

SELF-AGGRESSION AND CONGENITAL CLUBFOOT

Additional features to the septo-optic dysplasia complex

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Septo-optic dysplasia (SOD), often referred to as *de Morsier* syndrome, is a rare, highly heterogeneous condition defined loosely by any combination of the triad of optic nerve hypoplasia (ONH), midline neuroradiological abnormalities (such as agenesis of the corpus callosum and absence of the septum pellucidum) and pituitary hypoplasia with consequent hypopituitarism¹. The reported incidence of SOD is 1/10,000 live births and affects males and females equally¹. Clinical features may include various degrees of partial pituitary insufficiency (from panhypopituitarism to isolated GH, ACTH or ADH insufficiency), various intensities of psychomotor retardation, mild to severe visual impairment, thermoregulatory disturbances, conjugated hyperbilirubinemia, and seizures². Radiological abnormalities can be equally heterogeneous with a wide constellation of cortical dysplasias (e.g nodular periventricular heterotopia, holoprosencephaly and schizencephaly)³.

CASE

We report on a 10 year-old girl who presented with bilateral optic nerve hypoplasia, endocrine abnormalities characterized by growth hormone deficiency and hypothyroidism, and brain malformations characterized by absence of septum pellucidum, schizencephaly, and gray matter heterotopia. Even though the presence of all symptoms of the SOD triad in a single patient is already considered rare, our patient presented with additional features of self-aggression behavior and limb defects which supports the question whether septo-optic dysplasia should be regarded as a single precisely defined entity or, rather, a group of heterogeneous disorders.

A 10-year-old female patient was referred with amaurosis, endocrine defects (growth hormone deficiency and hypothyroidism) and self-aggressive behavior. The patient was born to nonconsanguineous parents. The patient's mother was only 14



Fig 1. Patient presenting a constant self-aggressive behavior characterized by self-inflicted injuries of her forearm leading to severe skin lesions.

years at the time of pregnancy and referred the administration of an injection with the intention to interrupt the pregnancy at the seventh month of gestational age.

The patient was born pre term at the eighth month of gestational age with vaginal delivery with a clinical history of anox-

AUTO-AGRESSÃO E PÉ-TORTO CONGÊNITO: CARACTERÍSTICAS ADICIONAIS À DISPLASIA SEPTO-ÓPTICA

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Fig 2. Congenital bilateral clubfoot.

ia. Her early development was abnormal and presented delayed neuropsychomotor acquisitions (cephalic sustain at the age of 2-year-old, never acquiring independent walking or speech). There was no family history of neurological diseases.

At the age of 6-month-old the patient was diagnosed as having bilateral optic nerve hypoplasia associated with hormonal deficiency characterized by hypothyroidism and growth hormone deficiency that were treated immediately with hormone replacement.

At the age of 8-year-old the patient started with a severe agitation associated with a self-aggressive behavior characterized by biting of her fingertips and forearms, which ended to inflict severe injuries (Fig 1).

On physical examination, she showed bilateral clubfoot (Fig 2) and the neurological examination was noteworthy for poor contact, spastic hypertonus and brisk tendon reflexes.

Laboratory evaluations, including a complete blood count, blood electrolytes, urea, creatinina and liver enzymes gave results at normal range. Hormonal evaluation was also normal under treatment.

Ophthalmologic evaluation revealed bilateral optic nerve hypoplasia and amaurosis.

Cranial MRI revealed absence of septum pellucidum, schizencephaly on the left parietal lobe, and gray matter heterotopia in the left lateral ventricle (Fig 3).

The patient was treated with risperidone with improvement of the self-aggressiveness and is currently under regularly clinical follow-up.

The hospital ethic commission approved this case report and the parents gave informed consent for publication.

DISCUSSION

The clinical entity of septum pellucidum agenesis associated with optic nerve abnormalities was firstly described by Reeves in 1941⁴ but it was only in 1956 that De Morsier associated optic nerve hypoplasia to septum pellucidum agenesis into the same clinical syndrome and coined the term “septo-optic dysplasia” (SOD)⁵, later to be recognized as De Morsier syndrome.

Typically the SOD is characterized by any combination of the triad of optic nerve hypoplasia, midline radiological abnormalities and pituitary hypoplasia with consequent hypopituitarism¹. The diagnosis of SOD is made by ophthalmologic examination in conjunction with neuroimaging and whenever the hypoplasia of the optic discs is seen in association with partial or complete absence of the septum pellucidum the diagnosis is established^{1,2,6}.

Our patient presents all the elements of the SOD triad, which is considered unusual and generally not found in a single patient, accounting for less than 30% of the SOD patients.

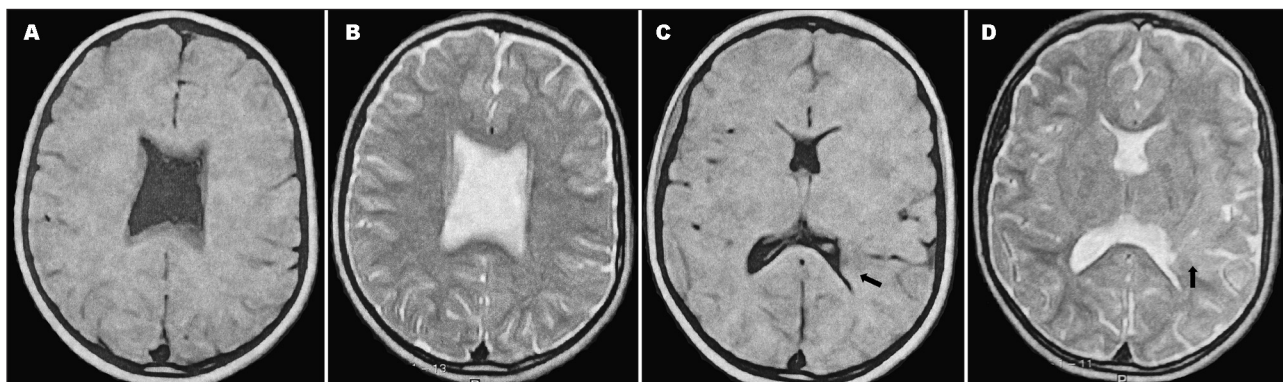


Fig 3. MRI axial T1 [A,C] and T2 [B,D] images showed absence of the septum pellucidum. MRI axial T1 [C] and T2 [D] images revealed closed lips schizencephaly in the left parietal lobe.

Several etiologies have been postulated to account for the sporadic occurrence of SOD, such as viral infections, environmental teratogens, and vascular or degenerative damage¹. However, the precise etiology of the condition still remains unknown and is most likely to be multifactorial, with a combination of genetic and environmental factors¹. In 2005 studies revealed that patients with SOD are born to mothers who are significantly younger than average⁷, and there are reports of maternal multidrug abuse in patients with SOD⁸. In our case, the patient's mother was only 14-years-old at the time of pregnancy and there was a report of the administration of parenteral injection with the intention to interrupt the pregnancy at the seventh month of gestational age. The specific causation of any of those factors, however, is difficult to prove.

The genetic basis for SOD was suggested when one family with SOD and several individuals with sporadic forms of the syndrome have been shown to have mutations in the *HESX1* (homeobox gene expressed in embryonic stem cells), gene located at chromosome 3p21.1–3p21.2. The expression of that gene is suggested to be responsible for the induction of the prosencephalic midline^{1,9}. Other genes as *SOX2* and *SOX3*, genes expressed throughout the developing CNS were also associated with SOD variants¹. Genetic investigation, however, was not available in our case.

Clinically, patients with SOD present, along with endocrine abnormalities, various intensities of psychomotor retardation. Our patient presented delayed acquisition of motor milestones but also presented with a severe self-aggressive behavior. Self-injurious behavior (SIB) is a severe and chronic form of aberrant behavior that poses serious risks to persons with intellectual disabilities¹⁰. The most common forms of SIB are head banging, self-biting, and self-scratching. Estimates of SIB are highest in individuals with severe and profound levels of intellectual disabilities¹⁰. SIB is a common feature of many disorders including Tourette's syndrome, schizophrenia, and is also common in individuals with certain disabilities such as Lesch-Nyhan syndrome¹⁰. Despite its relationship with intellectual disabilities it is under-reported in patients with SOD.

Another additional characteristic of our patient is the presence of bilateral congenital clubfoot. In 2002, Orrico et al.⁸ reported a case of SOD associated with deformities of toes (severe hypoplasia of the third metatarsus on the left and of the third, fourth and fifth metatarsus on the right and bilaterally medial deviation of the first and second metatarsus) as well as facial dysmorphism. In this report, SOD as well as the limb defects were thought to be related to the impairment of uteroplacental fetal blood flow during critical periods of development related to maternal use of cocaine⁸. Another limb defect as-

sociated with SOD is the presence of transverse limb defect, as recently reported¹¹. Congenital bilateral clubfoot, however, is rarely reported in association with SOD, in a large study evaluating 357 patients with congenital clubfoot, one patient presented SOD¹², and, to our knowledge, no other cases were reported.

From the imaging point of view SOD is characterized by the hypoplasia or complete absence of the septum pellucidum and may be associated with malformations of cortical development^{2,6}. The association of SOD with schizencephaly is found in up to 50% of the SOD patients and the presence of gray matter heterotopia is considered rare⁹.

This report reinforces the high heterogeneity of the SOD complex.

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