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Septo-Optic Dysplasia in an Infant with Early-Onset Obesity, Polydactyly, and Central Endocrine Deficiencies: A Case Report

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Abstract: ***Septo-optic dysplasia (SOD), also known as Morsier syndrome, is a rare congenital disorder involving optic nerve hypoplasia, midline brain anomalies, and pituitary hormone deficiencies. This report describes a 17-month-old male presenting with early-onset obesity, developmental delays, dysmorphic features, and polydactyly. Endocrine evaluations confirmed central diabetes insipidus and central hypothyroidism, while neuroimaging revealed classic SOD features. Despite normal genetic findings, clinical and imaging evidence supported the diagnosis. This case highlights the need for early identification and coordinated care to enhance outcomes and prevent long-term complications associated with SOD.***

Keywords: Septo-optic dysplasia, hypothyroidism, polydactyly, central diabetes insipidus, pediatric obesity

1. Introduction

Morsier syndrome or septo-optic dysplasia is a rare congenital disorder characterized by a classic triad of clinical manifestations: optic nerve hypoplasia, absence of the septum pellucidum and hypothalamic-pituitary dysfunction (1). Epidemiologically, this condition is equally distributed to both sexes, with an incidence of 1 in 10,000 live births (2). In Colombia, there are no specific epidemiological data that show the incidence of this disease except for individual cases published in the literature (3–5).

There is no single direct cause associated with the onset of SOD. Among affected infants, there is a high incidence of adolescent pregnancy, drug addiction and gestational diabetes (6). Young maternal age is one of the most recognized factors. It may be linked to elevated levels of estrogen and other endocrine disruptors, which can have a variety of effects (7). In addition, some medications with a vascular effect (valproic acid, phencyclidine, phenylpropanolamine, and cocaine) are associated with the development of SOD (8).

It is known that only 1% of all cases have documented point pathogenic mutations, where most are de novo. Initially, researchers described mutations of the HESX1 and SOX2 genes, followed by those of SOX3. Associations with other genes are increasingly being described: OTX2, PROKR2, FGF1, and FGF8 (9); these genes are essential for the formation of structures such as the optic nerves, pituitary gland, and forebrain during embryonic development.

Therefore, it is thought that the development of SOD is influenced by genetic factors and by the environment during pregnancy, which can interrupt or alter the proper development of the central nervous system in this condition. There are different hypotheses about the etiology of SOD, since it is striking that the different structures involved (already mentioned) have a different embryological origin. The vascular hypothesis, proposed since 1995 by Lubinsky (10), establishes a correlation with vascular disruption that affects the proximal trunk of the anterior cerebral artery as a possible cause of this condition.

Clinically, the presentation varies depending on the extent of anatomical involvement. Only 30% to 47% of individuals exhibit the typical trio (optic nerve head abnormalities, midline anomalies, and pituitary hormonal dysfunction), complicating the diagnostic process. The involvement of the pituitary gland may vary from a singular deficiency to a combined pituitary hormone defect (HPPC), with growth hormone (GH) being the most affected in 64%-70% of instances, followed by hypothyroidism (34-43%), adrenal insufficiency (17-27%), and diabetes insipidus (4-5%) (11). Obesity may manifest clinically in up to 31%, as indicated by the reviewed literature (12). Hypothalamic obesity is traditionally characterized as a syndrome involving persistent weight gain following any damage to the hypothalamus (13).

SOD presents neurologically in multiple forms. The Medical literature indicates that these children may exhibit intellectual disability, with a prevalence of up to 52%. Furthermore, a substantial percentage displays indications of autism spectrum disorder (ASD) in 35% (14). Other associated neurological disorders include epilepsy, a prevalent comorbidity in these patients (15). Malformations in the cerebral cortex, such as schizocephaly, polymicrogyria, and grey matter heterotopias, have been recorded, potentially clarifying the reported neurological abnormalities (16). A recent systematic analysis indicated that 35% of children with SOD display behaviours akin to autism spectrum disorders (ASD) (17). The MRI reveals the following main imaging findings: optic nerve hypoplasia (ONH) in 93.8% of patients, optic chiasm hypoplasia in 65.6%, lack of septum pellucidum in 40.6%, and neuronal migration problems in 20.6% of cases (18).

We now present a case characterized by notable weight gain and dysmorphic features, which led to an in-depth

investigation, culminating in a definitive diagnosis and subsequent initiation of hormone replacement therapy.

The purpose of this case study is to present a rare pediatric presentation of SOD, emphasize early diagnostic indicators, and discuss the role of multidisciplinary management.

2. Case Report

This is a 17-month-old male toddler who was born during the second pregnancy of a 36-year-old woman. During the pregnancy, the mother was under perinatologist supervision because of a pregnancy classified as high risk due to gestational diabetes diagnosed at 11 weeks (treated with metformin) and the threat of preterm labor until 25 weeks. There was no history of infections during pregnancy, and prenatal ultrasounds showed no anatomical malformations. He was born by caesarean at 38 weeks; his Apgar score was 9/9. Anthropometric measurements were as follows: Weight: 3491 g; Length: 51 cm.

The mother has an obstetric history of a first pregnancy that ended in an extreme preterm delivery at 24 weeks. The newborn died 4 days later from respiratory distress syndrome. The parents report no consanguinity. The patient is referred by the paediatrician for obesity. The mother points out that from the age of two months, she noticed a marked weight gain, despite receiving adequate nutrition: exclusive breastfeeding until 5 months, followed by complementary feeding initiated according to the paediatrician's recommendations. Figure 1 details the evolution of their anthropometric measurements, including weight and height.

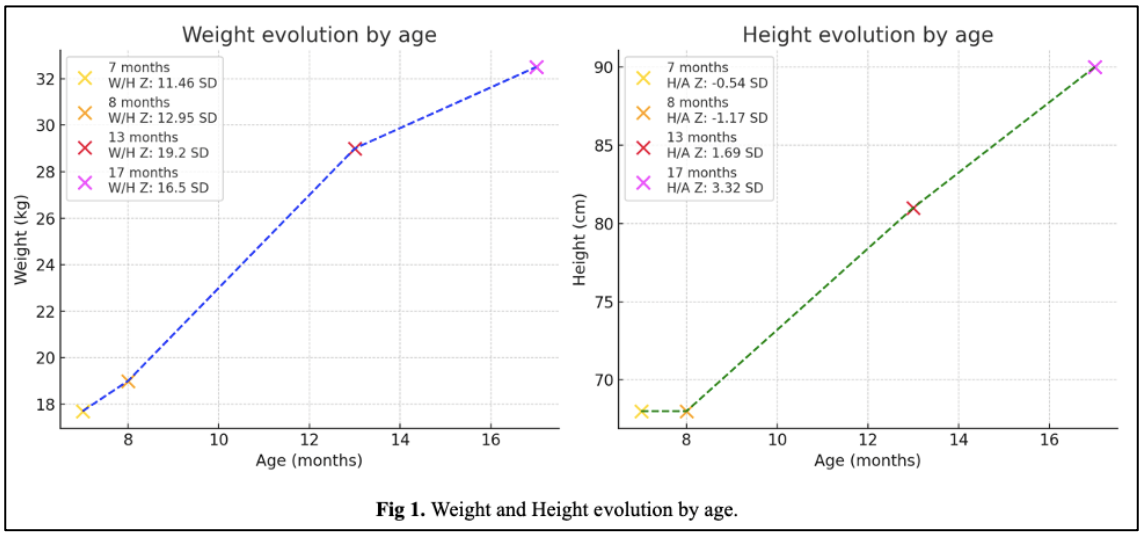

Fig 1. Weight and Height evolution by age.

As can be seen, the patient has presented a disproportionate weight gain for age and height, as well as tall height for age according to the WHO growth curves.

Physical examination revealed an epicanthal fold, left endotropia, wide nasal bridge, rounded facies, short neck, and micrognathia. The abdomen is globose due to abundant adipose tissue, and umbilical hernia is evident. In the genitals, he has a micropenis (1.5 cm at 13 months), partially hidden by fat, with testicles descending in a scrotal pouch. At the axial and extremity level, thick and marked skin folds are seen on all four limbs. In the right hand, polydactyly is identified, with a supernumerary finger adjacent to the thumb (Fig 2).

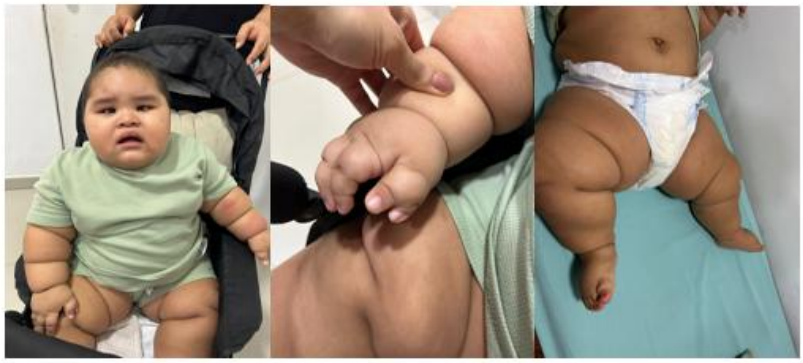

Fig 2. 17 month-old male with morbid obesity and dysmorphic features

The neurological examination revealed a notable delay in neurodevelopment, characterised by the late attainment of milestones: cephalic support around 4 months, sitting and rolling around 7 months, and he has not yet achieved standing at his current age.

At the 8-month check-up, the patient had central diabetes insipidus, shown by a urine osmolarity of 35.2 mOsm/L and a blood osmolarity of 283.5 mOsm/L. Treatment with desmopressin started, which helped to normalize the urine output and urine osmolarity. Treatment with desmopressin was initiated, achieving normalization of the diuretic rhythm and urinary osmolarity.

Initially, thyroid function was within normal ranges (TSH: 5.73 uU/mL; Free T4: 0.92 ng/mL). However, in subsequent controls, a significant increase in TSH (13.35 uU/mL) was observed with free T4 within normal limits (1.13 ng/mL) and negative antithyroid antibodies (antithyroglobulin and antiperoxidase). It was concluded that it was central hypothyroidism, so treatment with levothyroxine was initiated. The most recent assessment indicates no additional hormonal shortages, with ACTH at 44.21 pg/mL, prolactin at 10.28 ng/mL, morning cortisol at 6.24 µg/dL, and growth hormone at 1.2 ng/mL, all within normal ranges.

Magnetic resonance imaging (MRI) of the brain was performed, which confirmed the presence of findings of centro-optic dysplasia (see fig. 3).

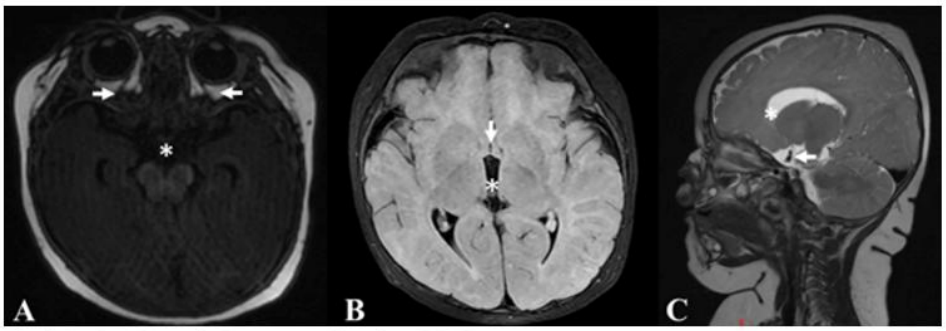

Fig 3. Brain Magnetic Resonance Imaging (MRI):
Image A: Axial T1 scan showing bilateral optic nerve atrophy (↑) and optic chiasm hypoplasia (*).
Image B: Axial FLAIR scan showing absence of the septum pellucidum (↑) and mild ventriculomegaly of the lateral ventricles.
Image C: Sagittal T2 scan showing hypoplasia of the corpus callosum, absence of the septum pellucidum (*). Hypoplasia of the optic chiasm, and absence of the neurohypophysis (↑).

We completed genetic analyses that revealed a standard 46, XY karyotype and a full exome devoid of any harmful mutations. Given the identified hormone shortages, clinical phenotype, and brain MRI findings, the patient is deemed to fulfil the diagnostic criteria for septo-optic dysplasia as the aetiology of his disease.

3. Discussion

The case illustrates the phenotypic variability associated with septooptic dysplasia and highlights the diagnostic challenges posed by a syndrome characterized by low prevalence and significant clinical heterogeneity. The patient presented with early morbid obesity, observed in 30% of cases, and notable dysmorphic features from the initial months of life. This prompted a multidisciplinary approach crucial for establishing a definitive diagnosis.

The association of structural abnormalities in neuroimaging, combined hormonal deficiencies, and ophthalmological manifestations shows a pattern compatible with the most complete forms of the SOD spectrum, which define it (with only 30% of patients presenting the classic triad), even though there is no family history or known genetic mutations, which are only observed in 1% of all cases. Therefore, it is important to point out that the classic triad does not always present simultaneously or is evident at birth, which forces clinical suspicion to be placed on the diagnostic radar and to maintain a rigorous longitudinal follow-up since endocrinological anomalies can appear over time.

The imaging results indicate that there is damage to the optic nerve, changes in the neurohypophysis, and abnormal tissue growth near the brain's lining (like what our patient has, which could be considered SOD plus). This finding highlights the importance of brain MRI as a diagnostic tool. The correlation between these findings and the observed phenotype is not always direct, since there are many controversies when interpreting these findings, a fact that reinforces the need to consider SOD as a spectrum entity rather than as a closed syndrome.

The association of the case with obesity, traits compatible with neurodevelopmental disorders, sleep disturbances, the appearance of diabetes insipidus and hypothyroidism of central origin, configure a clinical picture of broad pituitary involvement that, in some cases, can range from single hormonal deficiency (GH the most prevalent) to CPHD. In addition, it should be mentioned that hypothalamic obesity is characterized by intractable weight gain in the presence of congenital hypothalamic dysfunction, as is the case with this patient. The latter, often underestimated as a cardinal sign at an early age, can become an early clinical marker when it manifests itself disproportionately, as in the present case.

Regarding the factors that can increase the risk, although the exome study did not find specific genetic changes, these elements support the idea that the cause of the disease is multiple. This means that it combines problems of vascularization in early stages with a genetic vulnerability. Therefore, it is important to highlight the adverse prenatal context of our patient, such as gestational diabetes.

The follow-up of this patient highlights the need to maintain close surveillance on the appearance of new hormonal deficiencies throughout the development of this type of patient, as well as neurodevelopmental disorders. This suggests that SOD should be followed as a dynamic condition, requiring medical interventions adjusted to individual evolution.

This case contributes to the limited literature on SOD and underscores the diagnostic value of early phenotypic signs like polydactyly and obesity.

4. Conclusion

Septo-optic dysplasia presents as a complex and evolving clinical entity that requires early recognition and consistent follow-up. This case underlines the importance of considering atypical features like obesity and dysmorphic traits in early diagnosis. A collaborative, patient-centered approach can significantly enhance life quality and prognosis for children diagnosed with this syndrome.

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