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Optical Coherence Tomography Examination of the Retinal Pigment Epithelium in Best Vitelliform Macular Dystrophy

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Purpose: To describe the anatomic changes and natural history of vitelliform lesions in Best vitelliform macular dystrophy (BVMD) using spectral-domain optical coherence tomography (OCT).

Design: Prospective comparative case series.

Participants: Twenty patients (40 eyes) with molecular confirmation of mutation in the *BEST1* gene and 20 age-matched controls were included.

Methods: Color fundus photographs, fundus autofluorescence, and spectral-domain OCT were obtained, and these findings were compared between the 2 groups. Fifteen of the 20 patients with Best disease had more than 1 visit, and the imaging studies from each visit were compared with each other over time.

Main Outcome Measures: Evolution of visual acuity and clinical stage of BVMD correlated to OCT measurement parameters, including retinal pigment epithelium (RPE) thickness, central macular thickness, and integrity of the ellipsoid zone.

Results: Patients with BVMD demonstrated progressive disorganization and thinning of the submacular RPE on OCT when compared with normal controls. Concurrent with the appearance of "egg-yolk lesions," the OCT showed a cleft in the outer retina, creating an apical and basal separation of retinal layers. The apical complex of the vitelliform lesion eventually degenerated and flattened. Patients with such lesions nevertheless maintained reasonable visual acuity into the advanced vitelleruptive stages despite the disruption of normal anatomic changes.

Conclusions: Our study suggests that in BVMD, subretinal vitelliform material accumulation leads to a clear separation of the outer retinal layers. The level at which this cleft forms is a topic of discussion and interest, with the most likely levels of least resistance being the interdigitation zone or between the RPE and the Bruch's membrane. It is possible that RPE may continue to form a preserved photoreceptor-RPE complex that provides essential nutrients to the photoreceptors and in turn helps patients maintain better than expected visual acuity for years. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

Supplementary video available online at www.aaojournal.org.

Best vitelliform macular dystrophy (BVMD), also known as "Best disease," is due to a mutation located on chromosome 11q12-q13 in the *BEST1* gene.[1–8] The presentation is variable but often is characterized by expression of localized yellowish subretinal material, called "lipofuscin," that accumulates at the level of the retinal pigment epithelium (RPE).[5,9–14] Clinical diagnosis can be confirmed by an electrooculogram (EOG), which measures the standing potential of the RPE.[12,15–17] Best disease is an autosomal-dominant and, rarely, autosomal-recessive disease, and can be best confirmed by pedigree and mutational analysis. The 2 forms of genetic inheritance present differently. Autosomal recessive disease often leads to a more panretinal phenotype with multifocal vitelliform lesions and subretinal fluid collection.[18–22] We will be discussing the dominant form of the disease exclusively.

The disease evolves in clinical appearance over time, and various classifications have been described. The earliest lesion presents with normal to subtle RPE changes. This is followed by the vitelliform phase with what has been called an "egg-yolk lesion." A pseudohypopyon occurs when the gravitational drift of material in the subretinal space creates the appearance of fluid layering in the lesion. The vitelleruptive phase gives rise to an appearance akin to scrambled eggs when the subretinal material further disintegrates, forming clumps of yellowish material.[3,8,17,23–26] This eventually leads to atrophy and fibrotic scarring.[3] Acute hemorrhage, either isolated or in association with choroidal neovascularization (CNV), also may occur at this time. Subretinal hemorrhage in BVMD often simulates the appearance of scar tissue. These focal scar nodules have a relatively good prognosis and may resolve without

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permanent damage when treated or observed.[27,28] There is similarity in presentation between these lesions and CNV. These can be distinguished from true CNV by a lack of response to treatment with intravitreal anti−vascular endothelial growth factor agents or oral acetazolamide and absence of leakage on fluorescein angiography. This is a key point at which anti−vascular endothelial growth factor treatment may be effective in maintaining better vision in the 10% to 20% of cases among whom true CNV does arise.[3]

Multimodal imaging including fundus photography, fundus autofluorescence, fluorescein angiography, and optical coherence tomography (OCT) was used to provide further insight into the mechanism of these lesions. In particular, OCT imaging of vitelliform lesions has achieved greater resolution and has become the tool of choice for following macular structure in vitelliform lesions over the past few years.[29,30] It was previously postulated that the materials within the lesion are shed photoreceptor outer segments that accumulate over time because a lack of apposition between the retina and RPE decreases its phagocytosis turnover rate.[25,31−35] In this study, we focused on the analysis of serial OCT scans of a cohort of patients at different stages of Best disease, focusing particularly on the evolution of RPE anatomic changes with advancing disease.

Methods

Twenty patients with BVMD who met our inclusion criteria were identified and included. They had (1) clinically visible vitelliform lesion; (2) confirmed molecular testing for mutations of the *BEST1* gene; and (3) an abnormal Arden ratio (<1.5) on EOG performed according to the protocol approved by the International Society for Clinical Electrophysiology of Vision.[36] All other patients who did not fulfill any one of these criteria were excluded from the cohort. The only exception allowed was for younger children who could not undergo an EOG. Genetic sequencing analysis for the *BEST1* mutation was performed on all patients through a Clinical Laboratory Improvement Amendments−certified laboratory using Sanger sequencing. All mutations found had been previously reported and were predicted to be deleterious by nonclinical computer-based algorithms Sorting Intolerant from Tolerant and Polymorphism Phenotyping. The study was approved by the Medical Ethical Committee of the University of Michigan and conformed to the tenets of the Declaration of Helsinki. All patients were examined in the clinic, and the clinical stage of their vitelliform lesion was recorded. Imaging was performed at each visit using fundus photography (Topcon Medical Systems, Paramus, NJ), fundus autofluorescence, and OCT. A fluorescein angiogram was obtained if there was a suspicion for CNV.

Fundus autofluorescence was performed using previously described techniques with a fundus camera and bandpass filter for excitation centered at 488 nm and a matched barrier filter centered at 500 nm (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany).[37] The OCT volume scans (Spectralis HRA-OCT; Heidelberg Engineering) were obtained centered on the macula with 250 B-scans covering a linear fundus area measuring 30° in both horizontal and vertical orientations acquired. Additional postprocessing OCT measurements were made as follows: After the conventional anatomy was determined by the International Nomenclature for OCT, 3 distinct bands were recognized and identified at the level of the central-fovea scan: the external limiting membrane, ellipsoid zone, and RPE/Bruch's basement membrane. Although the measurements were taken only on the central OCT scan going through the fovea, we followed the sequential OCT scans over the entire macular area and the contour of each retinal layer. Thus, this gave us enough detail to differentiate the superior limits of the RPE from the overlying interdigitation zone. The RPE and Bruch's membrane often are indistinguishable from each other on OCT and are often referred to together as a complex. Thus, we will use the terms "RPE" and "RPE−Bruch's membrane complex" interchangeably unless otherwise stated. By using the Heidelberg Spectralis program in both white-over-black and black-over-white images, measurements of the RPE−Bruch's membrane complex thickness were performed within the center of the vitelliform lesion and 500 μm outside the nasal and temporal borders of the vitelliform lesion using the built-in caliper in the Heidelberg analysis software (Fig 1). All measurements were performed under the highest magnification of the image possible. The temporal and nasal borders of the lesion were identified on the 2-dimensional horizontal OCT scan passing through the foveal center. These were defined on OCT as the boundary zone delineating the end of perturbed and elevated retinal anatomy produced by the subretinal vitelliform deposition and of normal retinal anatomy with normal apposition of all retinal layers. The distance of 500 μm from the center of the lesion or fovea was chosen to allow measurement and comparison between patients in an area of retina outside the lesion that was devoid of any influence from the possible centrifugal spread of the vitelliform lesion. The status of the ellipsoid zone (labeled categorically as intact, partial, absent) was determined at each visit. The automated central macular thickness measurements, generated using a 19-horizontal-line protocol (6×6-mm area), each consisting of 1024 A-scans per line, were recorded (Spectralis Acquisition and Viewing Modules, version 6.3.4.0; Heidelberg Engineering). We used the same protocol and parameters and obtained measurements from a group of 20 age-matched patients with normal OCT scans for comparison. All normal controls had no history of retinal diseases or glaucoma. They were normal on clinical eye examination, and all had a vision of 20/20 or better.

Statistical calculations were performed in Microsoft Excel (Microsoft, Redmond, WA). The RPE−Bruch's membrane complex thickness differences between groups of patients were analyzed using a paired *t* test. Univariate statistical analysis with statistical analysis with single-factor analysis of variance was performed to assess the influence of disease stage on RPE−Bruch's

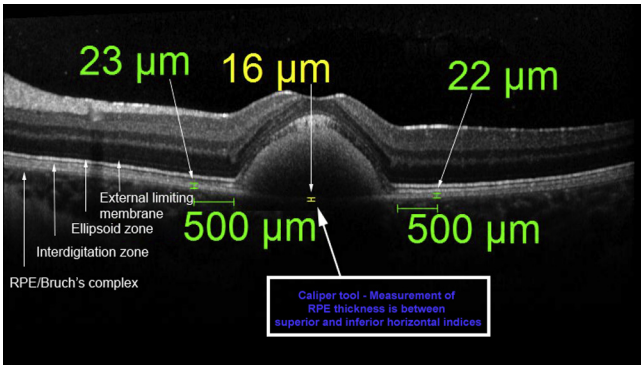

Figure 1. Algorithm for measurement of subfoveal retinal pigment epithelium (RPE) thickness and 500 μm from the nasal and temporal borders of the lesion. The RPE thickness was measured using the "Caliper Tool" built in the Heidelberg analysis software (Heidelberg Engineering, Heidelberg, Germany); the measurement is between the superior and inferior horizontal indices.