paediatric head which would produce a greater load on the ocular surface.

We agree that our case report is extremely rare but it does emphasise the fragile nature of the immature retinal vascular system.

GGW Adams, BJ Clark, S Fang and M Hill

Moorfields Eye Hospital
Strabismus and Paediatric, 162 City Road
London, London EC1V 2PD, UK

Correspondence: GGW Adams
Tel: +44 20 7566 2013
Fax: +44 20 7566 2972
E-mail: gill.adams@blueyonder.co.uk

Eye (2005) **19,** 1221–1222. doi:10.1038/sj.eye.6701727; published online 1 October 2004

Sir,

Stargardt's disease and retinitis pigmentosa: different phenotypic presentations in the same family

The hereditary macular dystrophies are progressive degenerations of retinal and choroidal tissue. Genetic studies have shown that a single mutation or mutations in different parts of the same one gene can result in different macular dystrophies. Mutations in the Stargardt's disease gene (ABCA4) was shown to cause also fundus flavimaculatus, autosomal recessive retinitis pigmentosa (RP), and cone rod dystrophy (CRD).[1,2] Since they are all the result of mutations in genes that are presumed to express in either the photoreceptor cells or the retinal pigment epithelium (RPE), it would not be surprising to find variable presentations in members of the same family.[1–3]

Here, we report an atypical macular dystrophy in a young female who has two brothers with typical RP.

Case report

A 21-year-old woman, presented with gradually progressing poor vision starting about 15 years ago. She denies a significant difference in day and night vision. Her parents were first-degree relatives and she had two brothers complaining of poor night vision. Visual acuity was 20/400 in both eyes. There was no nystagmus. Ophthalmic examination was unremarkable except fundus examination, which revealed a well-circumscribed one-disc diameter area of choroidal and RPE atrophy in the fovea OD (Figure 1a) and a larger area of severe choroidal and RPE atrophy associated with posterior bowing (posterior staphyloma) in the macular area with a whole thickness macular hole and a few pigment clumps OS (Figure 1b). There was minimal or no arteriolar attenuation with a pink optic disc bilaterally. A punctate retina pigment epitheliopathy could be noticed in the midperipheral retina bilaterally, which is evident in fluorescein angiography (FA). FA showed window defect in the fovea surrounded by a hypofluorescent circular area of choroidal atrophy OD and, hypofluorescence of the whole macular area because of severe choroidal and retina pigment epithelial atrophy OS (Figure 2). Electroretinography (ERG) revealed severely affected cone and rod responses in both eyes (Figure 3).

The first brother, 32 years old, had a BCVA of 0.6 OD and 0.7 OS. There were arteriolar narrowing, waxy-pallor optic discs, bone-spicule pigmentation of the peripheral

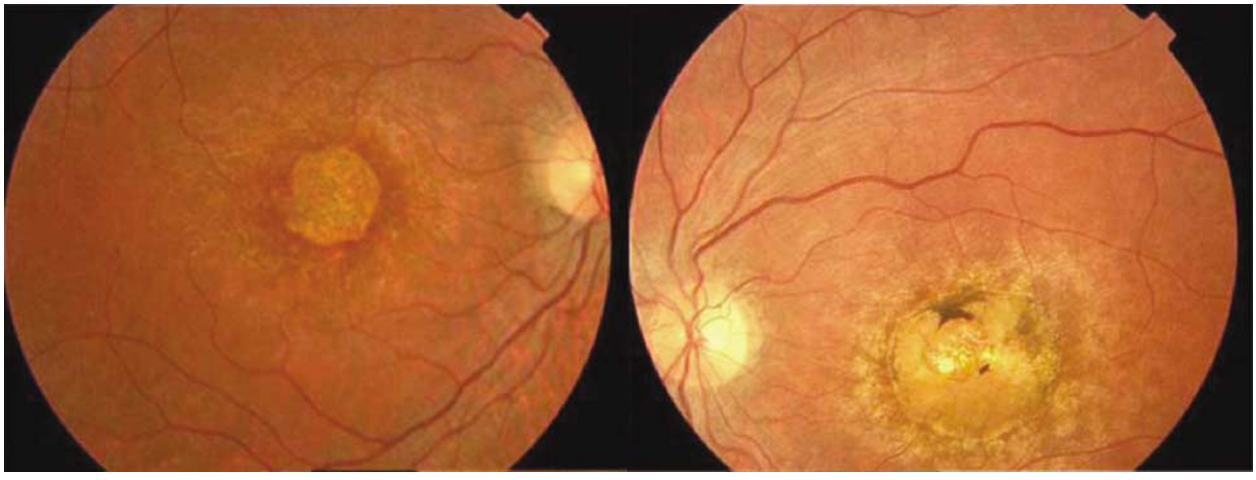

Figure 1 Fundus photographs of (a) the right eye and (b) the left eye of the patient.

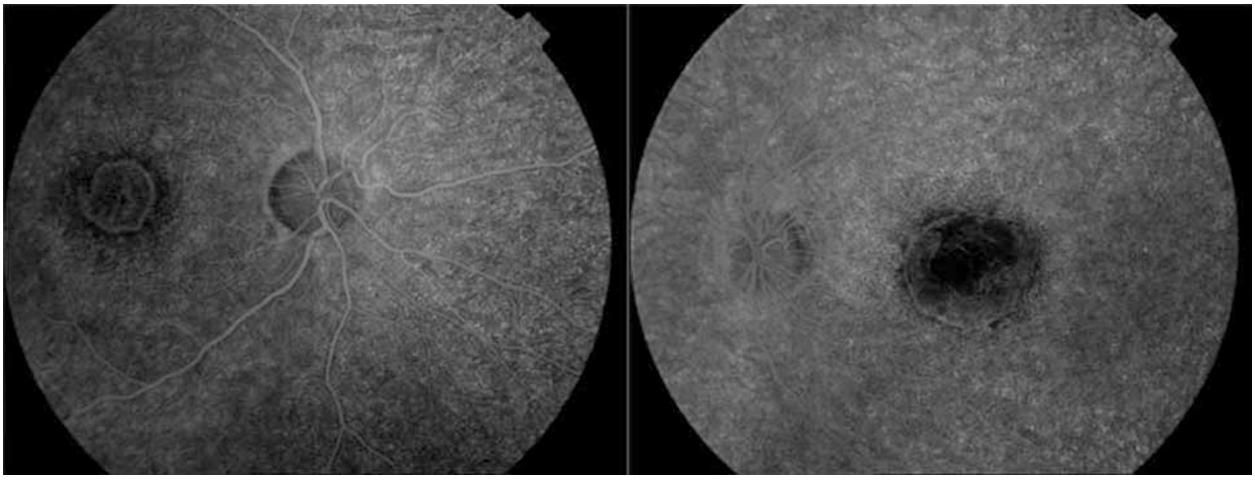

Figure 2 Fluorescein angiographies of (a) the right eye and (b) the left eye of the patient.

retina, and minimal atrophic maculopathy bilaterally in fundus examination (Figure 4). The second brother, 30 years old, had a BCVA of 0.9 in both eyes, and fundus examination revealed the same findings as the older brother, which is typical of RP. ERG revealed severely affected rod responses and moderately affected cone responses in the eyes of the brothers.

Genetic analysis of the family members with single-strand conformation polymorphism (SSCP) including mutations in the ABCA*4* gene and RDS/peripherin gene were negative. Ophthalmologic examination was normal in the other family members.

Patient returned to the clinic 2 years later with the same clinical findings. We performed the optic coherens tomography (OCT) and B-scan ultrasonography of the eyes this time. The central foveal thickness was 254 μm without any significant structural change in OD, and there was a posterior staphyloma-like posterior bowing of the structures in the foveal area (diameter: 2700 μm) in OCT associated with a macular hole OS (Figure 5). There was only a small irregularity in the foveal area in B-scan ultrasonographic examination of the left eye, which may represent the staphylomatous lesion seen in the OCT.

Comment

This special case offers some clinical entities in the differential diagnosis, some of which are Stargardt's disease, progressive CRD, inverse RP, Leber's congenital amaurosis (LCA), central areolar chroidal dystrophy, and Sorsby's fundus dystrophy, with a decreasing probability.[4,5]

Stargardt's disease usually inherited autosomal recessively causes visual loss beginning in the first two decades of life often with a normal fundus and later associated with macular atrophy and yellowish deep retinal flecks. Gass subdivided this disease into four subgroups according to clinical presentations: group 1 with vermillion fundi and hidden choroidal fluorescence; group 2—atrophic maculopathy with or without flecks; group 3—atrophic maculopathy
with late signs of retinitis pigmentosa; group 4—flecks not associated with macular atrophy. The presented case may be included in the third group of Stargardt's disease with severely affected scotopic and photopic ERGs.

The progressive CRD is characterized by progressive decrease in visual acuity and colour vision, which may start during the first decade of life but usually preserved until the third to fourth decades. In the early stages, retina is usually normal but later there may be typical signs of RP associated with characteristic bull's-eye macular lesion, some of which were also seen in our case. ERG can show markedly decreased or absent photopic responses and mildly decreased scotopic responses.[4,5]

Inverse RP is characterized by the presence of pigmentary disturbances similar to those occurring in classical RP, which occur solely in the pericentral retina sparing the peripheral retina. Both scotopic and photopic ERG responses are often subnormal consistent with region disease. This entity is sometimes considered as a type of CRD, at least some patients previously described as having inverse RP were likely to have had a form of CRD.[7]

Beginning of the visual deterioration after 6 years of age, absence of nystagmus and sluggish pupillary reaction are against the diagnosis of LCA in the presented case. Central areolar choroidal dystrophy and Sorsby's fundus dystrophy occur later in age and ERGs are usually normal.[4,5]

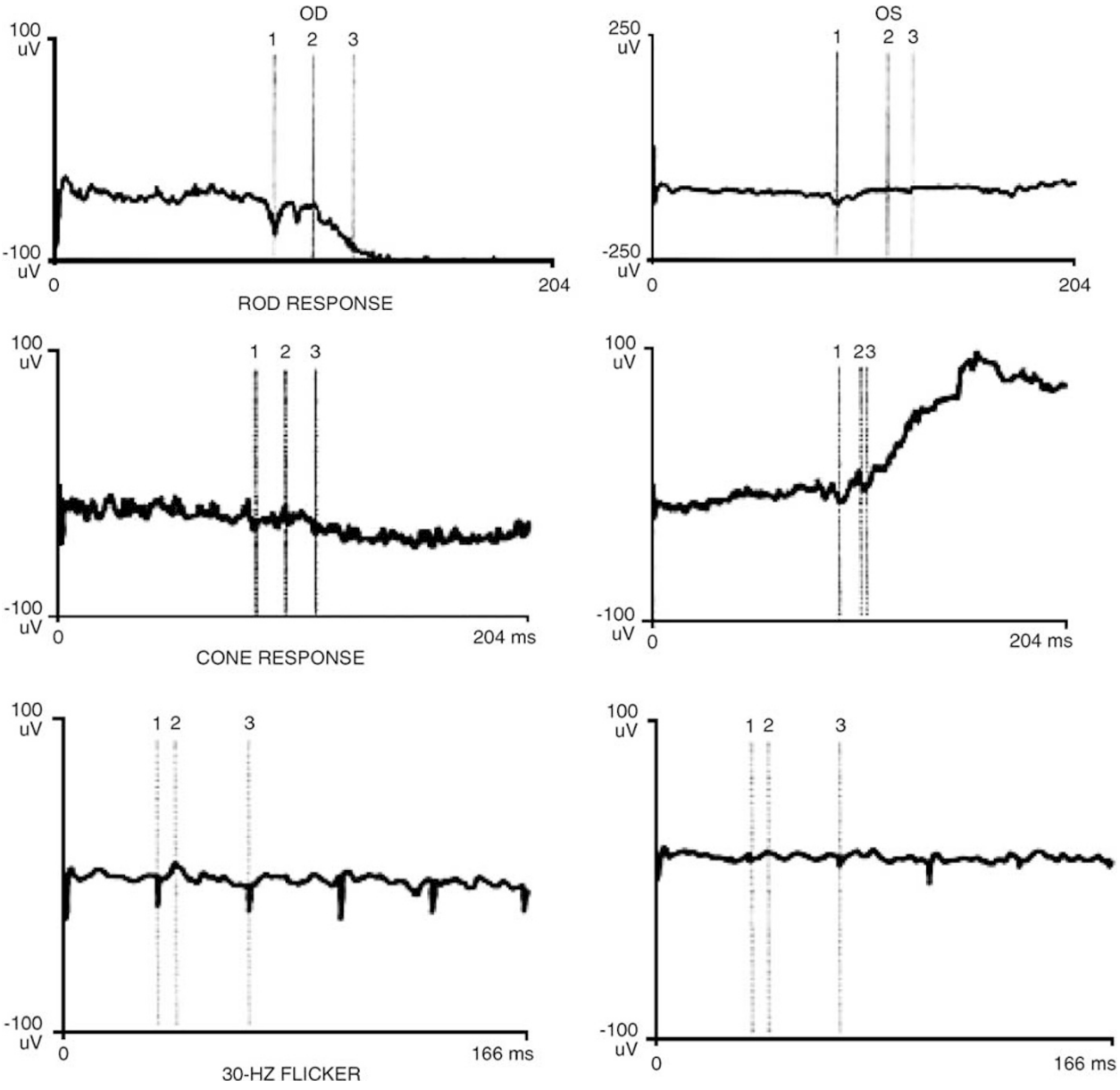

Figure 3 ERG of the proband (patient).

Although we cannot totally exclude CRD, the most possible diagnosis for the presented case seems to be Stargardt's disease (group 3); however, the presence of posterior staphyloma and macular hole makes this case interesting. Gass reported a case of cone dystrophy or dysgenesis, resembling our case, in a 32-year-old man who had bilaterally symmetric staphylomatous foveal lesion with pseudohole. There is one more recent report about another case of bilateral macular staphylomas in a 32-year-old woman with cone dystrophy[8] but not with Stargardt's disease.

The known molecular basis of the retinal dystrophies is the mutations in the human retinal degeneration slow (RDS) gene and the ATP-binding cassette transporter (ABCA*4*) gene. There are several reports in the literature about intrafamilial and interfamilial phenotypic variation among patients with retinal dystrophy caused by mutations of these genes.[9–11] Klevering *et al*[2,11] reported similar families displaying different combinations of patients: Stargardt's disease, CRD and RP as result of different mutations in the ABCA*4* gene.

In conclusion, the most striking feature of this possibly Stargardt's case is its association with a posterior staphyloma together with a macular hole in one of the eyes, which is, to the best of our knowledge, the first report in the literature. The second striking feature of the

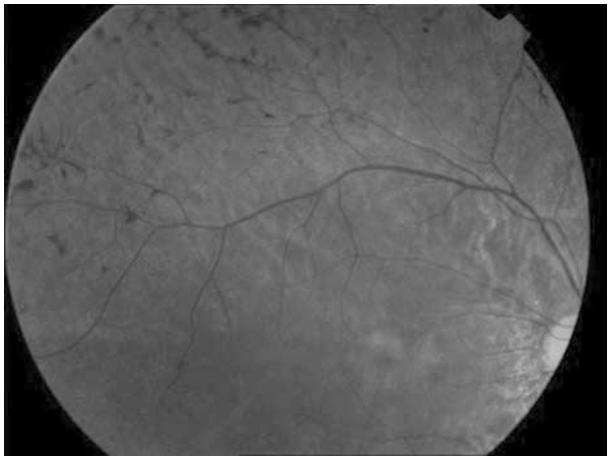

Figure 4 Fundus photograph of the 32-year-old brother.

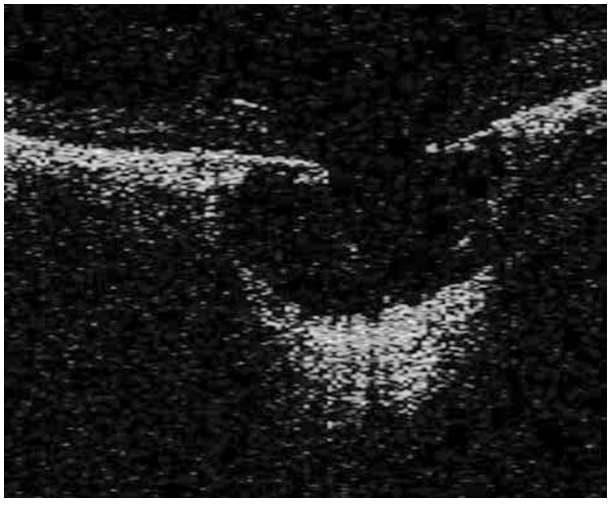

Figure 5 OCT picture of the left eye of the patient.

case is the presence of Stargardt's disease and classical RP in different members within the same family, which suggests that these dystrophies may be caused by mutations in the same one gene resulting in different macular dystrophies or they may even be different expressions of the same disease.

Acknowledgements

This study is partly supported by the Scientific and Technical Research Council of Turkey.

References

1 Fiore C. Different manifestations of tapetoretinal degeneration in the same family (author's transl). *J Fr Ophtalmol* 1981; **4**: 431–440.
2 Klevering BJ, van Driel M, van de Pol DJ, Pinckers AJ, Cremers FP, Hoyng CB. Phenotypic variations in a family with retinal dystrophy as result of different mutations in the ABCR gene. *Br J Ophthalmol* 1999; **83**: 914–918.
3 van Driel MA, Maugeri A, Klevering BJ, Hoyng CB, Cremers FP. ABCR unites what ophthalmologists divide(s). *Ophthalmic Genet* 1998; **19**: 117–122.
4 Fishman GA. Diffuse photoreceptor dystrophies. In: Fishman GA, Birch DG, Holder GE, Brigell MG (eds). *Electrophysiologic Testing in Disorders of the Retina, Optic Nerve and Visual Pathway*, 2nd edn. The Foundation of the American Academy of Ophthalmology: San Francisco, CA, 2001, pp 39–42.
5 Weleber RG, Gregory-Evans K. Retinitis pigmentosa and allied disorders. In: Ryan SJ (ed). *Retina*, Vol 1. Mosby: St Louis, 2001, pp 362–460.
6 Gass DMJ. Heredodystrophic disorders affecting the pigment epithelium and retina. In: Gass DMJ (ed). *Stereoscopic Atlas of Macular Diseases Diagnosis and Treatment*, Vol. I, 4th edn. Mosby: St Louis, 1997, pp 303–436.
7 Ferrucci S, Anderson SF, Townsend JC. Retinitis pigmentosa inversa. *Optom Vis Sci* 1998; **75**: 560–570.
8 Apte RS, Sunness JS, Goldstein BG, Park WL, Raden RZ, Elman MJ. Bilateral macular staphylomas in a patient with cone dystrophy. *Br J Ophthalmol* 2003; **87**: 1049–1051.
9 Wells J, Wroblewski J, Keen J, Inglehearn C, Jubb C, Eckstein A *et al*. Mutations in the human retinal degeneration slow (RDS) gene can cause either retinitis pigmentosa or macular dystrophy. *Nat Genet* 1993; **3**: 213–218.
10 Cremers FP, van de Pol DJ, van Driel M, den Hollander AI, van Haren FJ, Knoers NV *et al*. Autosomal recessive retinitis pigmentosa and cone–rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. *Hum Mol Genet* 1998; **7**: 355–362.
11 Klevering BJ, Maugeri A, Wagner A, Go SL, Vink C, Cremers FP *et al*. Three families displaying the combination of Stargardt's disease with cone-rod dystrophy or retinitis pigmentosa. *Ophthalmology* 2004; **111**: 546–553.

Ş Özdek[1], Z Onaran[1], G Gürelik[1], K Bilgihan[1], C Acar[2] and B Hasanreisoğlu[1]

[1]Ophthalmology Department, School of Medicine Gazi University, Ankara, Turkey

[2]Department of Molecular Biology Section Faculty of Science Biology, Hacettepe University Turkey

Correspondence: Z Onaran,
Gürler Sok. 14/8,
06180 Yenimahalle, Ankara, Turkey
Tel: +90 312 2026315
Fax: +90 312 2125794
E-mail: zafer100@hotmail.com

Eye (2005) **19,** 1222–1225. doi:10.1038/sj.eye.6701730; published online 4 March 2005