CASE REPORT

ERG and OCT findings of a patient with a clinical diagnosis of occult macular dystrophy in a patient of Ashkenazi Jewish descent associated with a novel mutation in the gene encoding RP1L1

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SUMMARY

A 57-year-old man with a past medical history of diabetes presented for consultation with a several year history of slowly progressive vision loss in both eyes, which continued to deteriorate over 7 years of follow-up. Multimodal imaging was performed and was significant for the following: on spectral domain optical coherence tomography, a gap lesion was present in the ellipsoid layer, beneath the umbo, as well as subtle macular changes on auto fluorescence imaging. Multifocal electroretinography was performed and was abnormal, and a clinical diagnosis of occult macular dystrophy was made. The patient was subsequently evaluated with genetic testing that revealed a novel p.P73S:c.217C>T nonsense mutation within the retinitis pigmentosa 1-like-1 (RP1L1) gene. The clinical significance of the identified variation will require further investigation.

BACKGROUND

Occult macular dystrophy (OMD) is a lesser known disease with progressive visual loss that has been characterised only recently with the aid of genetic testing and latest generation ophthalmic imaging modalities. The disease process was initially described in Asian populations and subsequently in Caucasian patients; both groups have demonstrated mutations in the retinitis pigmentosa 1-like-1 (RP1L1) mutation. Herein we present a case of OMD in a Caucasian patient of Ashkenazi Jewish descent, with a novel RP1L1 mutation. Genetic testing can be a useful adjunct in the workup and evaluation of patients suspected to have OMD.

CASE PRESENTATION

A 62-year-old man of Ashkenazi Jewish descent was referred for retinal consultation for evaluation of persistently poor visual acuity, despite bilaterally successful cataract surgery. His past medical history was significant for non-insulin-dependent diabetes mellitus, hypertension and 35 years of cigarette smoking. The patient denied any history of consanguinity or family history of ocular diseases. His 10 siblings and 10 children are all alive and all report no visual complaints.

The patients best-corrected visual acuity (BCVA) both pre-cataract and post-cataract extraction remained 20/80 in the right eye and 20/100 in

the left eye. And over the subsequent 7 years has decreased to a BCVA of 20/400 in the right eye and counting fingers in the left eye. A 24–2 Humphrey visual field demonstrated pronounced central defects in both eyes (figure 1).

Anterior segment examination was significant for well-placed posterior chamber implants. The optic nerves had pink, healthy rims with a cup to disc ratio of 0.2. The maculae were flat with normal pigmentation, as demonstrated by initial colour fundus photographs (figure 2). Fluorescein angiography was non-contributory; however, autofluorescence imaging demonstrated subtle macular pigmentary changes (figure 3).

Spectral domain optical coherence tomography (SD-OCT) of the macula was highly significant and demonstrated an optical gap in the foveal centre with localised loss of the photoreceptor ellipsoid zone (EZ) and the interdigitation zone (IZ) under the fovea (figure 4). Full-field electroretinography (ERG) demonstrated normal rod and cone responses in both eyes. Multifocal electroretinography (mfERG) demonstrated decreased central responses in both eyes, suggestive of a localised macular dystrophy (figure 5).

Genetic testing using next generation sequencing on the Illumina MiSeq platform with analysis using the variant discovery software NextGENe (SoftGenetics LLC, State College, Pennsylvania, USA) and reference genome GRCh37/hg19 was performed. Variants were confirmed by Sanger sequencing and revealed a heterozygous variation in the RP1L1 gene, specifically novel p.P73S:c.217C>T nonsense mutation sporadic cases were analysed with Alamut software (www.interactive-biosoftware.com). No other reportable secondary findings, as per American College of Medical Genetics guidelines.

DISCUSSION

OMD (OMIM #613587) was initially described in a Japanese population in 1989 with patients presenting with vision loss in spite of a normal funduscopic examination, fluorescein angiography [1] and diminished macular function on mfERG with a normal full-field ERG. The advent of SD-OCT has become an invaluable adjuvant tool in diagnosing OMD, with various hallmarks having been described.^{1–3}

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Figure 1 24-2 Humphrey visual fields demonstrating central scotomas in both eyes.

Figure 2 Colour fundus photos of the right eye (A) and the left eye (B) demonstrating normal retinal architecture.

Figure 3 Autofluorescence photos of the right eye (A) and the left eye (B) demonstrate subtle macular pigmentary changes.

Multiple inherited and non-inherited mutations to the RP1L1 gene on chromosome 8p have been linked to OMD.^{4–10} The expression of RP1L1 is limited to the retina where it encodes a 2400 amino acid photoreceptor-specific protein. It is similar in sequence to the retinitis pigmentosa gene (RP1).

Thus far, OMD has largely been described in Japanese and Korean families.^{1,2,5,8} There are limited reports of its occurrence in Caucasian patient of European descent with RP1L1 mutation.^{11,12} We herein describe how imaging (AF and SD-OCT) and electrophysiological testing demonstrated the pathognomonic findings of OMD in a patient of Ashkenazi Jewish descent, who was found to have a novel heterozygous variation in the RP1L1 gene, namely p.P73S:c.217C>T.

The optical gap phenotype (noted on SD-OCT) has been indiscriminately associated with several hereditary retinal dystrophies, including, but not limited to, rod monochromatism, and mutations in KCVN2 and ABCA4 genes. Solar retinopathy, laser-pointer injury and drug-induced (tamoxifen) toxicities have also been reported with optical gap-like lesions.

Historically, the entity was referred to as OMD, as the clinical examination was within normal limits. However, as in our case, multimodality imaging can reveal subtle abnormalities, such as disruption within the EZ. The disease is typically characterised by slowly progressive acuity loss.

Although SD-OCT does not always demonstrate pathology early in the course of the disease, it is a valuable tool in the diagnosis of OMD. As in our patient, notable findings have included deformities of the EZ^{2,3,7} and photoreceptor loss with disruption of the IZ. Other findings described have included decreased

Figure 4 Spectral domain optical coherence tomography images of the right eye (A) and the left eye (B) demonstrate a subfoveal optical gap characterised by loss of ellipsoid zone (single arrow) and interdigitation zone (double arrow).

Figure 5 Multifocal electroretinography showing decreased amplitude and increased implicit time in central responses in both eyes, indicative of a maculopathy.

central foveal thickness and external limiting membrane (ELM) disturbances.^{2,3} Focal macular changes on mfERG are the most sensitive markers of OMD, demonstrating reduced macular responses even prior to the appearance of outer retinal abnormalities on SD-OCT.¹¹

Confirmation of the clinical significance of the identified variation, novel p.P73S:c.217C>T nonsense mutation, will require that additional family members should be tested for the identified variation. The definitive impact of our findings herein is further limited by the inability to complete a segregation analysis of his rather large family that is located in far flung locales. However, telephone interviews confirmed that there were no visual complaints from his 10 siblings or 10 children. Physical examination and multimodality imaging studies were performed on two of the affected individuals progeny, with results that were completely within normal limits. The importance of serial clinical examinations of his progeny over time was discussed with the affected individual, as asymptomatic family members may manifest OCT findings prior to any subjective change in visual function.^{13–15}

Despite our increasing technological advances in diagnosing OMD, no treatment is available. These patients should be promptly referred for genetic counselling, low vision services and a low threshold for testing asymptomatic family members must be maintained. Genetic testing should be included in the workup OMD and may significantly enhance our understanding of this entity.

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Learning points

- ▶ Progressive visual loss in an adult patient in the absence of media opacification and systemic disease must undergo multimodal imaging to uncover retinal pathology.
- ▶ Patients of reproductive age with confirmed occult macular dystrophy (OMD) must be referred to genetic counselling.
- ▶ Low vision services should be offered to the patient with declining vision.
- ▶ Patient's family members should be screened for possibility of OMD.

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