The potential involvement of the pituitary transcription factor HESX1 in the septo-optic-pituitary hypoplasia with normal septum pellucidum but life-threatening neonatal phenotype

Hipoplasia septo-óptica-hipofisária em paciente com septo pelúcido normal porém com risco de morte neonatal e a participação potencial do fator de transcrição hipofisário HESX1

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ABSTRACT

Septo-optic dysplasia (SOD) is a heterogeneous developmental syndrome involving brain midline anomalies associated with pituitary-hypothalamic, ophthalmological and neurodevelopmental dysfunctions. The phenotype is highly variable making the disease classification difficult. We report a case of severe neonatal hypopituitarism leading to the discovery of cerebral malformations and optic nerve hypoplasia characterizing the SOD-like syndrome. Besides the mild MRI features with normal septum pellucidum, this patient exhibited a life-threatening endocrine phenotype. Rare mutations have been described in the HESX1 gene, which encodes a homeobox transcription factor, associated with various pituitary hormone deficiencies combined with SOD. We isolated the DNA coding region from this candidate gene for sequence analysis. In this 7-year follow-up case report and preliminary genetic screening we discuss diagnostic investigation after management of first clinical presentation, highlighting the neuroimaging on this syndrome.

Keywords: septo-optic dysplasia, septum pellucidum, hypopituitarism, HESX1

RESUMO

A displasia septo-óptica (DSO) é uma síndrome do desenvolvimento considerada heterogênea, pois envolve anomalias da linha média do cérebro associadas a disfunções oftalmológicas, neurológicas e do eixo hipotálamo-hipófise. O fenótipo é altamente variável dificultando a classificação da doença. Relatamos um caso de hipopituitarismo neonatal grave que levou à descoberta de malformações cerebrais e hipoplasia do nervo óptico, sendo caracterizada assim a síndrome DSO-like. Mesmo em presença de um septo pelúcido normal e com poucas alterações na ressonância magnética, este paciente apresentou um fenótipo endócrino de alto risco de morte no período neonatal. Mutações genéticas têm sido raramente descritas no HESX1 e estão associadas a várias deficiências hormonais hipofisárias combinadas com a DSO. O gene HESX1 codifica um fator de transcrição pertencente à classe de genes chamados homeobox. A partir deste gene candidato, foi isolada a região codificadora no DNA para análise por sequenciamento. Este relato de caso com seguimento clínico de 7 anos e estudo genético preliminar apresenta uma discussão da investigação diagnóstica a partir do quadro inicial, destacando as alterações de neuroimagem encontradas nesta síndrome.

Palavras Chave: displasia septo-óptica, septo pelúcido, hipopituitarismo, HESX1

INTRODUCTION

The septo-optic dysplasia (SOD) was first described by de Morsier in 1954 in patients with absent septum pellucidum (SP) and optic nerve hypoplasia1, and 15 years latter it was described in association with hypopituitarism2. The absence of SP is not mandatory for the diagnosis of SOD and only one third of the patients present the complete triad3. The diagnosis
is done when found two of the following characteristics: 1) midline neuroradiologic alterations, 2) uni or bilateral hypoplasia of the optic nerve, 3) hypopituitarism. Absence of SP and hypoplasia or agenesis of the corpus callosum are included among the possible midline neuroradiologic findings.

The incidence of the SOD is 1/10,000 live births and the prevalence is the same in males and females. The condition is usually idiopathic but some familial cases have been described. Recent studies have shown association of isolated optic nerve hypoplasia or SOD and young maternal age while gene mutations are rare. The HESX1 gene, also known as Rpx (Rathke’s pouch homeobox gene) is expressed in the early forebrain primordium and Rathke’s pouch. The initial pituitary development is controlled by the HESX1 transcripts which are detected between the 6.5th and 15.5th embryonic day. The failure of the primary cells to differentiate or proliferate during the pituitary embryogenesis results in congenital alterations, evidenced by hormone deficiencies and/or anatomical changes in the spectrum of the SOD syndrome. HESX1-deficient mouse embryos present a reduction in the prosencephalic tissue, anophthalmia or microphthalmia, abnormalities of the corpus callosum and SP, and small anterior pituitary disconnected to the posterior lobe. The midline brain defects in the mutant mice shows a phenotypic resemblance with the SOD in humans. Another types of HESX1-mutant mice have shown that the expression domain of human HESX1 is comparable to that in the mouse and includes the ventral forebrain and Rathke’s pouch. Until now, the genetic screening of more than 800 patients with SOD and pituitary hormone deficiency have found genetic mutations in less than 1% of the subjects, confirming the rarity of mutations of the HESX1.

**Case Report**

A breastfed 29 days-old boy was admitted to the pediatric emergency with severe dehydration, generalized tonic-clonic seizures and capillary glycemia 16 mg/dl, within 20 days of discharge from the maternity hospital. At birth, he had jaundice, hypoglycemia and absent visual fixation. The main emergency treatment was continuous intravenous glucose infusion which was maintained for several days. Ophthalmological assessment revealed vertical and horizontal nystagmus and bilateral optic disc hypoplasia, but neither midline facial defects nor remarkable findings were detected on neurological examination. In addition, the patient presented microenesis and bilateral micro-orchidism. The biochemical findings suggested conjugated hyperbilirubinemia (total bilirubin 4.6 mg/dl; direct bilirubin 2 mg/dl) and combined thyrotroph, corticotroph, somatotroph and gonadotroph deficits (freeT4 0.51 ng/dl; cortisol 0.3 μg/dl assessed during hypoglycemia; IGF-1 26.4ng/mL; GH 3.67 ng/mL; LH, FSH and testosterone below detection limits). The patient had no symptoms of diabetes insipidus. Hypoglycemia resolved after introduction of glucocorticoid replacement (prednisolone 5mg/m2/day) and levo-thyroxine was then associated to the hormone replacement therapy. Brain magnetic resonance imaging (MRI) performed at 2 months of age revealed pituitary hypoplasia. Since the posterior pituitary function remained preserved, the first clinical diagnosis was congenital anterior panhypopituitarism with bilateral amaurosis.

After the neonatal period, recombinant human GH replacement therapy was initiated when his growth rate fell to 1 cm/year (at 1.5 year-old), resulting with adequate growth response for the next years. New head imaging study defined better some features (Figure 1): the pituitary stalk absence and rudimentary optic chiasm supported the diagnosis of bilateral optic nerve hypoplasia (ONH). Images did not show significant malformations as cortical dysplasia/schizencephaly or absence of SP. Severe pituitary anomaly was confirmed by the observation of stalk agenesis, anterior pituitary hypoplasia and ectopic posterior pituitary (Figure 1 A,B).

During the follow-up, the neurocognitive development remained normal and no motor deficits or new episodes of seizure attacks were observed. He developed all neuro-psychomotor skills as expected for congenitally blind children receiving adapted health care, rehabilitation and education. Levo-thyroxine, glucocorticoid, growth hormone and testosterone replacements have been monitored and adjusted when appropriated.

According to the algorithm of combined pituitary hormone deficiency (CPHD) genetic screening using a phenotype-based strategy, we chose the main candidate gene for this case study. Peripheral blood was collected for DNA analysis of the HESX1 gene in a first attempt to identify the genetic defect causing CPHD associated with neuro-ophtalmological
abnormalities in the present case. The polymerase chain reaction (PCR) using intron-flanking primers, followed by direct sequencing of amplified genomic DNA, allowed us to isolate the coding sequence fragments of the HESX1 gene. Variants were found in the exons 1 and 3 after analysis of aligned DNA sequence chromatograms for the NCBI database reference sequence (NM_003865.2). These variants in the HESX1 coding sequence do not match any of the previously described mutations and therefore require additional molecular study. The family history was negative for endocrine disorders, dysmorphic features or metabolic conditions. There was no consanguinity between the parents.

**Figure 1**: Neuroimaging at 2-year old age. A, Sagittal 3D Fiesta weighted MRI demonstrating optic chiasm (OC) atrophy and anterior pituitary (AP) hypoplasia, in addition to the following normal structures: corpus callosum (CC) and septum pellucidum. (SP). B, Sagittal T1 weighted MRI revealing anterior pituitary hypoplasia (AP) and ectopic posterior pituitary (PP). C, Coronal T2 weighted MRI showing the septum pellucidum. D, Axial T1 weighted MRI showing bilateral optic nerves (ON) atrophy.

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**DISCUSSION**

Pituitary aplasia or hypoplasia causing hypopituitarism can be presented as a syndrome with midline forebrain defects such as in the septo-optic dysplasia. Association with neuro-ophthalmological midline defects characterizes a syndrome with a broad variety of phenotypes. In the present case, early clinical signs of hypopituitarism on neonatal period constituted a life-threatening condition and preceded the suspicion of SOD neuro-ophthalmological symptoms. The diagnosis of congenital hypopituitarism is often not straightforward; in the presented case, prolonged neonatal jaundice, hypoglycemia and the presence of micropenis suggests congenital hypopituitarism.

The large spectrum of malformations in the SOD also includes corpus callosum hypoplasia or absence and occasionally other cerebral abnormalities such as schizencephaly or cortical dysplasia. However, some patients have no cerebral midline malformations and do not qualify for the diagnosis by definition. Such heterogeneous features have resulted in some disagreement as to how SOD is defined and categorized. The following classification is based on distinct anatomic subsets.

<table>
<thead>
<tr>
<th>SOD Type</th>
<th>Description</th>
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<tr>
<td>SOD type I</td>
<td>Presence of schizencephaly</td>
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<tr>
<td>SOD type III</td>
<td>Complete absence of SP but no schizencephaly</td>
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<tr>
<td>SOD type III</td>
<td>Corpus callosum absence</td>
</tr>
<tr>
<td>SOD-Plus</td>
<td>Malformations of cortical development other than schizencephaly</td>
</tr>
<tr>
<td>SOD-like</td>
<td>A mild phenotype with ONH and pituitary anomaly but normal SP</td>
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According to this classification, the clinical picture of our patient suggests a SOD-like phenotype. Interestingly, the age of diagnosis in SOD-like patients was higher (median age 5.19 years, 12 patients) in the few cases of SOD-like that have been reported.

The work-up in patients with SOD can be complex depending on the phenotype. The appropriate clinical management requires a multidisciplinary team for the neuropsychiatric, endocrine, ophthalmological, neuroradiological and genetic questions. While the etiology of SOD remains unclear, some cases can be caused by specific genetic abnormalities because...
HESX1 gene mutations have been well characterized in association with this syndrome. Moreover, many data suggest an important role for HESX1 in forebrain, midline and pituitary development in mouse and human. Genetic variants found in this work need to be confirmed in the affected patient and family members. Then, the true contribution of HESX1 defects to the etiology of the presented SOD-like syndrome could be established by in-depth genetic analysis.

In conclusion, we presented a child with SOD-like syndrome having congenital anterior pituitary deficiency and ONH. Aspects on neuroimaging (mild MRI features with normal septum pellucidum) and normal neurocognitive development does not predict the pituitary function. The presentation of this case report emphasizes the early diagnosis of congenital hypopituitarism, which is crucial as patients undergo severe acute hypoglycemia and chronic adrenal, growth, gonad and thyroid insufficiencies that may lead to devastating consequences for neurological development and even survival. In addition, molecular analysis might contribute to expand our understanding of the clinical heterogeneity and inheritance patterns of hypopituitarism and central nervous system malformations.

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