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Bilateral macular detachment caused by bilateral optic nerve malformation in a papillorenal syndrome due to a new PAX2 mutation

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PURPOSE. *Papillorenal syndrome is an autosomal dominant entity due to PAX2 gene mutation, involving optic nerve and renal malformations.*
METHODS. *The authors report a 19-year-old man with bilateral macular detachment associated with optic nerve pit in one eye and morning glory syndrome in the other eye. The patient underwent three-port pars plana vitrectomy, endolaser photocoagulation, and C3F8 gas tamponade in his best eye. A medical history of vesicoureteric reflux and kidney hypoplasia led to genetic analysis.*
RESULTS. *Molecular genetic PAX2 analysis revealed a novel nondescribed mutation in exon 3. One year postoperatively, ophthalmologic outcomes were satisfactory with complete flattening of the retina and improvement of the best-corrected visual acuity to 11/10.*
CONCLUSIONS. *PAX2 is involved in the optic vesicles, genital tracts, kidney, and central nervous system embryogenic development. The association of optic nerve and renal malformations should lead to the suspicion of papillorenal syndrome with PAX2 mutation. (Eur J Ophthalmol 2008; 18: 656-8)*

KEY WORDS. *Macular detachment, Morning glory syndrome, Optic nerve pit, Papillorenal syndrome, PAX2, Renal-coloboma syndrome*

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INTRODUCTION

Morning glory syndrome (MGS) is a rare optic nerve anomaly characterized by a funnel-shaped excavated optic disc, surrounded by whitish glial tissue and from which numerous abnormal retinal vessels radiate (1). Optic nerve pit (ONP) is a crater-like hole in the surface of the optic disk, mostly in its temporal part (1). Both are thought to be the result of incomplete closure of an aberrant fetal fissure during the fifth or sixth week of gestation (1).
We report the case of a young man presenting with bilateral macular elevation associated with ONP in one eye and MGS in the other. After molecular genetic analysis, we diagnosed a papillorenal syndrome.

Case report

The patient is a 19-year-old man, referred for the first time to the Department of Ophthalmology in January 2006 for decrease of best-corrected visual acuity in his right eye.
He had a history of strabismus convergent with anisometropic amblyopia of the left eye known since the age

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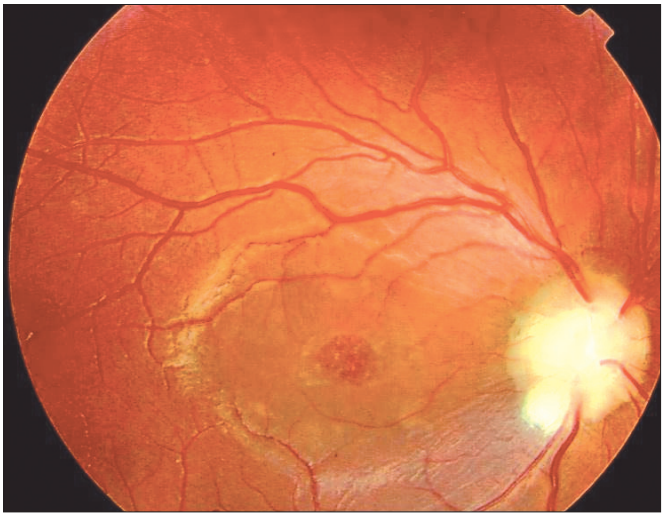

Fig. 1 - *Right fundus, myelinated nerve fibers, temporal optic disc pit, and pigmented peripapillary retinochoroidal atrophy, associated with macular detachment and focal thinning in the foveolar area.*

of 2 months. He also had a medical history of surgery for bilateral vesicoureteric reflux, and had been diagnosed with hypoplasia of both kidneys leading to severe renal failure.

On initial examination, his best-corrected visual acuity was 4/10 in the right eye and 1/10 in the left eye. The left eye fundus examination showed a characteristic feature of MGS. In the right eye, the fundus revealed myelinated nerve fibers, temporal ONP, and pigmented peripapillary retinochoroidal atrophy (Fig. 1). In both eyes, temporal to the optic nerve there was a schisis of the inner layers of the retina and, external to it, a retinal detachment of the macula (Fig. 1).

Optical coherence tomography (OCT) confirmed the outer layer detachment, and the presence of a schisis like cavity in the inner layers of the retina, connected to the optic disk by a small fistula. A marked focal thinning was present in the foveolar area (Fig. 2).

In April 2006 the patient underwent a three-port pars plana vitrectomy, photocoagulation with green monochromatic endolaser at the temporal border of the optic nerve, air–fluid exchange, and tamponade by C_3F_8 gas in his right eye.

In the meantime, the coincident findings of kidney and optic nerve malformations led us to perform genetic analysis in the patient and his first-degree relatives. After signed informed written consent was obtained, genomic DNA was extracted from peripheral blood leukocytes and the coding regions of *PAX2* gene were screened for mutations by direct sequencing.

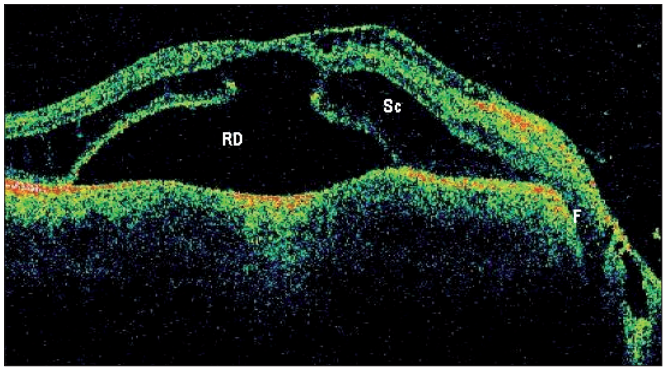

Fig. 2 - *Optic coherence tomography preoperatively through a horizontal plane: retinal detachment (RD), schisis of inner retinal layer (Sc), marked thinning of the foveolar portion of the retina and small fistula (F) between the optic disk pit and the schisis cavity.*

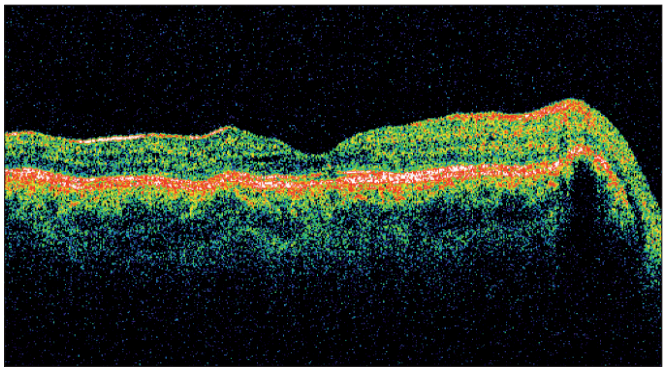

Fig. 3 - *One year postoperatively, complete resolution of the macular detachment in the right eye, disappearance of intraretinal schisis.*

RESULTS

Genomic DNA analysis from the patient detected a nonsense mutation in exon 3 (c.853C>T) leading to a stop codon (p.R104X) in the paired domain of the gene. The mutation was not present in his mother or in his sister.

Five months postoperatively, the best-corrected visual acuity was 7/10 with significant reduction of subretinal fluid at slit lamp examination confirmed by OCT. At the last examination, 1 year after surgery, best-corrected visual acuity had improved to 11/10 and we noted complete resolution of macular detachment in the right eye while no spontaneous retinal flattening was observed in the left eye. OCT confirmed disappearance of intraretinal schisis, absorption of the subretinal fluid, and closure of the fistula between the schisis cavity and the optic pit (Fig. 3).

DISCUSSION

Renal coloboma syndrome or papillorenal syndrome is a rare autosomal dominant pathology due to *PAX2* gene mutation and associated with ocular anomalies (colobomatous optic disc, ONP, MGS, optic nerve hypoplasia, chorioretinal coloboma, microphthalmia, cataract [2, 3]), renal malformations (renal hypoplasia, vesicoureteric reflux, multicystic dysplastic kidney [3]), and extrarenal manifestations (polydactyly, Arnold Chiari malformation, seizures [3]).

PAX2 gene belongs to the "paired-box" gene family and is located on chromosome 10q24-25. There are nine human *PAX* genes encoding for peculiar nuclear transcription factors (4), characterized by two DNA binding domains, a paired domain (exons 1 to 4), and a paired type homeodomain (exon 7). *PAX2* gene also contains an octapeptide sequence encoded by exon 5 and a transactivation domain (exons 8 to 12) (4, 5).

PAX2 is involved in the optic and otic vesicles, genital tracts, kidney, and central nervous system embryogenic development (5).

Renal coloboma syndrome presents marked phenotypic and genotypic variability. About 30 mutations have been recorded so far (the human *PAX2* allelic variant database: http://pax2.hgu.mrc.ac.uk), and most of them occur in the conserved paired box and octapeptide sequence, resulting in the loss of the DNA binding domain. The nonsense mutation we describe has never been reported. A mutation in exon 3 is involved in 18% of renal coloboma syndromes.

Macular detachment is a well-recognized and frequent complication of ONP or MGS.

Our OCT findings are in agreement with those of previous studies (6, 7) concerning the two-layer structure of optic pit maculopathy and the presence of a communication between the intraretinal schisis and the ONP. This strengthens the hypothesis of Lincoff et al (6) of a connection between the ONP and the inner retinal layers, creating first a schisis cavity, which leads secondarily to the outer layer detachment. The way the schisis cavity communicates with the subretinal space is unknown.

Various treatments have been suggested; vitrectomy, endolaser photocoagulation, and gas tamponade as a primary procedure seems to provide the best anatomic and functional results (6, 7) in ONP maculopathies.

Our report highlights the favorable anatomic, histologic, and functional outcomes after this surgical session, probably by laser sealing off the causal fistula between the optic nerve and the intraretinal schisis, blocking the origin of subretinal fluid.

CONCLUSIONS

Systemic defects are rarely associated with optic disk malformations, and if they do they affect mostly the central nervous system. Of special importance is the association of ONP or MGS with renal malformations, which should lead to the suspicion of *PAX2* mutation.

The authors have no proprietary interest.

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