Short communication

Congenital mydriasis as an initial sign of septo-optic dysplasia

M.C. Carrascosa-Romero a,*, R. Ruiz-Cano b, F. Martínez-López c, B. Alfaro-Ponce d, A. Pérez-Pardo e

a Sección de Neuropediatría, Complejo Hospitalario Universitario de Albacete, Albacete, Spain
b Sección de Endocrinología Pediátrica, Complejo Hospitalario Universitario de Albacete, Albacete, Spain
c Servicio de Oftalmología, Complejo Hospitalario Universitario de Albacete, Albacete, Spain
d Sección de Neonatología, Complejo Hospitalario Universitario de Albacete, Albacete, Spain
e Servicio de Pediatría, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

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A B S T R A C T

Septo-optic dysplasia (SOD) [MIM182230] consisting of a heterogeneous and uncommon condition characterized by the classic triad: optic nerve hypoplasia, abnormalities of pituitary hormone, and defects of the brain midline (including agenesis of the septum pellucidum and/or the corpus callosum; it has also been described associated cortical malformations, it was referred to as SOD plus syndrome).

We report the first known case in which the initial diagnostic sign of SOD was a bilateral mydriasis as a manifestation of hypoplasia of both optic nerves, pituitary hypoplasia and cerebral dysgenesis with neuronal migration disorder. We discuss the differential diagnosis of congenital mydriasis.

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Midriasis congénita como signo inicial de displasia septo-optica

R E S U M E N

La displasia septo-optica (DSO) [MIM182230] es una entidad heterogénea poco frecuente, caracterizada por la tríada clásica: hipoplasia del nervio óptico, anomalías de las hormonas hipofisarias y defectos de la línea media cerebral (incluyendo agenesia del septum pellucidum y/o del cuerpo calloso; también se han descrito malformaciones corticales asociadas, citado como síndrome DSO plus).

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* Corresponding author.
E-mail address: mccarrascosa@sescam.jccm.es (M.C. Carrascosa-Romero).

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Síndrome Congenital Clinico

Introduction

Antecedents

Congenital mydriasis is exceptional in the newborn, with under 30 cases reported in the literature, generally unilateral and related to the Horner syndrome and bilateral to a lesser extent. Referred causes in comprehensive differential diagnostic for congenital mydriasis include hereditary congenital mydriasis, total or partial aniridia, circum pupilar aplasia, Adie tonic pupil, III cranial pair congenital bilateral palsy, Parinaud syndrome, Gillespie syndrome and others secondary to trauma, infection (rubella, syphilis) or topical medication. All cases emphasize the importance of performing a full ophthalmological examination to discard optic nerve hypoplasia and other ocular anomalies in the newborn (NB) and lactating infant. As an objective the authors recommend including in the study brain magnetic resonance (BMR) displaying the optic nerves. In the patient of this case, BMR was diagnostic for septo-optical dysplasia (SOD) an infrequent and heterogeneous entity characterized by the association of midline defects such as the absence of septum pellucidum, optic nerve hypoplasia and in some cases hypophysis insufficiency and liver fibrosis. The expressions of this syndrome are highly variable including, at the ophthalmological level, nystagmus, strabismus, visual acuity deficits and less frequently pupil alterations.

Clinic case


Physical examination

NB weight 3.280 g. Normal cranium with permeable sutures, normal phenotype without dysmorphic traits. Normal skin, normal cardiopulmonary auscultation. Soft abdomen without megalia. Locomotor normal. Genitourinary normal. Neurological: strength, tone for general movements and normal primary responses, cranial pairs normal, no signs of pyramidal or extra pyramid involvement or ataxia. The ophthalmological examination revealed bilateral mydriasis with slow pupil response to lights and sensitive to the administration of 0.125% pilocarpine, associating erratic ocular movements without nystagmus and without gaze fixation and blue sclerotis.

Supplementary tests


BMR: corpus callosum present, absence of septum pellucidum with ventriculomegalias (Fig. 1). Hypophysis gland hypoplasia (Fig. 2). Hypoplasia of chiasma and optic nerves. Diminished left brain hemisphere with localized increased of the extra-axial space at the level of the Sylvian fissure with cortical thickened areas with heterotopia toward the left frontal horn, without observing schizencephaly images (Fig. 3). Genetic studies: no mutation found in gene HESX1.

Evolution

Toward complete blindness and slight-moderate delay in psychomotor development.

Referimos el primer caso clínico conocido, en el que el signo de diagnóstico inicial de DSO fue una midriasis bilateral, como manifestación de hipoplasia de ambos nervios ópticos, hipoplasia hipófisaria y disgenesia cerebral con alteración de migración neuronal. Discutimos el diagnóstico diferencial de la midriasis congénita.

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Fig. 1 – Brain magnetic resonance, coronal section (T1): absence of septum pellucidum with ventriculomegalias.
**Table 1 – Differential diagnosis for congenital mydriasis.**

<table>
<thead>
<tr>
<th>Alterations in ocular structures</th>
<th>Clinical characteristics</th>
<th>Etiology</th>
<th>Differential diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated congenital mydriasis</strong></td>
<td>Fixed and dilated pupils at birth without other ocular symptoms (no aniridia), normal vision and without other systemic involvement</td>
<td>Result of diminished cholinergic production or sensitivity and Iris sphincter aplasia or hypoplasia</td>
<td>Mydriatic pupils and minimum response to light. Pupils can be dilated with mydriatic agents (pilocarpine)</td>
</tr>
<tr>
<td><strong>Hereditary congenital mydriasis (OMIM 159420)</strong></td>
<td>Isolated congenital aplasia of the Iris sphincter</td>
<td>X-linked dominant inheritance, lethal in hemizygous male. The affected gene is not yet known</td>
<td>Pupils exhibit anomalous response to pharmacological agents</td>
</tr>
<tr>
<td><strong>Aniridia (OMIM 106210)</strong></td>
<td>Literally, “absence of the iris”, involving several parts of the eye. Generally bilateral (in both eyes), and incomplete</td>
<td>Heterozygotic mutation in gene PAX6 with locus 11p13</td>
<td>The external appearance of the aniridian eye is that of a large black central pupil and a small color strip. It usually associates additional anomalies: nistagmus, cataracts, glaucoma With the Sjogren-Marinesco syndrome (cerebellar ataxia, mental retard and congenital cataracts)</td>
</tr>
<tr>
<td><strong>Gillespie syndrome (OMIM 206700)</strong></td>
<td>Characterized by aniridia, cerebellar ataxia (with cerebellar vermis atrophy) and mental retard</td>
<td>Heterozygotic mutation in gene PAX6 with locus 11p13</td>
<td>Enhanced nephrourological studies</td>
</tr>
<tr>
<td><strong>WAGR syndrome (OMIM 194072)</strong></td>
<td>W: Wilms tumor A: aniridia: partial or total absence of the iris G: genito-urinary alterations or gonadoblastoma R: retardation: psychological retard</td>
<td>Adjacent genes syndrome due to deletion or micro deletion in chromosome region 11p13 including WT1 (607102) and PAX6 genes (607108)</td>
<td>Enhanced nephrourological studies</td>
</tr>
<tr>
<td><strong>Ocular innervation alterations (generally unilateral with anisocoria)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bilateral palsy of III cranial pair</strong></td>
<td>Ocular parasympathetic innervation: injury produces mydriasis with absence of photo motor reflexes. Extrinsic ocular motility (superior, inferior and middle rectus and inferior oblique) and eyelid elevator</td>
<td>Even though it can be congenital, pupil parasympathetic fibers are on the periphery of the III pair, indicating severe complication with urgent neurological study</td>
<td>Anisocoria in mydriasis due to parasympathetic palsy. Associated pathology: ptosis, exotropia and limitation of elevation, adduction and depression of ocular movements</td>
</tr>
<tr>
<td><strong>Parinaud syndrome</strong></td>
<td>Supranuclear parasympathetic palsy, component of the mid-brain dorsal syndrome</td>
<td>Generally acquired associated to mesencephalic injuries close to the Sylvian aqueduct and with neurological clinic (nistagmus, cephalea vertigo, ataxia), although it can be congenital</td>
<td>Anisocoria in mydriasis due to parasympathetic palsy. Associated pathology: Anisocoria with asymmetric bilateral mydriasis + lack of photo-motor reflexes + good response to convergence (miosis) + vertical gaze palsy</td>
</tr>
<tr>
<td><strong>Congenital Horner syndrome</strong></td>
<td>Dysfunction of the sympathetic nerve fibers comprised between the hypothalamus and spinal cord. Complete form: ptosis, miosis, facial anhydrosis and Iris hypochromia</td>
<td>Not more than 5% of cases are congenital associating heterochromia. More frequently due to birth trauma, can be associated to Klumpke brachial palsy</td>
<td>Anisocoria in miosis due to sympathetic palsy. In response to 1% hydroxyamphetamine bromhydrate. Classified as pre-ganglionic if anisocoria diminishes or post-ganglionic if the dilatation of the affected pupil is smaller than the normalized (increased anisocoria)</td>
</tr>
<tr>
<td><strong>Pupila tónica de Adie</strong></td>
<td>Unilateral idiopathic post ganglionic denervation (ciliary ganglion neurons), with tonic pupils (mydriatic with little mobility)</td>
<td>Idiopathic or caused by alterations in the posterior nerves of the parasympathetic system, generally due to viral (herpes zoster) or bacterial infection</td>
<td>Slow pupil sphincter constriction segmentary to light, poor near vision, no response as consensus reflex but with response to convergence stimuli. Response to pharmacological stimulation with week pilocarpine solutions on iris denervation</td>
</tr>
</tbody>
</table>
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Clinical characteristics</th>
<th>Etiology</th>
<th>Differential diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic mydriasis</td>
<td>Rupture of iris sphincter muscle</td>
<td>Birth trauma</td>
<td>Unilateral. Excluded without appropriate antecedents TORCH serology studies</td>
</tr>
<tr>
<td>Infectious mydriasis</td>
<td></td>
<td>Generally with previous history of rubeola or syphilis Mydriatic agents</td>
<td>Antecedent: pharmacological drugs</td>
</tr>
<tr>
<td>Pharmacological mydriasis</td>
<td></td>
<td>Mydriatic agents</td>
<td></td>
</tr>
</tbody>
</table>

Most frequent entities in congenital mydriasis differential diagnostic (ocular innervation alterations are generally unilateral and express more frequently with anisocoria than with mydriasis).

Discussion

Pupil dilatation anomalies are important signs of ocular or neurological alterations. However, in NB anisocoria and congenital mydriasis are very infrequent and, when appearing, are generally more related to ocular innervation alterations (anisocoria) than to ocular structure alterations (Table 1 for differential diagnostic). Accordingly, bilateral congenital mydriasis is very rare and when occurring it is usually related to genetic aniridia, generally due to mutations in gene PAX6 (aniridia, OMIM 106210; Gillespie syndrome, OMIM 206700, characterized by the triad comprising aniridia, cerebellum ataxia and mental retard), or due to deletions/micro-deletions which constitute adjacent gene syndromes (WAGR syndrome, OMIM 194072, with Wilms tumor, aniridia, genitourinary alterations or gonadoblastoma and mental retard; or WAGRO when associating obesity). In general, neurological alterations that produce bilateral mydriasis are related to severe neonatal encephalopathies including in the first place hypoxic ischemic encephalopathy, whereas congenital causes of mydriatics due to parasympathetic palsy or miosis due to sympathetic palsy are generally expressed as anisocoria.

Fig. 2 – Brain magnetic resonance, sagittal section (T1): hypophysis gland hypoplasia. Presence of slightly thin corpus callosum.

Fig. 3 – Brain magnetic resonance, axial section (T2): hypoplasia of the chiasma and optic nerves. Diminished left brain hemisphere with localized increase of the extra-axial space at the level of the Sylvian fissure together with cortical thickening areas with heterotopia in the direction of the left frontal horn.

The bilateral congenital mydriasis of this case was secondary to SOD with atrophy of both optic nerves and possibly associated iris denervation. SOD, known as De Morsier syndrome (OMIM 182230) since the first description of this disease
made by Doctor De Morsier in 1956, is an infrequent congenital condition which occurs in 2–3 individuals for every 100,000. It comprises the characteristic triad including malformations in the middle line of the central nervous system (CNS) with absence of septum pellucidum, ocular anomalies which give rise to hypoplasia in one or more frequently both optic nerves and simple or multiple deficiencies of the hypothalamus-hypophysis hormones. Even though the presence of hormonal deficiencies is not a constant finding it must be studied regularly as it would be a base for specific treatment (generally GH but also hormonal deficiencies can be found including adrenocorticotropin, thyroid stimulant, etc.). Neuro-radiological findings are varied, BMR reveals multiple and heterogeneous morphological anomalies ranging from isolated agenesia of the septum pellucidum to multiple malformations such as corpus callosum agenesia, empty sella with or without hypophysis ectopia, or cortex involvement with neuronal migration disorders. Malrotation of hypocampus structures are a frequent finding. In addition, cerebellum hypoplasia is referred as well as vermis agenesia, fusion of dentate nuclei and cerebellum hemispheres, hydrocephalia, schizencephaly and porencephaly.

In this case, BMR evidenced the absence of septum pellucidum, with ventriculomegaly and hypoplasia of the optic nerves and chiasm, together with other cerebral structural anomalies (which some authors defined as the SOD plus syndrome). At examination time hypophysis hypoplasia has not compromised hypophysis hormones and its clinical evolution together with blindness has exhibited slight psychomotor retard without convulsions.

Usually, the diagnostic is established early if it courses with hormonal alterations expressing clinical signs in the neonatal period, or on the basis of ophthalmological clinical signs, i.e., hypoplasia of one or both optic nerves. Amongst ophthalmological findings, SOD can express as congenital nystagmus, which was found to be pendular in horizontal, vertical and rotation direction, and erratic nystagmus; bitemporal hemianopsiae, astigmatism, hypotelorism, strabismus with exotropia and esophoria, diminished visual acuity or visual disability which could reach blindness and motor clumsiness due to visual impairment. Pupil response is varied ranging from normal up to the presence of Marcus-Gunn pupil. The authors have found association to common oculomotor nerve palsy with optic nerve hypoplasia involving diminished visual function and nystagmus, where BMR reveals the absence of septum pellucidum, corpus callosum thinning and posterior ectopia of the hypophysis in 2 cases and infundibular hypoplasia in the third one. However, to this date the authors have not found in the literature congenital bilateral mydriasis as an initial sign of SOD.

In what concerns the origin, even though possible Mendelian inheritance has been postulated with mutation in gene HESX1 with genetic map in locus 3p21.2-p21.1, said mutation does not seem to occur frequently in sporadic cases. According to the study by McNay et al., mutations in HESX1 are a rare cause (less than 1%) of septo-optical dysplasia and hypopituitarism, and the large number of patients with familial SOD in whom mutations were not identified suggests an etiological role of other genetic factors. For this reason, for some authors this is not a genetically determined disease.

In conclusion, this paper presents the first known clinical case in which the first diagnostic sign of SOD was bilateral mydriasis as an expression of hypoplasia of both optic nerves, hypophysis hypoplasia and cerebrum dysgenesia with alteration of neuronal migration. Therefore, in the presence of congenital mydriasis, brain and optic nerve magnetic resonance is indicated.

Conflict of interests

No conflict of interests has been declared by the authors.

REFERENCES