De Morsier Syndrome: two case reports at the city of Petropolis

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Abstract

Introduction: De Morsier syndrome (septo-optic dysplasia) is a rare central nervous system malformation characterized by two out of three findings: agenesis of the septum pellucidum and/or corpus callosum, optic nerve hypoplasia and pituitary hormone abnormalities. It is often a diagnostic challenge to the pediatrician and, due mostly to the complication of hypopituitarism and the possibly associated malformations, entails great morbidity to the affected patients. Objective: We report two cases at the city of Petropolis/RJ, diagnosed at different ages, and present the possible evolutions for the syndrome. Case descriptions: Case 1: Newborn by domiciliary delivery brought to the hospital after birth, presented hypoactivity and hypotonia with 54 hours of life. A transfontanelle ultrasound was requested, which showed corpus callosum agenesis; and the fundscopy showed bilateral optic nerve hypoplasia, which provided the diagnosis for septo-optic dysplasia. Case 2: 8-year-old grandschooler, presented to the pediatrics ambulatory with blindness and low stature. Because of an inappropriate bone age, he was sent to the pediatric endocrinology ambulatory care, where he was, after hormonal exams and magnetic resonance, diagnosed with De Morsier syndrome. Discussion: Septo-optic dysplasia can present at birth with other abnormalities or much later on, when growth failure occurs in a child with visual abnormalities. We brought in the case of an 8-year-old, diagnosed because of endocrine and visual abnormalities besides low stature, with an atypical evolution of the syndrome; and one of a 2-day-old child, whose diagnosis was possible because of clinical examination, unlike most cases described in the literature.

Keywords: Septo-Optic Dysplasia, Agenesis of Corpus Callosum, Hypopituitarism.

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INTRODUCTION

De Morsier’s syndrome (or septo-optic dysplasia) is a rare disease, with an estimated incidence of 1 in 10,000 live births, characterized by midline defects (corpus callosum and/or pellucid septum), optic nerve hypoplasia and pituitary hormonal abnormalities\(^1\)\(^,\)\(^3\).

The syndrome diagnosis requires at least two of the three characteristics, and ophthalmic examination, cranial MRI and pituitary hormone assessment can confirm it\(^1\)\(^,\)\(^3\).

Some 62% of the patients have hypopituitarism that, when treated early, can significantly improve the prognosis associated with the disease\(^6\).

The occurrence of a wide variety of developmental disorders (corpus callosum dysgenesis, schizencephaly, microphthalmia, anophthalmia, strabismus, optic tract hypoplasia, early or late puberty, micropenis, autism, cardiac and skeletal malformations) has been recognized as part of the spectrum of malformations in this syndrome\(^1\)\(^,\)\(^3\), and it makes its early diagnosis even more important, seeking to reduce the morbidity associated with the disease.

We report two cases of septo-optic dysplasia, the first diagnosed in the neonatal period due to an unspecified clinical manifestation; and the second at school age, already with blindness and developmental delay, highlighting the peculiarities associated with the syndrome and the importance of its early recognition and treatment - when possible.

CASE REPORT

Case 1:

Female patient, born at term at home birth without medical care, brought to the Alcides Carneiro Teaching Hospital (HEAC) after birth. Mother with low titer reagent anti-HCV during prenatal care, and morphological ultrasound indicating hydrocephalus without further follow-up examination. At physical examination, with 54h of life, she presented with hypoactivity and hypotonia, especially in the extensor group of the cervical muscles. Transfontanellar ultrasonography showed agenesis of the corpus callosum and colpocephaly, later confirmed by magnetic resonance imaging of the skull.

A red reflex test proved to be inconclusive, and an ophthalmologic evaluation was performed on the fifth day of life. Fundoscopy showed bilateral optic nerve hypoplasia, suggesting the hypothesis of De Morsier syndrome.

Hormonal dosages did not show any findings indicative of hypopituitarism (Table 1). The child was referred for follow-up at the Pediatric Genetics, Ophthalmology and Endocrinology outpatient clinics.

Case 2:

Male patient, 8 years old, in first consultation at the Pediatric Outpatient Clinic of the Petrópolis School of Medicine (FMP), complaining of bilateral blindness and short stature. Mother with a history of untreated toxoplasmosis during pregnancy. Upon examination, the child saw only shadows. A wrist radiograph showed a bone age of 4 years, and the child was referred to the FMP Pediatric Ophthalmology and Endocrinology outpatient clinics.

In the first consultation at the Endocrinology outpatient clinic, hormonal dosages showed a decrease in TSH and free T4, without changes in the other exams (Table 1). The child was then started on levothyroxine.

At the next appointment, a computed tomography scan of the skull and sella turcica showed no changes.

The child was then referred to the Genetic Clinic of the Fernandes Figueira Institute (IFF), where a magnetic resonance imaging of the skull indicated a partially empty saddle, reduced volume of the hypothalamic-chiasmatic region, bilateral thinning of the optic nerves, and agenesis of the pellucid septum. In addition to hormonal changes, the hypothesis of septo-optic dysplasia was suggested.

The child returned to the Pediatric Endocrinology outpatient clinic, where she maintained follow-up. At age 13, she had increased prolactin and decreased IGF-1, GH, FSH and LH, unchanged in previous examinations. In the same year, she was started on GH, which was suspended after three months at the request of the family, due to complaints of dyspnea.

At the age of 20, she started follow-up at the Endocrinology outpatient clinic. He was referred to the gynecomastia preoperatively and is under investigation for obstructive sleep

Table 1. Hormonal dosages in cases 1 and 2.

| Substance dosed | Case 1     | Case 2     |
|-----------------|------------|------------|
| ACTH            | High       | Normal     |
| Cortisol        | Normal     | Normal     |
| GH              | Normal     | Low        |
| IGF-1           | Normal     | Very low   |
| TSH             | Normal     | Low        |
| Free T4         | Normal     | Low        |
| Prolactin       | Not measured | Very high |
| FSH             | Normal     | Low        |
| LH              | Normal     | Low        |
| Glycemia        | Normal     | Normal     |
apnea syndrome (OSAS). Currently with a height of 1.51m and weight of 48.8 kg.

**DISCUSSION**

Optic nerve hypoplasia is one of the leading causes of childhood blindness and visual impairment in the United States. It is a congenital disease, histologically characterized by a subnormal number of axons in the optic tract, resulting in small and pale optic discs. When it occurs in association with endocrine and central nervous system abnormalities, it is considered part of a spectrum of diseases known as septo-optic dysplasia.

There is a diagnosis of septal-optic dysplasia when two or more of the classic triad findings are present. The three components of the triad appear together in only 30% of patients with the syndrome. Some 62% of patients have hypopituitarism and 60% have an absent pellucid septum. The most frequent neurological associations are seizures, developmental delay and cerebral palsy.

Familial cases of the disease are rare (less than 1%), suggesting that the precise etiology is probably multifactorial. There are several risk factors, such as primiparity, malnutrition, prematurity, viral infections (i.e. cytomegalovirus) and use of prescribed drugs (i.e. antiepileptic drugs) or illicit drugs (the latter with little backing from the medical literature). There can also be vascular alteration in the carriers of the disease. All brain structures involved in the syndrome are developing at different embryological stages, have different origins and are vulnerable to vascular events, which could suggest a sequence of vascular interruption, possibly involving the anterior cerebral artery. Thus, it is worth paying attention to vascular abnormalities, given its possible association with the anomalous development of midline brain structures.

Regarding the ophthalmological alteration, there may be a failure to differentiate retinal ganglion cells. There may also proliferative retinopathy, which should be thoroughly evaluated and promptly treated, in order not to further loose visual acuity.

The most common hormone deficiency appears to be growth hormone (GH). However, central hypothyroidism is the earliest diagnosed deficiency. Hormonal deficiencies may develop over time, which leads to the need for lifelong follow-up.

Our first patient, a few days old, presented two of the three findings upon diagnosis; our second patient, eight years old, had the three components of the triad, and hormonal deficiencies developed over the twelve years of follow-up. As reported in the literature, hypothyroidism was the first hormone deficiency diagnosed, followed by GH deficiency. However, the child also presented hyperprolactinemia, an association credited with the stimulatory effect of HRT on prolactin secretion, but very rarely described in association with septo-optic dysplasia.

Clinically, manifestations may range from absent to severe, including hypoglycemia, jaundice, microenesis with or without cryptorchidism, nystagmus, hypotonia, spasticity, and varied midline abnormalities. In older children, short stature is a significant finding that should always be valued.

Our first case presents a particularity in relation to the other cases in the literature: early diagnosis (within a few days of life), suspected only due to hypotonia upon physical examination, finding whose range of possible differential diagnoses varies widely, encompassing not only central causes (cerebral dysgenesis, spinal cord injury, hypoxic-ischemic encephalopathy) and various myopathies, as well as acute systemic diseases (e.g. sepsis, congestive heart failure and inborn errors of metabolism). Additional data on physical examination may suggest either cause, but often the diagnosis is still challenging for pediatricians.

In addition to clinical findings and fundus evaluation, the use of cranial magnetic resonance imaging, the most accurate examination for assessing brain malformations that characterize the syndrome, is essential, and other possible associated midline malformations are excluded. The karyotype should be assessed in patients with additional brain deformities or extraneural structures. In this situation, an abnormal karyotype is an additional factor of worse prognosis in terms of development.

The earlier the diagnosis of the syndrome and the treatment of hormonal deficiencies, the better the prognosis in most cases, as untreated hormonal abnormalities bring an additional burden on neurological development in a child already impaired by visual impairment. In addition, there are risks of hypoglycemia, adrenal crisis and, consequently, death, which makes it frequent follow up an imperative, not only with an ophthalmologist, geneticist and neurologist, but also - and especially - a pediatric endocrinologist.

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