A novel variant of autosomal recessive best vitelliform macular dystrophy and management of early-onset complications

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Abstract:
To report an adult with autosomal recessive Best vitelliform macular dystrophy with a new homozygous BEST1 mutation, the management of a cystoid macular edema with intravitreal aflibercept in the proband, and the findings in the parents, carriers of heterozygous BEST1 mutations. A 28-year-old female presented with blurry and reduced vision in her both eyes with bilateral vitelliform macular lesions. The patient's parents were also examined. Examinations included electrooculogram (EOGs), imaging studies, and BEST1 gene testing. Interventions included treatment with intravitreal aflibercept for both eyes. The patient presented with visual acuity of 20/20 OD 20/30 OS, RPE changes, multifocal subretinal yellowish deposits resembling vitelliform deposits and subretinal fluids. Cystoid macular edema developed after one month, causing vision reduction (20/28 OD 20/30 OS). Visual acuity recovered to 20/20 OU after serial intravitreal aflibercept injections. The proband showed subnormal EOG Arden ratios. Molecular testing showed the homozygous missense variant c.695T>G p. (Ile232Ser) In exon 6 of the BEST1 mutations and to the best of our knowledge, this variant, which was confirmed by conventional Sanger sequencing, has neither been annotated in databases nor been described in the literature so far (Human Genome Molecular Database 2018.1). In the heterozygous parents, EOGs were subnormal, and minimal autofluorescence changes were seen.

Clinical Relevance: Prompt recognition and treatment of cystoid macular edema management effectively restore vision. Awareness and recognition of recessive inheritance permit correct diagnosis and counseling.

Keywords:
Autosomal recessive bestrophinopathy, BEST1 gene, deleterious mutations, vitelliform

INTRODUCTION
More than 200 mutations in BEST1 gene have been identified and published until recent date.[1-3] Mutations are associated with best vitelliform macular dystrophy (VMD, MIM 153700), adult-onset VMD (MIM 608161), retinitis pigmentosa 50 (RP50, MIM 613194), and autosomal dominant vitreoretinochoroidopathy (MIM 193220). All were considered that they were exclusively inherited in an autosomal dominant fashion. The gene accountable for BVMD is BEST1, which encodes the retinal pigment epithelium Ca2+-dependent Cl- current and mutations are likely to abolish its activity affecting RPE metabolism, and as a consequence, outer retinal function with which the RPE is closely associated.[4,5]

Best VMD (BVMD) has often incomplete penetrance. However, asymptomatic family members who carry BEST1 mutations exhibit abnormalities on electrooculography (EOG).[6] The suppressed light peak of the EOG is thought for the 585 amino acid transmembrane protein bestrophin-1, located on the basolateral aspect of retinal pigment epithelial (RPE) cells.[1]

Bestrophin-1 is a member of the RFP protein family in both vertebrates and invertebrates. Bestrophins are expressed in various tissues and organs, but bestrophin-1 is expressed predominantly in the RPE, where it functions as a Ca2+-dependent Cl− current and mutations are likely to abolish its activity affecting RPE metabolism, and as a consequence, outer retinal function with which the RPE is closely associated.[4,5]

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to result from a compromised chloride channel function of bestrophin-1 in the RPE.\cite{1,2,3,4,5,6,7}

Recently, a phenotype caused by autosomal recessive (AR) mutations in BEST1 was described; AR bestrophinopathy (ARB, OMIM 611809), which is a rare ocular disease. In 2006, Schatz et al.\cite{9} reported the first documented instance, in which compound heterozygosity for two mutations (Y29X and R141H) caused an exceptionally severe and early-onset BVMD phenotype. Nevertheless, it was defined by Burgess et al.\cite{10} in 2008, who reported a series of a patient with unequivocal AR BVMD and described differences in the clinical appearance of these patients compared with (AD) BVMD, despite being reported 2 years earlier. In brief, the distinctive features of arBVMD were reported to be subretinal or intraretinal fluid in the absence of subfoveal vitelliform lesions, disseminated punctate retinal flecks, hyperopic refraction, and subnormal delayed rod- and cone-driven electroretinogram responses.\cite{11} It results from biallelic mutations in BEST1 and is characterized by multifocal vitelliform dystrophy with subretinal fluid. An association with hypermetropia and angle-closure glaucoma has been described.\cite{12} Herein, and we review the clinical features and new mutation of one family with arBVMD.

Other conditions which can mimic the phenotypic appearance of arBVMD include multifocal best disease, adult-onset VMD, multifocal pattern dystrophy associated with peripherin/RDS mutations, acute, exudative polymorphous vitelliform maculopathy, and paraneoplastic syndromes or metastases.\cite{13,14,15} Furthermore, chronic central serous choroidopathy can present with serous retinal detachments, cystoid maculopathy, and subretinal fibrin despite that fibrin does not cause hyperautofluorescence. Boon et al.\cite{16} studied clinical and genetic heterogeneity in 15 patients with a multifocal vitelliform phenotype, nine of these patients carried a BEST1 mutation, and one a peripherin/RDS mutation. Not only were the phenotypic appearance of patients with BEST1 mutations diverse, but also some of the patients without mutations in BEST1 presented with a fundus appearance identical to our patients in this study.

Initial differential diagnoses to our patients included acute exudative polymorphous vitelliform maculopathy, Vogt-Koyanagi-Harada disease, and fundus flavimaculatus. Comprehensive screening by sequencing of the entire BEST1 gene is, therefore, essential for the correct classification of these patients’ conclusion.

Subretinal fluid and intraretinal fluid are fairly common complications in BVMD and other similar macular diseases.\cite{17} Recently, favorable short-term outcomes of choroidal neovascularization (CNV) treatment with intravitreal antivascular endothelial growth factor (VEGF) drugs have been reported in adBVMD.\cite{18,19} and other adult-onset vitelliform phenotypes linked to BEST1 mutations.\cite{20,21}

Herein, we report a family with arBVMD due to BEST1 mutations, in which the proband presented with early-onset subfoveal vitelliform lesions complicated by cystoid macular edema (CME), the treatment of CME with intravitreal aflibercept (Eylea), and the findings in the carrier parents.

**Case Report**

A 28-year-old Saudi girl (proband, Case II: 1) presented in February 2018 with blurry vision in both eyes and bilateral vitelliform macular lesions, complicated by CME after 2 months from the first presentation. Her parents (the father, Case I: 1, and the mother, Case I: 2), who were both asymptomatic, were also evaluated.

**Diagnostic workup**

In addition to a full ophthalmologic examination, the examination of the proband and her parents included spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF). The International Society for Clinical Electrophysiology of Vision – standard EOGs\cite{22} were recorded on all subjects. Intravenous fundus fluorescein angiography was also performed as well.

At the time of 2.0 mg/0.05 ml aflibercept intravitreal injections, which were performed serially every month for three consecutive months, then after visual and clinical improvement, only observation with clinical fundus examination and OCT macula was performed.

**Molecular genetic testing**

Diagnostic testing for BEST1 gene mutations was performed at the Bioscientia Labor Ingelheim Genetic Testing Laboratory, Germany. For this, whole blood samples were collected from the proband and her parents and shipped to the laboratory, where genomic DNA was extracted, polymerase chain reaction amplified and sequenced as previously described.\cite{23}

**Results**

**Case II: 1 (proband)**

The proband’s visual acuity by Early Treatment Diabetic Retinopathy Study charts at presentation was 20/20 right eye. Her fundus examination revealed RPE changes, multifocal subretinal yellowish deposits, and subretinal fluids. She had visual acuity of 20/30 left eye and her fundus findings included RPE changes, multifocal subretinal yellowish deposits, and subretinal fluids extending along the inferotemporal arcade, most clearly seen with FAF as shown in Figure 1. Fundus photographs from this visit are shown in Figure 1. Our initial impressions included fundus flavimaculatus, familial drusen with CNVM, chronic central serous chorioretinopathy, and Vogt-Koyanagi-Harada; we conducted our investigation based on our list of differential diagnosis, uveitis workup, Human Leukocyte Antigen typing, FAF, Fluorescein Angiography, OCT, and EOG were done.

An EOG was performed on the proband and the Arden ratio was found to be 1.52 for the right eye and 1.59 for the left eye, respectively, both of which were less than the normal range (>1.65).\cite{24} Reduced vision occurred in the
right eye (20/28) over a period of 2 months following the development of CME. Fundus photographs, intravenous fluorescein angiography, SD-OCT, and FAF at this stage are shown in Figure 1. Reduced visual acuity occurred with CME, and the first aflibercept (Eylea) treatment was performed. The SD-OCT shown in Figure 1 illustrates the fluid pockets and vitelliform lesions. The FAF findings in the right eye and left eye of the proband are illustrated in the bottom row of Figure 1, where areas of abnormal FAF extending well beyond the discrete subfoveal vitelliform lesions are apparent.

After serial bilateral 2 mg/0.05 ml intravitreal aflibercept injections performed under topical anesthesia, visual acuity returned to 20/20 left eye and was maintained at 15 months of follow-up. This functional improvement in both eyes was associated with a significant reduction in retinal exudative changes and improvement in retinal microanatomy by SD-OCT criteria illustrated in Figure 2. Fluid pockets in both eyes improved but persisted with mild intraretinal cystic edema. Significant reduction in the edema was noted; however, only a thin fluid cleft persisted. Aflibercept treatment of both eyes was performed in conjunction with OCT. Over time, visual acuity increased to 20/20 in both eyes. The response to the treatments is shown in Figure 2.

**Case I: 1 (father)**

At age of 56 years, these male participants had an uncorrected visual acuity of 20/20 in both eyes. He had almost normal fundus examination aside from vitelliform deposits in both eyes around the arcades [Figure 3, first row]. The OCT was normal. The Arden ratio of his EOG was 1.95 for the right eye and 1.86 for the left, which is within the normal range.\(^2\)

**Case I: 2 (mother)**

At age of 53 years, this white female participant had an uncorrected visual acuity of 20/20 in both eyes. She had mild visual acuity and had normal fundus examination aside from vitelliform deposits in both eyes around the arcades [Figure 3, first row]. The OCT was normal. The Arden ratio of her EOG was 1.17 for the right eye and 1.14 for the left eye, which is considered a reduced value.\(^2\)

**Molecular genetic test results**

After the exclusion of inflammatory and infectious etiologies such as toxoplasma, toxocara, and lymphocytic choriomeningitis virus, diagnostic BEST1 gene testing was performed to determine the possibility that our proband case could have been BVMD and if so, whether she had a heterozygous de novo dominant mutation or a recessive form of the disease. Testing revealed homozygous missense variant 695T > G p.(Ile23Ser) in exon 6 of the BEST1 gene of the patient.

Parents’ genetic testing revealed heterozygous missense variant c. 695T > G p.(Ile23Ser) in axon 6 of the BEST1 gene. Figure 4 illustrates the family pedigree. To the best of our knowledge, this variant, which was confirmed by conventional Sanger sequencing, has neither been annotated in databases nor been described in the literature so far (Human Genome Molecular Database 2018.1).

**Discussion**

Although uncommon, BVMD can occur as a recessive trait due to biallelic BEST1 mutations.\(^1\) Unlike that reported by Burgess et al.,\(^3\) however, similar to the case reported by Schatz et al.,\(^9\) our proband presented with early-onset subfoveal vitelliform lesions. This supports the notion that BVMD represents a spectrum of diseases in severity, age at onset, and mode of inheritance. The vitelliform phenotype remains one of the disease manifestations even when BVMD is inherited as a recessive trait.

CME can complicate both dominant and recessive forms of BVMD. These fluids can be challenging to detect because the overlying vitelliform lesions can partially or entirely obscure them. The excellent microanatomical and functional response of CME in both eyes of our proband is consistent with the favorable short-term outcomes reported by others.
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Our results indicate that this treatment modality is useful also in arBVMD complicated by CME. Although the outcome in our patient has been excellent, care must be taken in generalizing our results to other patients with BEST1 mutations. It is possible that her vision could also have improved without any intervention. This point is illustrated by a previously reported case with adBVMD,[22] resulting from an Asp-302-Ala (D302A) BEST1 mutation. She developed a subretinal hemorrhage in association with minor blunt trauma and reduced visual acuity in the right eye at the age of 12 years and she has been followed up without any treatment in this eye for 10 years. Despite an initial moderate (20/50) visual acuity loss, on the resolution of the subretinal hemorrhage, visual acuity recovered spontaneously to 20/30 by 8 months and 20/20 −2 by 17 months even with the presence of the central fibrotic lesion with surrounding subretinal fluid. The acuity in the fellow eye of this patient when the hemorrhage occurred in the right eye was 20/20 and remained so through the recovery of the right eye to 20/20 − 2.

The ideal number of injections cannot be determined from this study, although our patient experienced significance improvement after the first three injections.

With intravitreal anti-VEGF drugs for CNV in adBVMD[15,16] and adult-onset vitelliform phenotypes linked to BEST1 mutations,[17,18] our results indicate that this treatment modality is useful also in arBVMD complicated by CME.

Although the outcome in our patient has been excellent, care must be taken in generalizing our results to other patients with BEST1 mutations. It is possible that her vision could also have improved without any intervention. This point is illustrated by a previously reported case with adBVMD,[22] resulting from an Asp-302-Ala (D302A) BEST1 mutation. She developed a subretinal hemorrhage in association with minor blunt trauma and reduced visual acuity in the right eye at the age of 12 years and she has been followed up without any treatment in this eye for 10 years. Despite an initial moderate (20/50) visual acuity loss, on the resolution of the subretinal hemorrhage, visual acuity recovered spontaneously to 20/30 by 8 months and 20/20 −2 by 17 months even with the presence of the central fibrotic lesion with surrounding subretinal fluid. The acuity in the fellow eye of this patient when the hemorrhage occurred in the right eye was 20/20 and remained so through the recovery of the right eye to 20/20 − 2.

The ideal number of injections cannot be determined from this study, although our patient experienced significance improvement after the first three injections.

The EOG findings in our proband were consistent with a diagnosis of BVMD and with the marked compromise bestrophin-1 function in the RPE that would be expected from two missense mutations at the highly conserved codon 141.[3‑5,7,8,23,24] The R141H mutation has been characterized in vitro,[1] showing chloride channel currents reduced to approximately 20% of wild-type bestrophin-1. The fact that our proband presented with a markedly reduced but not absent light rise is consistent with the observed residual activity of the R141H mutant.[1] These findings are very similar to those reported by Schatz et al.[9] in their compound heterozygotes (Y29X/R141H) but less severe effect on retinal function than the mutations reported by Burgess et al.[1] in their series of patients with AR bestrophinopathy. In addition to that, Li et al.[4] have studied two mutations (P274R and I201T) that are associated with recessive bestrophinopathy and have found that the Ca2+-dependent Cl− current activity mediated by BEST1 is entirely absent in the former and markedly diminished in the latter.

Caution in counseling participants who carry these BEST1 variants is warranted, since it has been shown that some BEST1 mutations are responsible for late-onset clinical phenotypes that do not affect the chloride fluxes in vitro and therefore are not expected to alter the EOG in vivo.[5]}

In conclusion, we described a family, in which the proband presented with the clinical picture of adult-onset vitelliform

Figure 2: Treatment response over 15-month period illustrated the intraretinal cystic changes. First row fundus photographs, thickness map and optical coherence tomography demonstrate cystoid macular edema at presentation. The second-row images were taken after receiving the first bilateral intravitreal aflibercept injections, while the third row after receiving the second bilateral intravitreal aflibercept injections. The last row images show the treatment response demonstrated by the improvement of cystoid macular edema at a 15-months follow-up appointment

Figure 3: Color fundus photographs of both eyes showing bilateral, round subretinal yellowish deposits (vitelliform) around the arcades, first row case I: 1 (father) and bottom row case I: 2 (mother)
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The light peak of the electroretinogram is dependent on...

Clinical and genetic heterogeneity in multifocal...

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Figure 4: Pedigree chart

Differences in CME of both eyes, and reduced visual acuity, which benefited from intravitreal aflibercept injections treatment. Screening for BEST1 mutations should be performed even if the parents have normal EOG and imaging results because carriers of arBVMD mutations are asymptomatic and also devoid of the EOG changes that are typically seen in adBVMD families, even when vitelliform lesions are absent. Had we not pursued BEST1 diagnostic testing, we would have incorrectly concluded that this patient did not have BVMD, despite the presence of vitelliform lesions that were highly suggestive of the disease. Making the correct diagnosis in such cases has important implications, both now and in the future, especially when specific treatments for BVMD develop.

Patient Consent
Written consents were obtained from each patient.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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