Congenital Anomalies
Clinical and Laboratory Research
THE JAPANESE TERATOLOGY SOCIETY

250 *Congenital Anomalies* 2016; **56**, 250–252 doi: 10.1111/cga.12170

CASE REPORT

Syndromic microphthalmia-3 caused by a mutation on gene SOX2 in a Colombian male patient

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ABSTRACT **Syndromic microphthalmia-3 is a rare congenital syndrome associated with brain anomalies, esophageal atresia and genital anomalies. This is the case of a 4-year-old male with bilateral microphthalmia, short stature, neurodevelopmental delay, genital anomalies, and maternal exposition to glyphosate during pregnancy. Genetic testing detected a previously reported pathogenic heterozygous mutation in the *SOX2* gene, confirming a diagnosis of syndromic microphthalmia-3. Whenever a patient presents bilateral microphthalmia, it is necessary to determine whether it is isolated or syndromic; afterwards, genetic testing should be performed in order to offer an effective genetic counseling.**

Key Words: congenital malformations, *SOX2* gene, Syndromic microphthalmia

INTRODUCTION

Syndromic microphthalmia-3 (MCOPS3; MIM #206900), is a congenital syndrome with an autosomal dominant inheritance pattern, whose main clinical features include brain anomalies, neurocognitive delays, seizures, sensorineural hearing loss, esophageal atresia, short stature, microcephaly and genital anomalies like cryptorchidism and micropenis (Numakura et al. 2010; Shah et al. 1997; Bardakjian and Schneider 2005; Fantes et al. 2003; Ragge et al. 2005; Pedace et al. 2009). It is important the term "anophthalmia" has been misused, since anophthalmia is rarely compatible with life (François 1958; Chitayat et al. 2007) and a histological diagnosis is required (Morini et al. 2005).

This is the case of a 4-year-old male Colombian patient with bilateral microphthalmia, multiple accompanying congenital malformations and an antecedent of exposition to glyphosate during the first trimester of pregnancy.

CASE REPORT

This is the case of a 4-year-old male with bilateral microphthalmia, born to healthy non-consanguineous parents from the Andean Region of Colombia (Fig. 1). He was a product of a dichorionic-diamniotic twin pregnancy that ended via c-section at 34 weeks of gestational age; furthermore, the twin sister was non-affected. Physical examination at birth showed bilateral microphthalmia; hence, the patient was referred to a Clinical Genetic consultant. The patient has been attending the consultation irregularly since he was 4 months old.

Upon clinical interviews, the patient's mother declared exposition to glyphosate herbicide during her first trimester of pregnancy, denied seizures and a delay in psychomotor development. During the last visit to the Clinical Genetic consultant, the patient was still incapable of walking, sitting or communicating verbally in spite of being 4 years old, and his weight, height and cephalic perimeter were respectively 12.5 kg, 91 cm and 46 cm ($0^{-}1^{st}$ percentile); moreover, diastasis recti, hypoplastic testicles, and micropenis were also evidenced.

The brain computed tomography's radiological evaluation reported a hypoplasia of corpus callosum and a lack of ocular

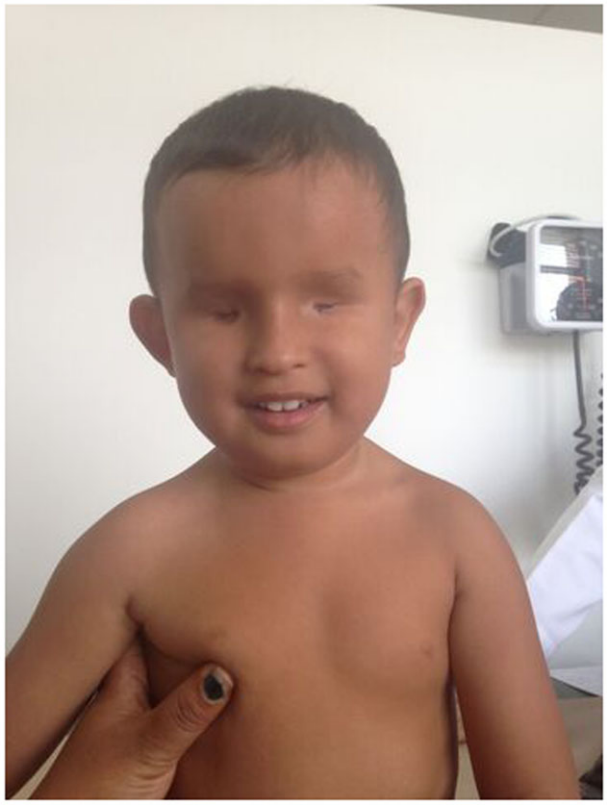

Fig. 1 Frontal photograph evidencing bilateral microphthalmia. Permission was obtained from the parents for presentation.

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Received October 13, 2015; revised and accepted May 17, 2016.

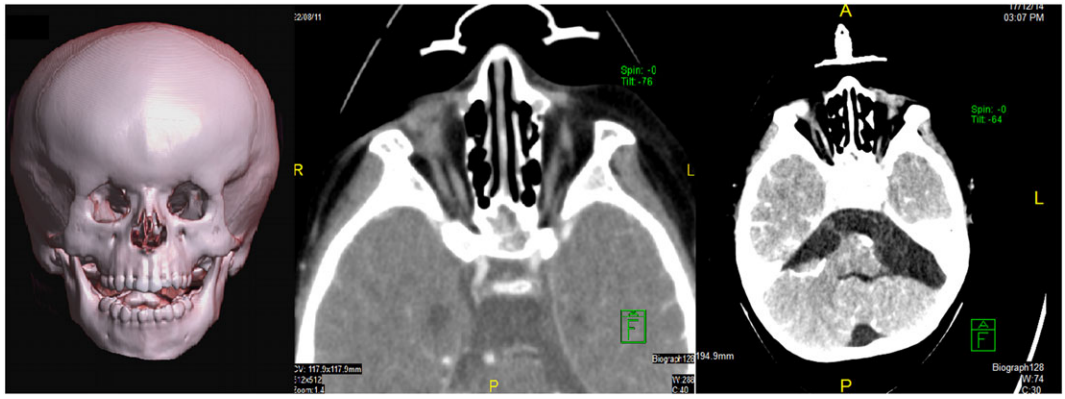

Fig. 2 Brain computed tomography: (left) tridimensional reconstruction of the skull, (center and right) axial slices evidencing a lack of ocular globes with rudimentary extraocular muscles and optic nerves.

globes with rudimentary extraocular muscles and optic nerves (the latter depicted in Fig. 2); furthermore, the upper gastrointestinal endoscopy demonstrated a double esophageal stenosis. Therefore, a monogenic condition was suspected and a NGS panel was performed on the patient, revealing the heterozygous mutation c.70_89del(p.Asn24Argfs*65) on gene *SOX2* which genetically confirmed a diagnosis of MCOPS3.

DISCUSSION

MCOPS3 is a rare congenital syndrome caused by a mutation in *SOX2* gene (Fantes et al. 2003). Many similarities are found between the patient and the described phenotype by other authors in medical literature; nevertheless, this patient has a hypoplasia of corpus callosum, which is an unusual but previously reported finding in MCOPS3 patients (Male et al. 2002; Zenteno et al. 2005). Even though it is common to find seizures in this type of patient, the mother denied these.

The heterozygous mutation c.70_89del(p.Asn24Argfs*65) on *SOX2* gene found on the patient's NGS panel had been previously reported as disease-causing for MCOPS3 (Zenteno et al. 2006; Gerth-Kahlert et al. 2013). Thus, this ruled out the exposure to glyphosate as a possible cause for MCOPS3. This was necessary, since other authors had demonstrated glyphosate's teratogenic effects on vertebrates (Paganelli et al. 2010). On the other hand, parental testing was not necessary since dominant autosomal diseases can not come from healthy parents, allowing one to conclude the mutation is *de novo*.

To sum up, in order to successfully evaluate patients with bilateral microphthalmia, it is important to define whether it is syndromic or isolated. This is the case of a syndromic microphthalmia, since it was accompanied by other congenital malformations, psychomotor and growth delays, and abnormal brain computed tomography and upper gastrointestinal endoscopy. Additionally, whenever the phenotype suggests a syndrome caused by chromosomic alterations, a karyotype or an array-based CGH array should be performed; on the other hand, if a monogenic condition is suspected like in this case, a NGS panel with candidate genes for that condition must be performed. In severe bilateral microphthalmia, the genetic cause can be identified in approximately 80% of cases, with the most common cause being *de novo* heterozygous loss-of-function mutations in genes *SOX2* or *OTX2* (Williamson & FitzPatrick, 2014). A NGS panel with candidate genes for microphthalmia was performed on this patient: SOX2, OTX2, RAX, FOXE3, BMP4, PAX6, BCOR, CHD7, STRA 6 and GDF6 (Bardakjian et al. 2004; Chassaing et al. 2013). The latter determined the molecular etiology and the inheritance pattern of the syndrome, which enabled to offer an adequate genetic counseling.

ACKNOWLEDGMENT

We thank Icesi University and Clinical Foundation Valle del Lili for their constant support.

DISCLOSURES

None.

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