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# DE MORSIER SYNDROME ASSOCIATED WITH PERIVENTRICULAR NODULAR HETEROTOPIA

## Case report

*Mônica Jaques Spinosa[1], Paulo Breno Noronha Liberalesso[2], Simone Carreiro Vieira[1], Alfredo Löhr Júnior[2]*

ABSTRACT - *Introduction:* Septo-optic dysplasia (De Morsier syndrome) is defined as the association between optic nerve hypoplasia, midline central nervous system malformations and pituitary dysfunction. *Case report:* Third child born to nonconsanguineous parents, female, adequate pre-natal medical care, cesarean term delivery due to breech presentation, Apgar score 3 at the first minute and 8 at 5 minutes, symptomatic hypoglycemia at 18 hours. Neurological follow-up identified a delay in acquisition of motor and language developmental milestones. Epileptic generalized seizures began at 12 months and were controlled with phenobarbital. EEG was normal. MRI revealed agenesis of the pituitary stalk, hypoplasia of the optic chiasm and periventricular nodular heterotopia. Ophthalmologic evaluation showed bilateral optic disk hypoplasia. Endocrine function laboratory tests revealed primary hypothyroidism and hyperprolactinemia. *Conclusion:* The relevance of this case report relies on its uniqueness, since periventricular heterotopia had not been described in association with septo-optic dysplasia until 2006.

KEY WORDS: De Morsier syndrome, septo-optic dysplasia, periventricular nodular heterotopia, primary hypothyroidism.

**Síndrome de De Morsier associada a heterotopia nodular periventricular: relato de caso**

RESUMO - *Introdução:* Displasia septo-óptica (síndrome de De Morsier) é definida como a associação entre hipoplasia do nervo óptico, malformações de linha média do sistema nervoso central e disfunção pituitária. *Relato de caso:* Terceiro filho, pais não consangüíneos, sexo feminino, pré-natal adequado, parto cesário a termo por apresentação pélvica, Apgar 3 no primeiro minuto e 8 no quinto minuto, hipoglicemia sintomática com 18 horas de vida. Durante o acompanhamento neurológico identificou-se atraso na aquisição dos marcos de desenvolvimento motor e linguagem. Crises epilépticas generalizadas iniciaram com 12 meses de vida sendo controladas com fenobarbital. EEG era normal. Ressonância magnética revelou agenesia de haste pituitária, hipoplasia de quiasma óptico e heterotopia nodular periventricular. Avaliação oftalmológica demonstrou hipoplasia bilateral de disco óptico. Investigação da função endócrina revelou hipotireoidismo primário e hiperprolactinemia. *Conclusão:* A relevância deste relato reside em seu ineditismo, já que heterotopia periventricular não havia sido descrita em associação com displasia septo-óptica até 2006.

PALAVRAS-CHAVE: síndrome de De Morsier, displasia septo-óptica, heterotopia nodular periventricular, hipotireoidismo primário.

In 1941, Reeves[1] first described a patient with septum pellucidum agenesis and optic nerve abnormalities. De Morsier[2], in 1956, associated optic nerve hypoplasia to septum pellucidum agenesis and coined the term "septo-optic dysplasia" (SOD), later to be recognized as De Morsier syndrome. The following descriptions of patients with optic nerve hypoplasia and septum pellucidum agenesis included endocrinological abnormalities related to malfunctioning of the hypothalamic-pituitary axis, with predominance of growth hormone (GH) deficiency resulting in growth failure[3-5]. Billson and Hopkins[6], in 1972, indicated that the absence of septum pellucidum could represent an inconstant feature. Patel et al.[7] confirmed this finding in 1975, reporting 4 cases of SOD, 2 of which had normal septum pellucidum. In 1990, Brenner et al.[8] reported midline abnormalities of corpus callosum and cerebellum in 2 affected sib-

Unidade de Neurologia Infantil Pequeno Príncipe, Curitiba PR, Brasil (UNIPP): [1]Residente de Neuropediatria; [2]Médico da Unidade de Neurologia Infantil.

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*Dra. Mônica Jaques Spinosa - Rua Johann Sebastian Bach 71 - 80820-140 Curitiba PR - Brasil. E-mail: monicaspinosa@yahoo.com*

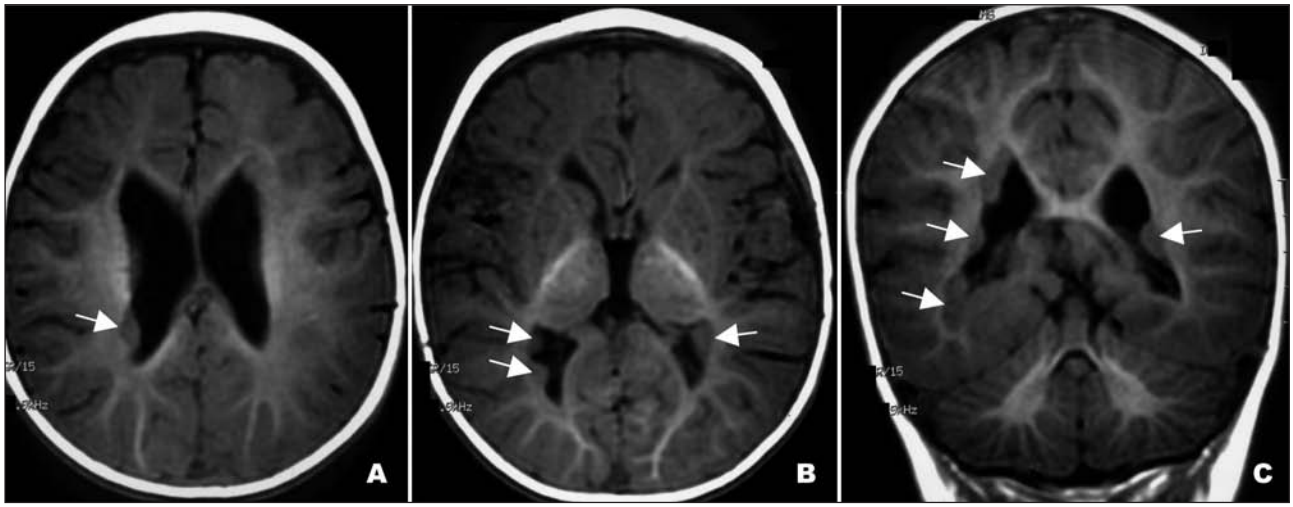


*Fig 1. MRI showing multiple foci of periventricular nodular heterotopia at left frontal and bilateral parieto-occipital regions, on T1-weighted axial (A,B) and coronal (C) cuts.*

lings. Recent studies conclude that SOD has variable phenotypic expression that may include optic nerve hypoplasia, midline central nervous system malformations and pituitary dysfunction.

This case report was approved by the ethics committee of Pequeno Príncipe Hospital and parental written informed consent was obtained for publication.

## CASE

Third child born to nonconsanguineous parents, female, adequate pre-natal medical care, cesarean term delivery due to breech presentation, Apgar score 3 at the first minute and 8 at 5 minutes, birth weight 3150g, symptomatic hypoglycemia at 18 hours. Neurological follow-up identified a delay in acquisition of motor and language developmental milestones. Electroencephalogram (EEG) was normal at 9 months. Magnetic resonance imaging (MRI) at 10 months revealed agenesis of the pituitary stalk and hypoplasia of the optic chiasm suggestive of SOD, normal septum pellucidum, multiple foci of periventricular nodular heterotopia at left frontal and bilateral parieto-occipital regions, focal thickening of the quadrigeminal plaque causing relative stenosis of the distal half of the cerebral aqueduct without any evidence of obstruction of the supratentorial ventricular system (Figs 1 and 2). At 12 months, was admitted at the pediatric neurology unit of Pequeno Príncipe Hospital, Curitiba, Brazil, for epileptic seizures. The patient presented with 7 episodes of epileptic seizures at the same day, described by the mother as a scream followed by hyperextension of all 4 limbs and cervical hyperextension, evolving to a generalized clonic phase. All episodes lasted less than 1 minute and some occurred while the patient was febrile. Epileptic crisis were controlled with phenobarbital 5 mg/kg/day given bid. Clinical and neurological examination identified hypertelorism, midline frontal bulging, neurodevelopment delay with milestones compatible with a 5-month-old child and axial and apendicular hypotonia. EEG was repeated, again yielding normal results. Ophthalmologic evaluation showed bilateral optic disk hypoplasia. Echocardiogram was normal. Endocrine function was assessed by measurement of TSH, T3, T4, GH, FSH, LH, ACTH, prolactin and cortisol levels. Results showed primary hypothyroidism (low T3 and T4 with high TSH levels) and high prolactin levels. Treatment with levothyroxine was instituted. The patient was not tested for HESX1 mutations due to the unavailability of this genetic test.

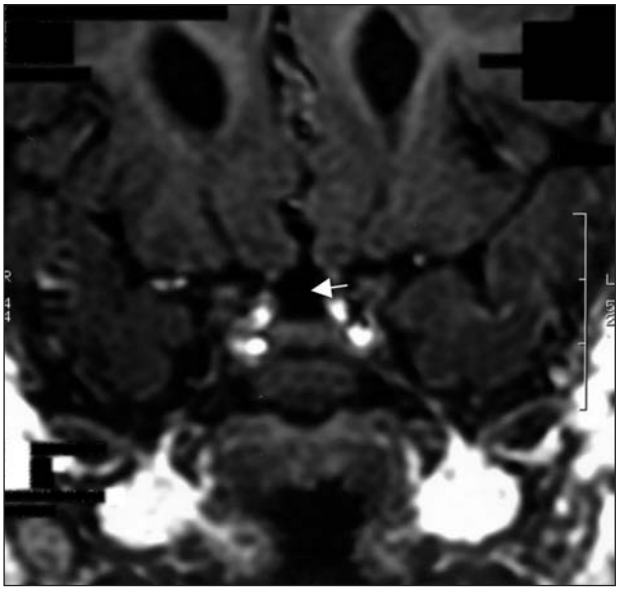

*Fig 2. MRI showing agenesis of the pituitary stalk on T1-weighted coronal cut.*

## DISCUSSION

Concerning phenotypic variability, Thomas et al.[9], in 2001, emphasized that only 30% of the patients

present with the complete triad of optic nerve hypoplasia, midline central nervous system malformations and pituitary dysfunction. Birkebaek et al.[10], reported a series of 55 patients with optic nerve hypoplasia, 49% with agenesis of septum pellucidum and 64% with hypothalamic-pituitary axis neuroradiologic abnormalities on MRI. Forty-nine percent of the patients had endocrine dysfunction, 85% of which also presented with abnormal neuroimage of the hypothalamic-pituitary axis. Agenesis of septum pellucidum was found by Birkebaek et al.[10] to be associated to endocrinopathy, since the frequency of hormonal disturbances was higher in the group with abnormal septum pellucidum (56%) than in patients with no abnormalities in this structure (39%). However, this difference was statistically significant only with respect to ADH deficiency (p=0.04). Our patient had a normal septum pellucidum and displayed no clinical or laboratorial signs of hypothalamic-pituitary axis dysfunction. Hyperprolactinemia was attributed to primary hypothyroidism, a well known association accredited to the stimulatory effect of TRH in the secretion of prolactin. There have been no reports of the association between SOD and primary hypothyroidism and hyperprolactinemia until 2006. The association between SOD and hyperprolactinemia was described by Izenberg et al.[11] in 2 of the 4 patients in their sample. Birkebaek et al.[10] reported that 35% of patients with normal septum pellucidum and abnormal hypothalamic-pituitary axis on neuroimage, such as our patient, showed no endocrine dysfunction of central cause.

The genetic basis for SOD was suggested by Wales et al.[12] in 1996, with the report of two siblings with SOD born of consanguineous parents. In 1998, Dattani et al.[13] performed the genetic study of these patients, along with 18 other cases of sporadic SOD, searching for mutation in the HESX1 gene (*homeobox gene expressed in embryonic stem cells*), locus 3p21.2-p21.1. The choice of this candidate gene was based on the finding that mice with a null Hesx1 gene exhibited malformations of optic nerves and midline structures that were analog to SOD in humans[13]. The siblings were found to be carriers of a homozygous missense mutation in the HESX1 gene. Nine family members, including their parents, were asymptomatic carriers of the mutation in heterozygosis, suggesting an autosomal recessive mode of inheritance. In this study, no mutations were found on patients with sporadic SOD. Mutations in the HESX1 gene were confirmed by other studies. Thomas et al.[9] analyzed a sample of 228 patients with congenital pituitary defects, 105 with SOD. Three different heterozygous missense mutations were identified in 4 patients of 3 different pedigrees. Phenotype varied widely between isolated GH deficiency and SOD. Family members were scanned for HESX1 mutations. In all cases an asymptomatic parent was found to harbor the mutation, along with an asymptomatic sibling of one affected individual. This study showed that even though most sporadic cases cannot be attributed to HESX1 gene mutations, a pattern of heterozygous autosomal dominant inheritance with incomplete penetration exists. This is consistent with a similar finding in mice, where heterozygous Hesx1 mutations were expressed as low penetrance mild phenotype[13]. Tajima et al.[14] described a Japanese patient with sporadic SOD and a heterozygous frameshift mutation of the HESX1 gene. Neither parent harbored the mutation, indicating a *de novo* occurrence. Mutations in the HESX1 gene have been found in 5/93 patients with undescendent or ectopic posterior pituitary by Brickman et al.[15], indicating that this gene is implicated as a genetic basis for a variety of midline central nervous system defects.

The association between SOD and periventricular nodular heterotopia has not been reported in medical literature to this date. However, in 2002, Mitchell et al.[16] described 20 children with ectopic posterior pituitary, four of which had associated periventricular heterotopia. None of them displayed optic nerve or septum pellucidum abnormality. Two patients were screened for HESX1 mutations and in 1 of them a heterozygous mutation was found. In all 4 patients, similarly to our case, periventricular heterotopia was characterized by few subependymal nodules, ranging from 1 to 7. The authors concluded that their finding supports a role for the HESX1 gene in the genesis of both ectopic posterior pituitary and periventricular heterotopia and their place in the wide spectrum of SOD.

Schizencephaly has been reported by some authors in 50% of the patients with SOD[17]. Barkovich et al.[17] neuroradiologically classified SOD in two subtypes, according to the presence of schizencephaly or lack thereof. Sener[18] described a patient with SOD and bilateral rolandic cortical dysplasia, suggesting the term "cortico-septo-optic dysplasia". Miller et al.[19] named the association of SOD and disorders of neuronal organization "SOD-Plus".

SOD appears to be at the high severity end of a spectrum of central nervous system malformations that involve, in various degrees, optic nerves, hypothalamic-pituitary axis and other midline structures

such as the septum pellucidum and the corpus callosum. A genetic basis is clearly implicated in some cases and the fact that the same gene has been shown to de defective in patients with different phenotypes further strengthens the link between these disorders.

In conclusion, the relevance of this case report relies on its uniqueness, since periventricular heterotopia had not been described in association with SOD until 2006. However, periventricular heterotopia has been connected to ectopic posterior pituitary and HESX1 mutation, signaling that this neuronal organization disorder may indeed be part of this spectrum, as other cortical development abnormalities seem to be. A thorough understanding of these complex associations seems to lie in the comprehension of the intricate course of forebrain and cortical development and the role of HESX1 gene in this process.

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