrogyria (Figures 3,4,6).

Besides, the patient had nodular heterotopic periventricular grey matter also in the right frontal lobe (Figure 5). The pituitary gland was normal. With this constellation of findings, a diagnosis of SOD – Plus syndrome was made.

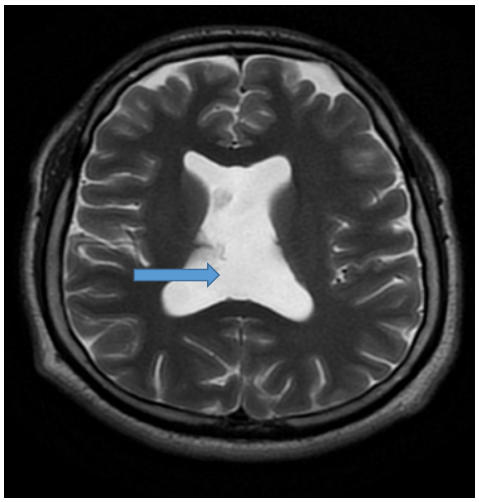

Figure 1: Axial T2-weighted image. It is clearly seen the lack of the septum pellucidum (Blue arrow). Both cerebral hemispheres are normally separated.

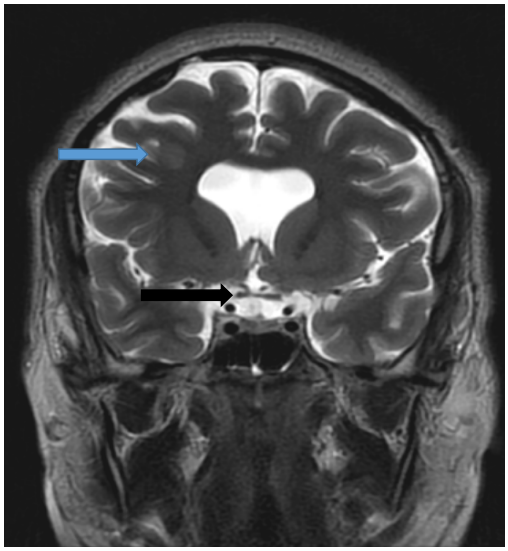

Figure 2: Coronal T2-Weighted image. Absence of the septum pellucidum. Hypoplasia of the optic chiasm, with more noticeable affection of the right side (black arrow). Area of polymicrogyria in the right frontal lobe (Blue arrow).

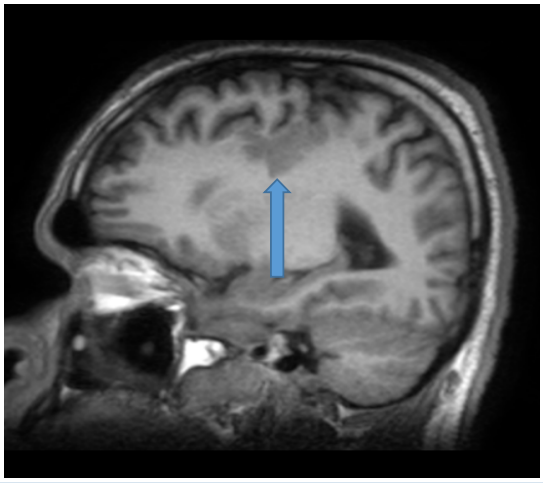

Figure 3: Sagittal T1-weighted image. It is observed an abnormal brain cortex which is thickened and irregular, representing polymicrogyria (Blue arrow).

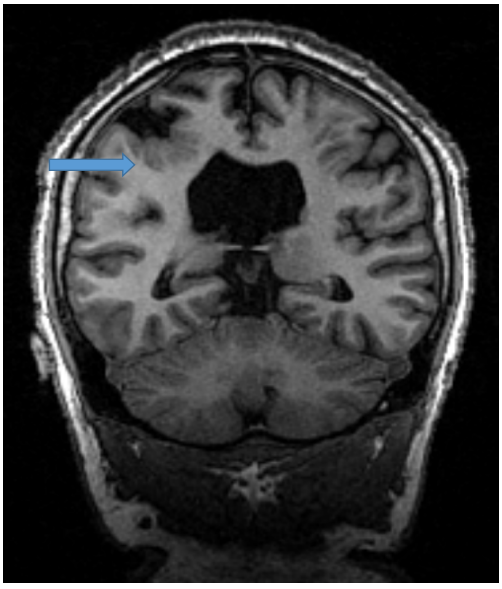

Figure 4: Coronal Bravo image. Polymicrogyria in the right frontal lobe (Blue arrow).

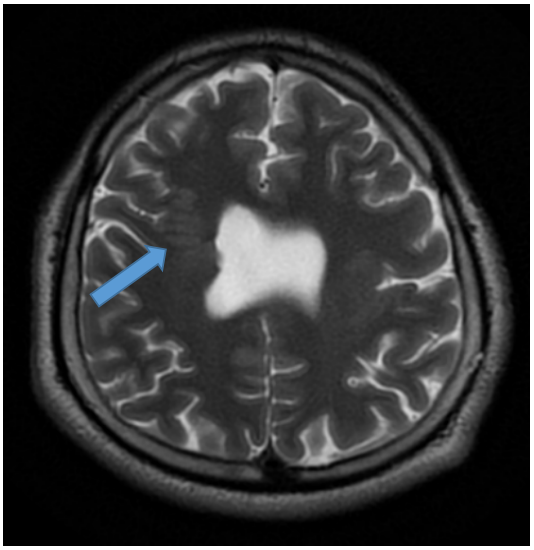

Figure 5: Axial T2-weighted image taken in a superior level. Abnormal brain cortex in the right frontal lobe with heterotopia (notice how the grey matter abuts the right lateral ventricle wall, Blue arrow). Also, it is seen lack of the septum pellucidum.

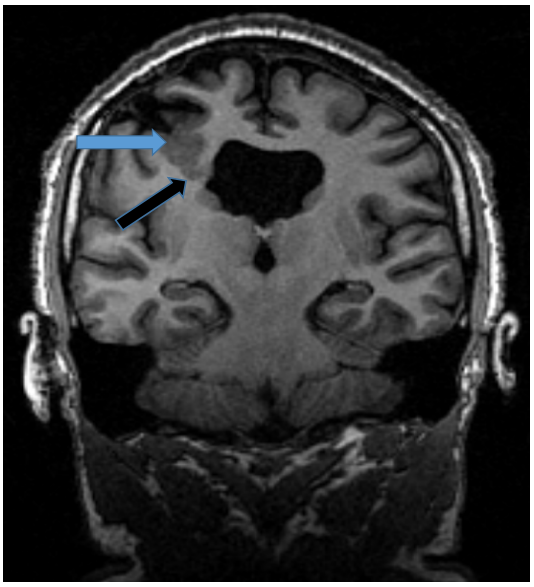

Figure 6: Coronal Bravo image. Polymicrogyria in the right frontal lobe, the brain cortex in this zone is thickened and irregular (Blue arrow). There also can be seen grey matter abnormal adjacent to the right lateral ventricle (Black arrow).

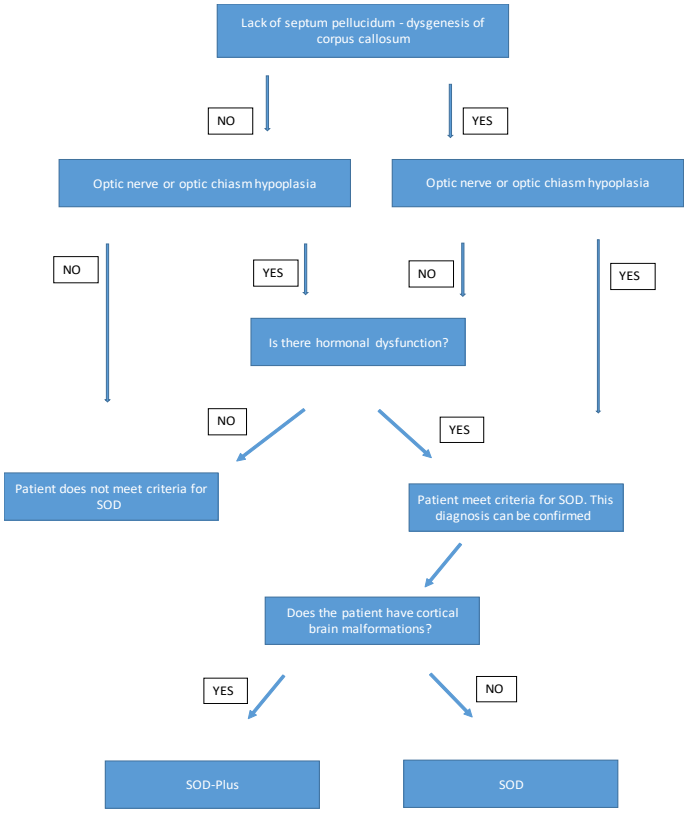

Diagram 1: Algorithm Proposed for the Diagnosis of Sod.

Etiology of this condition

SOD is definitively a heterogeneous entity with an extensive range of clinical and radiological features, thereby, some authors have considered, that SOD is rather a syndrome that a single disease [3].

Multiple etiologic agents such as vascular insults, viral infections, maternal age, and genetic mutations [6,7,8,9] have been associated with the origin of SOD. The vast majority of cases are sporadic; however, an increasing number of early developmental transcription factors and related pathway genes have been implicated in the etiology of SOD, i.e., HESX1, SOX2, SOX3, OTX2, PROKR2, FGF1, and FGF8 [4,10]. As a result, the phenotype and radiological manifestations vary significantly across individuals.

In general terms, the radiological features found in this disorder, imply abnormal forebrain development that has been described to present during early pregnancy, about 4-6 weeks of gestation, which is a crucial period for the formation of the neural plate [6]. The recognition of this phenomenon, embryologic common aspects between the optic pathway and pituitary gland, as well as researching on genetics, have led to the discovery of possible genetic mutations that could be linked to SOD. The primary genes linked to SOD were HESX1 [6,7] and SOX2 [6], and more posteriorly SOX3 [5].

The first one, the gene HESX1, perhaps is the most studied. This is a paired-like homeobox gene, acting mainly as a transcriptional repressor and is one of the earliest markers for murine pituitary development [6]. The homozygous mutations are fully penetrant, while the heterozygous mutations are variably penetrant and frequently related to less severe forms of the disease. SOX2 mutations have been demonstrated in association with serious bilateral ocular abnormalities, defects of the corpus callosum and pituitary hypoplasia. In addition, other features like developmental delay, male genital tract abnormalities, oesophageal atresia, and sensorineural hearing loss, have also been described [6,7,11,12].

The presence of phenotypical differences between twins with these anomalies [13], confirm that this condition is undoubtedly heterogeneous. The genes SOX2 and SOX3, which are implicated in SOD, are also linked to the aetiology of other disorders such as holoprosencephaly, microphthalmia or anophthalmia [7,9,10,11,12,13,14,15]. In spite of the discovery of these genes and its demonstrated association with SOD. It is thought that only less than 1% of the patients can be confirmed as carriers of those mutations [6], therefore, other contributors and different genetic abnormalities must be part of the aetiology. Indeed, another gene, the OTX2, is also being related to SOD [18]. It is considered a transcription factor that is essential for the formation of anterior structures of the forebrain. This gene has been implicated in anophthalmia-microphthalmia syn-

dromes and pituitary malformations in humans [18,19,20].

Having said that, it is important to remember that other factors, such as alcohol, maternal age, vascular insult during early pregnancy, environmental toxics and drugs have been associated with the origin of this complex condition [6,7]. In fact, it has been established a clear association between alcohol consumption and brain midline structures malformations [21,22].

From our point of view, this variability and the uncertainty of the exact origin of the disease is of paramount importance. Since, this complex genetic – environment interaction, explains how the SOD may differ from one patient to another.

Radiological and clinical features in sod

SOD is one of those disorders where the role of the radiologists is essential for a correct diagnosis. Taking into account, that the condition is widely heterogeneous, sometimes it is difficult to make the diagnosis at first. Since the description of the disease by the Swiss George de Morsier in 1956 [7], this disorder has been hard to classify due to the diversity of findings and clinical manifestations.

As it was said before, two out of three criteria for SOD rely on images (Absence of septum pellucidum-Dysgenesis of the corpus callosum and optic nerve hypoplasia). Although, frequently the first medical image is a Brain CT, where the optic chiasm and the optic nerves are not easily evaluated. Lack of Septum pellucidum can be normally visualized on CT and MRI, and if so, the radiologist should be aware of the potential diagnosis. Barkovich in 1989, remarked the importance of identifying the dysgenesis of the septum pellucidum [23], additionally, in this article, he considered two subsets of patients with SOD, regarding whether the patients also had schizencephaly or not [23]. Also in this article, Barkovich proposed an interesting algorithm to address the diagnosis of these patients. This is important, keeping in mind the concept of SOD plus which will be developed ahead.

Consequently, since the radiological perspective, perhaps, the most important clue for the diagnosis is the absence of the septum pellucidum, since, it can be the only finding [24]. Nonetheless, there is bad news, this finding is not always present [10]. That´s why a meticulous analysis of the images is required as well as the correct interpretation of clinical history.

The modality of choice to diagnose SOD is the MRI, since, it is ideal to identify and assess the structures that are involved in this condition. Sagittal T1 or T2-weighted images allow us to visualize the corpus callosum and the optic nerves. Both, axial and coronal, T2-weighted images, depict adequately the ventricular system and whether the septum pellucidum is present or not. Additionally, on T2-weighted images we can assess CSF spaces, optic chiasm, brain cortex, and other findings that may be present. The optic chiasm is nicely visualized on coronal images, both T1 and T2-weighted images.

Besides the septum pellucidum and corpus callosum, other features should be analysed. As part of the triad, optic nerve hypoplasia and optic chiasm hypoplasia are frequently seen in these patients. Other potential findings are, microphthalmia, anophthalmia, coloboma, pituitary hypoplasia or ectopia, pituitary stalk hypoplasia, and other findings more recently described, reduction in the diameters of the midbrain, medulla and pons [4] as well as olfactory tract hypoplasia.

Optic pathway structures can also be evaluated by measuring the optic nerves, either in its intra-orbitary or pre-chiasmatic segments. Similarly, the optic chiasm can be measured on appropriate coronal images. Indeed, Maresky et al [25], found a positive correlation between patient´s age and the size of the optic structures in children, with a normal enlargement of these structures as patients are getting older. The main findings of this publication are represented in Table 1 (Reproduced with permission).

Table 1: Patients divided into five groups according to age. The number of participants (N) in each group, Mean Diameter (MD) of the orbital optic nerve and prechiasmatic optic. Along with Standard Deviation (SD) for each mean diameter and corresponding SDs are listed for each group. Differences in N for different measurements of the same age group are due to the fact that some measurements were not attainable from some MRIs.

Age group	Age (years)	Orbital optic nerve			Prechiasmatic optic nerve		
		N	MD (mm)	SD	N	MD (mm)	SD
I	0-1.49	15	2.2	0.16	16	2.92	0.24
II	1.5-2.9	20	2.38	0.22	17	3.08	0.26
III	3-5.9	36	2.64	0.23	35	3.2	0.38
IV	6-11.9	20	2.9	0.43	19	3.44	0.4
V	12-18	21	3.1	0.44	16	3.59	0.268

About optic structures in the adult population, there are also publications that have found normal measurements for both, optic nerves and optic chiasm. Mncube and Goodier [26] found that the optic chiasm has a normal width between 11.13 mm and 16.92 mm with a mean value of 13.63 mm. Another study by Wagner et al [27], showed that on coronal MR images, the optic chiasm has an area between 33.3 mm2 and 54.1 mm2 and width between 10.6 mm and 17.4 mm. For the authors of the latter study, values outside this range can be considered as abnormal.

One study in Brooklyn, New York, found dysgenesis of septum pellucidum in 4 out of 5 patients with SOD [10]. A retrospective study carried out in Oman, which included only 5 cases [32], showed that 3 out of 5 patients, had an absent septum pellucidum, while, 5 out of 5 cases had visual impairment and optic nerve hypoplasia. Therefore, assessment of the optic pathway is crucial in this condition. Endocrine deficits were detected in 4/5 patients, which demonstrates that also it is important to evaluate the pituitary gland and to review lab tests of the patients along with the interpretation of the images.

Besides the typical findings, there are other potential features that can be associated with SOD [23,29,30]. The term SOD-Plus, was proposed by Miller in 2000 [28], for those cases in which, were also seen developmental delay and other neurological issues, non-explained, by the mid-line defect itself. It is known that SOD may be accompanied by brain cortex abnormalities such as polymicrogyria, schizencephaly, grey matter heterotopias and cortical dysplasia, being schizencephaly the most frequently related to SOD [23,29,30]. When we have a case of SOD and brain cortex abnormalities, actually, this is a SOD-Plus case [29]. In 1996, a case of cortical dysplasia and SOD was published [31], and the term cortico-septo-optic dysplasia was proposed, however, these patients are generally diagnosed as SOD-plus.

Another publication that analyzed 6 adult patients with drug-resistant epilepsy [33]. Demonstrated that 6 out of 6 patients presented cortical malformations, as the cause of seizures. A bigger study, where 17 patients with SOD were included, showed that only 1 patient (6%) of the total, was classified as classic SOD. Whereas 13 patients (76%) were categorized as SOD plus [34]. In this study, only 18% of the patients had normal septum pellucidum and they were considered as SOD-like. As a result, we can state that it is more likely to have SOD plus rather than classic SOD. Consequently, it is crucial to assess MRI scans properly, since the possibility of overlooking an additional disorder is high in patients with SOD.

A meticulous assessment of the brain cortex may be hard, but necessary. The brain cortex should be homogenous and the transition between the gray matter and the white matter should be well defined and smooth. Malformations of cortical development are macroscopic or microscopic abnormalities of the cerebral cortex, that are originated due to an interruption of the normal process of cortical formation. These disorders are common causes of neurodevelopmental delay and epilepsy [35,36]. A complete review of cortical malformations is beyond the scope of this article, however, in the table 2, are presented the key features in the four conditions that have been traditionally related to SOD, schizencephaly, focal cortical dysplasia, grey matter heterotopia and polymicrogyria.

Neurodevelopmental delay is a highly prevalent condition, among patients with SOD, with a proportion even of 78% in one series [34]. One study additionally mentioned the presence of brain atrophy in a patient with SOD and infantile spasms [37]. In contrast, multiple works have shown hydrocephalus, thus, it is possible that a higher percentage of SOD patients also have brain volume reduction or brain atrophy, among other radiological findings.

Seizures and intellectual delay, are the dominant neurological symptoms. Other less common manifestations should make us think of the diagnosis. For instance, hypoglycemia is common in SOD [10]. Dyskinetic cerebral palsy, infantile spasms and mydriasis, are other ways of presentation of SOD [37,39,40]. Even, other cases have been reported of SOD accompanied by olfactory tract hypoplasia, infantile obesity and complex microphthalmos [40,41,42].

Table 2: Key features in the malformations of cortical development associated with SOD.

Disorder	Main features-Key findings
Schizencephaly	Transcortical cleft that communicates the pial surface with the ventricular wall. This cleft is lined by gray matter.
Polymicrogyria	Abnormal cortex, thickened and irregular. The affected region has lobulated contours, consequently, the cortical-subcortical transition is not smooth but lobulated.
Grey matter heterotopia	Bands or nodules of gray matter located in an abnormal position, adjacent to the ependymal line or in a subcortical area.
Focal cortical dysplasia	Focal cortical thickening with abnormal signal intensity. Transmantle sign. Blurring of the cortical-subcortical transition. There are 2 forms of this condition.

How to adress the interpretation of mri to make the diagnosis of sod

Brain MRI may be challenging, and in most cases of SOD, the process of making the diagnosis relies on the radiologists, since most patients are being studied for different symptoms and they have not been diagnosed yet.

The absence of the septum pellucidum is perhaps the main finding that points towards the precise diagnosis, nonetheless, as we stated before, it is not always present. Consequently, looking at other midline structures such as the corpus callosum and the pituitary gland is mandatory, as well as a careful observation of the optic chiasm, ventricular system and, brain cortex. Obviously, these steps must be included in the Brain MRI interpretation. However, for the case of SOD, we suggest an algorithm to easily make the diagnosis, with the starting point in the assessment of the septum pellucidum/corpus callosum and the optic nerve/optic chiasm. Diagram 1 depicts this algorithm.

Conclusion

SOD, is definitely a highly heterogeneous condition with different possible manifestations. Since severe cases that are diagnosed in the early childhood, to adults with seizures and otherwise normal, as the case presented in this review. Classically it has been described as a triad formed by agenesis-dysgenesis of the septum pellucidum or corpus callosum, hypoplasia of the optic nerves and hormonal deficits linked to pituitary dysfunction. To make the diagnosis, it is necessary to have at least two out of the three criteria. In spite of some genetic mutations clearly associated with SOD, most of the cases are sporadic. Therefore, many authors believe, this is multifactorial, with potential agents such as vascular supply, drugs, alcohol and other toxic or environmental factors.

Clinical and radiological manifestations are variable and usually the patients are being studied by seizures of other symptoms when they undergo the MRI, thereby, the role of radiologists is essential for making the diagnosis promptly. From the radiological perspective, agenesis of the septum pellucidum has been the key feature for the diagnosis, however, there are several series in the literature demonstrating that not all the patients lack of the septum pellucidum or corpus callosum. Therefore, assessment of the optic pathway and the pituitary gland should be mandatory. The hypoplasia of the optic nerves is also key for the diagnosis and can be appropriately assessed on MRI scans. In this article, we highlight the importance of supporting our analysis by measuring the optic nerve or the optic chiasm, which is easy on MRI.

SOD has been described in association with some neurological disorders, particularly with schizencephaly and other brain cortex abnormalities. If this is the case, the actual name of the condition would be SOD plus. Surprisingly, according to different studies, SOD plus is much more frequently seen than classic SOD, thereby, when radiologists diagnose a potential case of this disorder, should be aware of ruling out malformations of the cortical development, by carefully looking the brain cortex. Key features of those conditions are presented in this article.

Regardless this entity is uncommon, at some point radiologists, neurologists, and other specialists, will face cases with SOD or SOD-Plus, and keeping in mind that for some authors its incidence is increasing, it is important to know about this entity and how to address the interpretation of medical images.

Learning points

1. SOD is confirmed when two out of three criteria are met. These criteria are dysgenesis of the septum pellucidum and/or corpus callosum, optic nerve hypoplasia and hormonal dysfunction.
2. Absence of the septum pellucidum is a key feature, however, not all cases present this way.
3. SOD is highly heterogeneous either clinically or radiologically, that's why the radiologist should be aware of this condition.
4. SOD-Plus is the term that has been coined when SOD presents with other cortical brain abnormalities, and this condition is more frequent than SOD alone.
5. MRI is the modality of choice to diagnose SOD, and at the same time is the preferred technique to evaluate the optic chiasm and brain cortex.
6. Measurements of the optic nerve and the optic chiasm can be easily taken on MRI, and by comparing with the normal values, the diagnosis may be easier.

Disclosures

No disclosures. I would like to thank to my Hospital and specially to the patient who authorized the use of the images in this publication.

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