Autosomal Recessive Best Vitelliform Macular Dystrophy

Report of a Family and Management of Early-Onset Neovascular Complications

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Objectives: To report a child with early-onset autosomal recessive Best vitelliform macular dystrophy and compound heterozygous BEST1 mutations, the management of a choroidal neovascular membrane with intravitreal bevacizumab in the proband, the benefits of amblyopia therapy in the fellow eye, and the findings in the parents, carriers of heterozygous BEST1 mutations.

Methods: A 5-year-old white girl presented with monocular visual acuity loss and bilateral vitelliform macular lesions. Her parents were also examined. Examinations included electro-oculograms (EOGs), electroretinograms, imaging studies, and BEST1 gene testing. Interventions included off-label treatment with intravitreal bevacizumab in the left eye and amblyopia therapy in the right eye.

Results: The proband presented with visual acuity of 20/200 OD with an atypical subfoveal vitelliform scar and 20/16 OS with asymptomatic vitelliform deposits. Subfoveal choroidal neovascularization developed at age 6 years, causing marked vision loss (20/200 OS). Visual acuity recovered to 20/20 OS after serial intravitreal bevacizumab injections. Amblyopia therapy improved visual acuity to 20/50 OD. The proband showed subnormal EOG Arden ratios and mild electroretinogram changes. Molecular testing showed missense BEST1 mutations (R141S and R141H) in the proband. Unlike dominant Best vitelliform macular dystrophy, in the heterozygous parents EOGs were normal and minimal autofluorescence changes were seen.

Conclusions: Choroidal neovascularization treatment with bevacizumab was associated with vision restoration. Amblyopia treatment also yielded significant benefit. Patients presenting with vitelliform lesions should be screened for BEST1 mutations, even when parents have normal EOG and imaging results.

Clinical Relevance: Prompt recognition and treatment of choroidal neovascularization and amblyopia management effectively restores vision. Awareness and recognition of recessive inheritance permits correct diagnosis and counseling.


UNTIL RECENTLY, IT WAS BELIEVED THAT Best vitelliform macular dystrophy (BVMD) was inherited only as an autosomal dominant (ad) trait. The gene responsible for BVMD is BEST1, which encodes the retinal pigment epithelium (RPE)-expressed protein bestrophin-1. Bestrophin-1 is a member of the RFP protein family found in both vertebrates and invertebrates. Bestrophins are expressed in many tissues and organs, but bestrophin-1 is expressed predominantly in the RPE, where it is believed to function either as a calcium-activated chloride channel, a regulator of intracellular calcium concentration, or both.1-5 Best vitelliform macular dystrophy is often incompletely penetrant, but asymptomatic family members who carry BEST1 mutations usually exhibit abnormalities on electro-oculography (EOG).6 The suppressed light peak of the EOG is thought to result from compromised chloride channel function of bestrophin-1 in the RPE.5,7

In 2006, Schatz et al8 reported the first documented instance in which compound heterozygosity for 2 mutations (Y29X and R141H) caused an especially severe and early-onset BVMD phenotype. In 2008, Burgess et al9 reported a series of patients with clear-cut autosomal recessive (ar) BVMD and described differences in the clinical appearance of these patients compared with patients with ad-BVMD. In brief, the distinctive features of arBVMD were reported to be subretinal or intraretinal fluid in the absence of subfoveal vitelliform lesions, disseminated punct...
tate retinal flecks, hyperopic refraction, and subnormal delayed rod- and cone-driven electroretinogram (ERG) responses. Burgess et al proposed the term autosomal recessive bestrophinopathy to characterize the presentation of these arBVMD cases and noted that the unusual case reported by Schatz et al likely was an instance of autosomal recessive bestrophinopathy as well.

Choroidal neovascularization (CNV) is a fairly uncommon complication in BVMD and other similar macular diseases. Recently, favorable short-term results of CNV treatment with intravitreal anti–vascular endothelial growth factor (VEGF) drugs have been reported in adBVMD and in other adult-onset vitelliform phenotypes linked to BEST1 mutations. Herein, we report a family with arBVMD due to BEST1 mutations in which the proband presented with early-onset atypical subfoveal vitelliform lesions complicated by CNV, the treatment of CNV with intravitreal bevacizumab (Avastin), the benefits of antiamblyopia treatment in the fellow eye, and the findings in the carrier parents.

**METHODS**

**PATIENTS**

A 5-year-old white girl (proband, case II:1) presented in August 2007 with monocular visual acuity loss and bilateral vitelliform macular lesions, complicated by CNV at age 6 years. Her parents (the father, case I:1, and the mother, case I:2), who were both asymptomatic, were also evaluated. Lastly, in the “Comment” section, the case and course of our proband is compared with a patient with adBVMD and a clinically similar vitelliform lesion to that of the right eye of our proband, who was seen before anti-VEGF drugs were available. Similarities and differences between these 2 cases will be illustrated to provide a framework for making rational and medically appropriate decisions with respect to treatment of exudative complications in BVMD.

**DIAGNOSTIC WORKUP**

In addition to a full ophthalmologic examination, examination of the proband and her parents included spectral-domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany, and Cirrus; Carl Zeiss Meditec, Dublin, California) and fundus autofluorescence (FAF) (Spectralis). International Society for Clinical Electrophysiology of Vision–standard EOGs were recorded on all subjects. International Society for Clinical Electrophysiology of Vision–standard dark-adapted rod-driven and mixed and light-adapted transient and flicker cone-driven ERGs were recorded on the proband with DTL electrodes. In our experience, these electrodes yield outcomes comparable with another non–contact lens electrode, the HK loop electrode. Intravenous fluorescein angiography was also performed with a RetCam (Massie Laboratories, Pleasanton, California) on the proband under anaesthesia at the time of 1.25-mg bevacizumab intravitreal injections, which were performed serially every month for 2 months, then every 2 to 3 months between January 2008 and December 2009.

**MOLECULAR GENETIC TESTING**

Diagnostic testing for BEST1 gene mutations was performed at the Carver Nonprofit Genetic Testing Laboratory of the University of Iowa. For this, whole blood samples were collected from the proband and her parents and shipped overnight to the laboratory, where genomic DNA was extracted, polymerase chain reaction amplified, and sequenced as previously described.

**CASE II:1 (PROBAND)**

The proband’s visual acuity by Early Treatment Diabetic Retinopathy Study charts at presentation was 20/200 OD with an atypical subfoveal vitelliform scar and 20/16 OS with asymptomatic atypical vitelliform deposits extending along the inferotemporal arcade, most clearly seen with FAF. Fundus photographs from this visit are shown in Figure 1.

At age 6 years, an EOG was performed on the proband. The Arden ratio of the EOG was 1.1 OD and 1.4 OS, which is less than the normal range (>1.65) and less than the usually accepted cutoff of 1.5 for adBVMD.
In addition, the proband’s full-field cone-driven flash ERGs were low normal in amplitude to transient stimuli (80-90 µV; normal 95% confidence interval [CI],19 70-175 µV) and normal to flicker stimuli (approximately 100 µV; normal 95% CI,19 58-142 µV) but delayed in timing, much more so to flicker stimuli (transient: right eye, 31 milliseconds; left eye, 29 milliseconds; normal 95% CI,19 26.0-29.2 milliseconds; flicker: 43 milliseconds in both eyes; normal 95% CI,19 25.8-30.7 milliseconds).19 Rod-driven and mixed ERGs were normal.

Rapid vision loss occurred in the left eye (20/200) over a period of several months following development of a subfoveal CNV at age 6 years. RetCam photographs, intravenous fluorescein angiography, SD-OCT, and FAF at this stage are shown in Figure 2. The former 2 imaging studies were obtained under anesthesia at the time rapid visual acuity loss occurred and the first bevacizumab treatment was performed. Fundus examination in the left eye was remarkable for the change in appearance of the vitelliform lesions compared with baseline (large arrow) and the presence of subretinal blood and fluid (thin arrows). Leakage at and around the foveal region was seen on intravenous fluorescein angiography (large arrows), consistent with the presence of a neovascular membrane in the left eye. During the examination under anesthesia, a progressively filling neovascular stalk could be clearly seen (not shown). The SD-OCT shown in Figure 2 (right eye, third row; left eye, fourth row) illustrate the fluid pockets (asterisks) and the vitelliform lesions (arrows), which in the left eye were accompanied by the noted clear-cut neovascular component. The FAF findings in the right eye (left) and left eye (right) of the proband are illustrated in the bottom row of Figure 2, in which areas of abnormal FAF extending well beyond the discrete subfoveal vitelliform lesions are apparent.

After serial bilateral 1.25-mg intravitreal bevacizumab injections performed under anesthesia, visual acuity returned to 20/20 OS and was maintained at 27 months of follow-up. This functional improvement in the left eye was associated with a significant reduction in retinal exudative changes and improvement in retinal microanatomy by SD-OCT criteria (Figure 3). Fluid pockets in the right eye improved but persisted (asterisks) with mild intraretinal cystic edema (arrows). In the left eye, the clinical appearance improved significantly compared with the acute CNV stage. Only a thin fluid cleft persisted temporally to the vitelliform fibrovascular lesion (thick arrows on the OCT), but the fovea (thin arrow) was attached and no intraretinal edema could be seen. Bevacizumab treatment of the right eye was performed in conjunction with amblyopia treatment (patching the left eye for 2 h/d and spectacle correction: OD, +1.25 sph +0.75 cyl ×90°; OS, +0.50 sph +0.25 cyl ×85°). Over time, visual acuity improved to 20/50 OD. Response to the treatments is shown graphically in Figure 4.

CASE I:1 (FATHER)

At age 43 years, this white male subject had an uncorrected visual acuity of 20/20 OU. He had a near normal fundus examination, except for drusenoid deposits in the left macula (Figure 5, white arrows in the scanning laser ophthalmoscope image). The OCT was normal and so was FAF, except for small, hypofluorescent spots on FAF in the left macula, which corresponded to the drusenoid deposits seen ophthalmoscopically. The Arden ratio of his EOG was 1.95 OD and 1.86 OS, which is within the normal range.21,22

CASE I:2 (MOTHER)

At age 41 years, this white female patient had an uncorrected visual acuity of 20/20 OU. Also in her case, fundus examination and OCT (Figure 5, bottom row) were normal, and FAF showed only a small, nonspecific, hypofluorescent spot in the left macula. The Arden ratio of her EOG was 3.50 OD and 2.52 OS, which too is well within the normal range. Together with the findings in the father, these results did not support the more traditional diagnosis of dominant BVMD.

MOLECULAR GENETIC TEST RESULTS

After having excluded inflammatory/infectious etiologies such as Toxoplasma, Toxocara, and lymphocytic choriomeningitis virus, diagnostic BEST1 gene testing was performed to determine whether our proband could have BVMD and, if so, whether she had a heterozygous de novo dominant mutation or a recessive form of the disease. Testing revealed compound heterozygosity of the proband (II:1) for Arg141Ser (R141S) and Arg141His (R141H) mutations and that each parent carried 1 of these 2 mutations. This confirmed the autosomal recessive hypothesis, explaining the normal EOG results in the parents.

COMMENT

Although uncommon, BVMD can occur as a recessive trait, due to biallelic BEST1 mutations.8,9 Unlike that reported by Burgess et al,9 but similar to the case reported by Schatz et al,8 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 heritability. The vitelliform phenotype remains one of the disease manifestations even when BVMD is inherited as a recessive trait.

Both dominant and recessive forms of BVMD can be complicated by CNV. These membranes can be difficult to detect because the overlying vitelliform lesions can partially or completely obscure them. The excellent long-term microanatomical and functional response of CNV in the left eye of our proband is consistent with the favorable short-term outcomes reported by others with intravitreal anti-VEGF drugs for CNV in adBVMD11,12 and in adult-onset vitelliform phenotypes linked to BEST1 mutations.13,14 Our results indicate that this treatment modality is effective also in children with arBVMD complicated by CNV.

Although the outcome in this 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 have in part improved also without intervention. This point is illustrated by a previously reported case...
Figure 2. Imaging findings in the proband at the time of choroidal neovascularization development. First and second row: RetCam (Massie Laboratories, Pleasanton, California) color photographs (large arrow indicates change in appearance of vitelliform lesion; thin arrow, the presence of subretinal blood and fluid) and fluorescein angiograms (large arrows indicate leakage at and around the foveal region; thin arrows, the presence of subretinal blood and fluid). Third (right eye) and fourth (left eye) row: Spectral-domain optical coherence tomography. Red-free scanning laser ophthalmoscope images are presented to show where scans 1 to 3 were performed (green lines). Asterisks indicate fluid pockets; arrows, vitelliform lesions. Bottom row: Fundus autofluorescence. The left image shows the right eye and the right image, the left eye. Arrows indicate abnormal areas.
with adBVMD, 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 resolution of the subretinal hemorrhage, visual acuity recovered spontaneously to 20/30 by 8 months and to 20/20−2 by 17 months in spite of the central fibrotic lesion with surrounding subretinal fluid. The fundus appearance and SD-OCT findings of this 22-year-old patient at the last follow-up were undistinguishable from the right eye at presentation in our proband. The acuity in the fellow eye of this patient when the hemorrhage occurred in the right eye was 20/20 and remained so through recovery of the right eye to 20/20−2.

Although there was no history of trauma in our proband to account for the subfoveal fibrotic and exudative lesion in the right eye and, therefore, the process that led to the formation of the observed changes was likely different, the lesion that developed in the patient with adBVMD with the D302A mutation resembled closely the finding in the right eye of our proband at presentation. Visual acuity in this eye remained 20/20 during the 10-year follow-up without treatment. Thus, in adBVMD, atypical stalklike vitelliform lesions such as those in the right eye of our case can develop also in conjunction with posttraumatic hemorrhage, and not necessarily CNV, and can be associated with spontaneous improvement and a fairly good functional prognosis.

Of course, there are important distinctive features between our proband and the adBVMD case with the D302A mutation. First, the latter developed her subretinal hemorrhage, and not CNV, prior to the availability of anti-VEGF treatment. Today, given the apparent safety of intravitreal bevacizumab, it would certainly be inappropriate to recommend observation alone in a patient with an angiographically confirmed CNV and a documented, rapid loss of vision in her better eye coincident with the development of the CNV. Still, the excellent outcome in the patient reported by Chung et al23 reminds us that some patients with hemorrhagic complications from BVMD can do well with observation alone. Therefore, documentation of CNV is essential to recommend intravitreal anti-VEGF treatment. Second, unlike our proband who presented with profound visual loss in the right eye early on and experienced equally profound and rapid acuity loss in the left eye shortly thereafter, the patient with adBVMD discussed herein developed only a moderate degree of visual acuity loss in the right eye when the left eye was still 20/20 and at an age when the visual development of the patient was complete. Waiting for spontaneous resolution of the subretinal fluid in our young proband carried the added risk of vision loss from amblyopia and provided a strong argument for intervention as opposed to observation. We propose that when at least 2 of the 3 features seen in the proband (angiographic evidence of a CNV and/or presence of new blood, rapid decline in visual acuity, and reduced vision in the fellow eye) are present then treatment with an intravitreal anti-VEGF drug is entirely appropriate. The ideal number of injections cannot be determined from this study, although our patient experienced the majority of her improvement after the first 3 injections.

Important to the discussion of intervention in these cases, adjunctive amblyopia treatment in the right eye, the worst eye at presentation in our proband, afforded additional visual acuity recovery, despite sizable subfoveal atypical vitelliform lesions also associated with exudative phenomena. This is consistent with the good outcome experienced, at a later age, in the presence of a
similar lesion by the adBVMD case. These results indicate that amblyopia treatment should also be pursued in these patients and that one should not assume that the presence of subfoveal lesions and/or of exudative complications precludes functional recovery. To this end, while the fluid reduction that occurred in the right eye following intravitreal bevacizumab injections may have made a contribution to improvement in visual acuity, it seems prudent to conclude that the majority of the improvement in acuity in the right eye of this child was due to amblyopia treatment. Therefore, when lesions of this type are seen in a child, amblyopia treatment alone may be the most appropriate course of action when acuity loss is not recent and/or clear angiographic evidence of active CNV is not present.

The EOG findings in our proband were consistent with a diagnosis of BVMD and with the marked compromise of bestrophin-1 function in the RPE that would be expected from 2 missense mutations at the highly conserved codon 141. The R141H mutation has been characterized in vitro, 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. The proband presented also with cone ERG changes, consistent with a mild, generalized adverse effect on retinal cone function secondary to the primary RPE defect in bestrophin-1. These findings are very similar to those reported by Schatz et al in their compound heterozygotes (Y29X/R141H) but less severe an effect on retinal function than the mutations reported by Burgess et al in their series of patients with autosomal recessive bestrophinopathy.

In our family, neither the R141S nor the R141H mutation exerted an overt phenotypic effect by itself and were associated with normal EOG results, as reported by Schatz et al in a carrier of the R141H mutation. This is also consistent with the observation that, when cotransfected with wild-type bestrophin-1, R141H exerts only a modest reduction (approximately ~20%) in chloride conductance. This behavior is unlike the dominant negative effect exhibited by mutations that cause adBVMD. It is not clear whether carriers of recessive mutations like the R141H and R141S reported herein may be prone to developing late-onset vitelliform maculopathies or other retinal phenotypes or not. Caution in counseling subjects who carry these BEST1 variants seems warranted, since it has been shown that some BEST1 mutations responsible for late-onset clinical phenotypes do not affect the chloride fluxes in vitro and, therefore, are not expected to alter the EOG in vivo.

In conclusion, we described a family in which the proband presented with the clinical picture of early-onset vitelliform lesions, monocular CNV, and visual acuity loss, which benefited from intravitreal bevacizumab injections and amblyopia treatment. Screening for BEST1 mutations should be performed even if the parents have normal EOG and imaging results because carriers of arBVMD mutations are not only asymptomatic but also devoid of the EOG changes that are, instead, typically seen in adBVMD families, even when vitelliform lesions are absent. Had we not pursued BEST1 diagnostic testing despite the normalcy of EOG testing in the parents, we would have incorrectly concluded that this child did not have BVMD, despite the presence of vitelliform lesions that were highly suggestive of the disease. Making the cor-

Figure 5. Scanning laser ophthalmoscope fundus image, spectral-domain optical coherence tomography, and fundus autofluorescence findings in the parents (case I:1, father, top row; case I:2, mother, bottom row). The green lines in the scanning laser ophthalmoscope images show the location of the spectral-domain optical coherence tomography scans. Thick arrows indicate drusenoid deposits; thin arrow, a small, nonspecific, hypofluorescent spot in the left macula.
rect diagnosis in such cases has important implications, both now and in the future, when specific treatments for BVMD may be developed.

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Additional Information: All ophthalmologic diagnostic procedures were performed in a standard university-based practice setting as part of routine patient care and conformed to university-wide rules, Health Insurance Portability and Accountability Act rules, and the Declaration of Helsinki. No institutional review board approval was necessary because no research procedure was performed on this patient. The investigation and publication of genotype-phenotype correlation data are approved by the University of Tennessee Health Science Center institutional review board under protocol 6657.

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