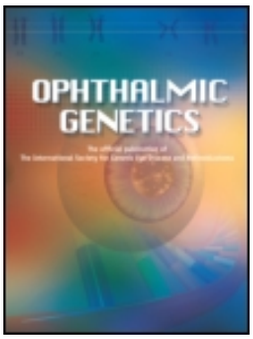

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CASE REPORT

Ophthalmologic Abnormalities in Mowat-Wilson Syndrome and a Mutation in *ZEB2*

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ABSTRACT

Mowat-Wilson syndrome is a genetic disorder characterized by a distinct facial appearance, moderate-to-severe mental retardation, microcephaly, agenesis of the corpus callosum, Hirschsprung disease, congenital heart disease, and genital anomalies. Ophthalmological abnormalities have been rarely described in patients with this condition which is caused by mutations in the *ZEB2* gene. We report a 9-year-old female with this syndrome who has severe ocular abnormalities including bilateral microphthalmia, cataract, and retinal aplasia.

KEYWORDS: Mowat-Wilson syndrome, *ZEB2* gene, Smad interacting protein 1

INTRODUCTION

Mowat-Wilson syndrome (MWS; OMIM 235730), also known as syndromic Hirschprung disease, was first described in 1998 in six children who shared a phenotypically distinct facial appearance, mental retardation, microcephaly, intestinal symptoms and short stature.[1] A deletion involving chromosome 2 (del(2)q21-q23) was noted in one of these patients.[2] The distinct facial phenotypic appearance resembled that of a patient previously described by Lurie who also had an interstitial deletion of chromosome 2 at locus q22-q23.[3] In 2001, the genetic etiology of MWS was identified as a heterozygous mutation in the *ZEB2* gene at chromosome 2q22. *ZEB2* is a zinc finger E-box-binding homeobox 2 gene, also known as *SIP1* (Smad interacting protein 1) or *ZFHX1b* (zinc finger homeobox gene 1b) that has been shown to be essential for normal axial and neural patterning through the bone morphogenetic pathway (BMP).[4] Attenuation of BMP results in abnormalities in the formation of neural tissue.[5]

Over the last decade there have been numerous reports of patients with MWS but little has been published regarding the ocular manifestations of the disease. In a review of 170 published cases, seven involved a description of a variety of eye abnormalities such as microphthalmia (including iris coloboma and cataract), iris/retinal/optic disc colobomas (three patients), and Axenfeld anomaly (one patient).[6] One patient with coloboma and high myopia had a missense mutation in the *ZEB2* gene as well as trisomy 21. Various other ocular abnormalities have been described including ptosis, strabismus, astigmatism, and iris heterochromia.[6]

While the disorder appears to be quite rare, with less than 200 patients described to date, recognizing its distinct clinical manifestations is important so ophthalmologists can assist in the diagnosis and management of patients.[6] We herein describe a female patient with MWS and significant ophthalmological abnormalities.

CASE REPORT

The patient first presented at 9 months of age for evaluation of a syndrome that included abnormal facial features with wide eyebrows (Fig. 1), an enlarged fontanelle, congenital heart disease (pulmonary stenosis, ventricular septal defect (VSD), atrial septal defect (ASD), patent foramen ovale), and very poor vision. She was born full term and was delivered vaginally after a normal pregnancy. At 6 days of age a heart murmur was identified and attributed to a combination of pulmonic stenosis, ASD, and VSD. A pulmonary valvuloplasty was done at 2.5 months of age. Her past medical history was complicated by recurrent otitis media, pyelonephritis, and vesicoureteral reflux.

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On ophthalmologic evaluation, the patient was noted to have no light perception (NLP) vision, microphthalmia of the right eye, and corectopia with a pupil size of 6 mm OD and 7 mm OS. She had a severely underdeveloped retina, and optic nerve hypoplasia of the left eye. The left lens was clear. Upon further examination under anesthesia she was noted to have severe optic nerve pallor, two areas of retina and choroid colobomas in the temporal quadrant, extensive chorioretinal and retinal pigment epithelium (RPE) atrophy, as well as extensive retinal atrophy with only one remaining superonasal vascular arcade (Fig. 2). In the right eye, there was no appreciable view of the posterior pole due to extensive lens opacities and korectopia. Work-up eventually revealed a *ZEB2* mutation (c.1278delA) and a diagnosis of Mowat-Wilson syndrome was made. She is currently being evaluated to determine if she has Hirschprung disease.

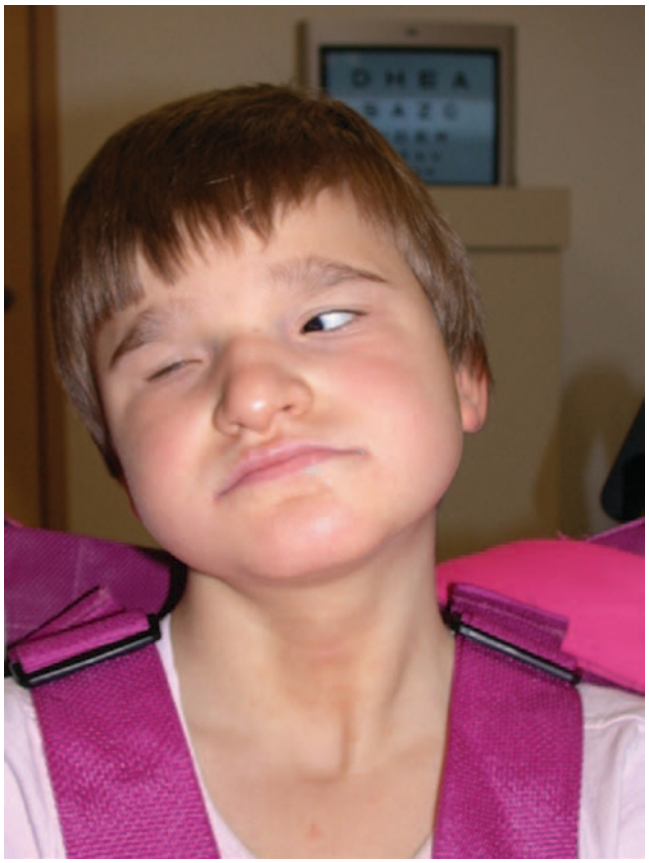

FIGURE 1 Characteristic facial appearance of our patient with Mowat-Wilson syndrome. Note right microphthalmia, short philtrum, flared nasal aspect of eyebrows and bulbous nose.

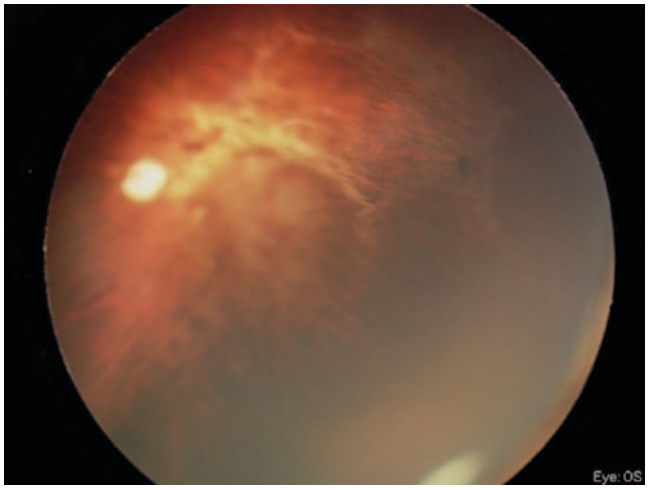

FIGURE 2 Wide-angle photograph of left fundus. The optic nerve is very pale. There are vague retinal details and some prominent and tortuous choroidal vessels.

DISCUSSION

Mowat-Wilson syndrome has been extensively studied over the last decade, yet little has been published regarding its ocular manifestations. It is clear that some patients with this condition have ocular abnormalities that range from ptosis, strabismus, and iris/retinal colobomas, to more severe ones such as extensive retinal atrophy and optic nerve hypoplasia/aplasia as observed in the case that forms the subject of the present report. We believe the ocular abnormalities are the result of the genetic defect since the ZEB2 protein is involved in neural patterning. It interacts in signaling cascade with BMP and transforming growth factor β that play a major role in patterning the development of neural-crest-derived cells such as the central nervous system, craniofacial mesectoderm, midline structures, and enteric nervous system and any defect in this gene creates the constellation of features described above.[5,6] Ophthalmologists may encounter patients with MWS and can recognize the distinctive facial dysmorphism and associated systemic and ocular findings. Genetic testing may be a means to support the diagnosis.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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