Near-Infrared Fundus Autofluorescence in Subclinical Best Vitelliform Macular Dystrophy

MAURIZIO BATTAGLIA PARODI, PIERLUIGI IACONO, CLAUDIA DEL TURCO, AND FRANCESCO BANDELLO

• PURPOSE: To describe fundus autofluorescence (FAF) on short-wavelength FAF and near-infrared FAF in the subclinical form of Best vitelliform macular dystrophy.
• DESIGN: Cross-sectional prospective study.
• METHODS: Patients affected by the subclinical form of Best vitelliform macular dystrophy (positive testing for *BEST1* gene mutation, fully preserved best-corrected visual acuity, normal fundus appearance) were recruited. Each patient underwent a complete ophthalmologic examination, including electro-oculogram (EOG), short-wavelength FAF, near-infrared FAF, spectral-domain OCT (SD OCT), and microperimetry. Main outcome measure was the identification of abnormal FAF patterns.
• RESULTS: Forty-six patients showing mutations in the *BEST1* gene were examined. Forty patients presented a bilateral Best vitelliform macular dystrophy, 2 patients showed a unilateral Best vitelliform macular dystrophy, and 4 patients had a bilateral subclinical form. Patients with the unilateral form (2 eyes) and patients with the subclinical form (8 eyes) were analyzed. Three BEST1 sequence variants were identified: c.73C>T (p.Arg25Trp), c.28G>A (p.Ala10Thr), and c.652C>G (p.Arg218Gly). Short-wavelength FAF was normal in all eyes. Near-infrared FAF detected a pattern consisting of a central hypo-autofluorescence surrounded by a round area of hyper-autofluorescence. A bilateral reduced EOG response was detected in 1 patient. SD OCT revealed a thicker, well-defined, and more reflective interdigitation zone in 2 patients (4 eyes, 40%). Microperimetry of the central 10 degrees revealed a slight, diffuse reduction of retinal sensitivity. Mean retinal sensitivity within the central 2 and 4 degrees was lower and matched the hypo-autofluorescent area detected on near-infrared FAF. Additional relative scotomata were detected within the 10-degree area. No change in clinical, functional, or FAF pattern was found over the follow-up.
• CONCLUSIONS: Subclinical Best vitelliform macular dystrophy is characterized by the absence of biomicroscopic fundus abnormality and fully preserved visual acuity, but shows an abnormal near-infrared FAF pattern, with central hypo-autofluorescence. (Am J Ophthalmol 2014;158:1247–1252. © 2014 by Elsevier Inc. All rights reserved.)

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From the Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy (M.B.P., C.D.T., F.B.); and Fondazione G. B. Bietti per l'Oftalmologia, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy (P.I.).

Inquiries to Pierluigi Iacono, Fondazione G. B. Bietti per l'Oftalmologia, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Via Livenza 3, Rome, Italy; e-mail: pierluigi.iacono@libero.it

BEST VITELLIFORM MACULAR DYSTROPHY IS AN early-onset autosomal dominant dystrophy[1] determined by mutations in the bestrophin gene (*BEST1* gene, formerly known as *VMD2*) on chromosome 11q13.[2] Best vitelliform macular dystrophy is clinically characterized by large bilateral deposits of lipofuscin-like material in the subretinal space, with a typical phenotypic manifestation taking the form of a vitelliform macular lesion evolving gradually into more advanced stages.[3–7]

Data are scarce regarding subclinical forms of Best vitelliform macular dystrophy, which carry mutations in the *BEST1* gene and are characterized by the absence of biomicroscopic fundus abnormality in association with preserved visual functions.[8–10] Electro-oculogram (EOG) examinations and optical coherence tomography (OCT) have detected alterations in a subset of patients,[8–10] but no specific study has been performed to identify anomalous subclinical Best vitelliform macular dystrophy patterns on fundus autofluorescence (FAF).

The aim of the present study is therefore to describe the FAF patterns on both short-wavelength FAF and near-infrared FAF in eyes affected by subclinical Best vitelliform macular dystrophy.

METHODS

ALL FAMILIES AFFECTED BY BEST VITELLIFORM MACULAR dystrophy referred for clinical evaluation were recruited consecutively for a cross-sectional prospective study. Written informed consent was obtained from all subjects. The protocol was approved by the Institutional Review Board of Ospedale San Raffaele and the procedures adhered to the tenets of the Declaration of Helsinki.

Both affected and unaffected relatives were screened for the *BEST1* mutation and underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA) determined by ETDRS charts, biomicroscopic examination, EOG, short-wavelength FAF, near-infrared FAF, spectral-domain OCT (SD OCT), and microperimetry.

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TABLE 1. Clinical Findings in Patients With Subclinical Best Vitelliform Macular Dystrophy

Case	Patient Age/Sex	Eye Involvement	Variant	BCVA	EOG	OCT
1	12/M	Monolateral	c.73C>T	20/20	2.45	Normal
2	45/F	Monolateral	c28G>A	20/20	2.40	Normal
3 (OD)	53/M	Bilateral	c.652C>G	20/20	1.12	Thickened IZ
3 (OS)				20/20	1.15	Thickened IZ
4 (OD)	56/M	Bilateral	c.652C>G	20/20	2.35	Thickened IZ
4 (OS)				20/20	2.45	Thickened IZ
5 (OD)	60/F	Bilateral	c.73C>T	20/20	2.84	Normal
5 (OS)				20/20	2.70	Normal
6 (OD)	26/F	Bilateral	c.73C>T	20/20	3.22	Normal
6 (OS)				20/20	3.45	Normal

BCVA = best-corrected visual acuity; EOG = electro-oculogram; IZ = interdigitation zone; OCT = optical coherence tomography.

The key features for the diagnosis of subclinical forms of Best vitelliform macular dystrophy were the absence of any symptoms and the normal appearance of the macula. A control group of 10 healthy subjects without any ocular pathology underwent the same ophthalmologic examinations, providing the standard values for each test.

FAF readings were obtained using a confocal scanning laser ophthalmoscope (Heidelberg Retinal Angiograph 2; Heidelberg Engineering, Heidelberg, Germany). Near-infrared FAF imaging was carried out using a diode laser at 787 nm wavelength for excitation and a barrier filter for detection of emitted light above 810 nm. Short-wavelength FAF images of ocular fundi were obtained at an excitation wavelength of 488 nm, and a barrier filter of 500 nm was used for the detection of emitted light. One hundred single images were averaged to obtain a high-quality image for both short-wavelength FAF and near-infrared FAF. BCVA was assessed on standard ETDRS charts at a distance of 4 meters by an examiner unaware of the purpose of the study.

SD OCT was carried out using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) by means of a 7-line raster scan centered on the fovea. All scans were positioned within the macular area and throughout the fovea, based on the findings of color fundus photography and FAF.

Two examiners well trained in AF evaluation and masked to the purpose of the investigation evaluated the SD OCT, short-wavelength FAF, and near-infrared FAF images independently. Divergent interpretations were discussed with a third senior examiner.

Microperimetry was performed by means of the MP-1 Microperimeter (Nidek Technologies, Padua, Italy), using the Goldmann III stimulus on a white background at 4 Asb. Automatic static perimetry was carried out in the examinations in a 4-2 double-staircase strategy, using fovea-centered pattern stimulations 10 degrees wide with a stimulation time of 200 ms.

Arden ratios under 1.5 were regarded as abnormally low, those over 2.0 were taken as normal, and those between 1.5 and 2.0 were considered borderline.[11]

The primary outcome of the study was the identification of abnormal FAF patterns. Secondary outcome measures included the detection of alterations on microperimetry, SD OCT, and EOG.

RESULTS

FORTY-SIX PATIENTS (18 FAMILIES) SHOWING MUTATIONS in the *BEST1* gene were examined. Forty patients presented a bilateral Best vitelliform macular dystrophy, 2 patients showed a unilateral Best vitelliform macular dystrophy, and 4 patients had a subclinical form. More specifically, the study included 10 eyes (the 2 clinically unaffected eyes of the 2 patients with unilateral Best vitelliform macular dystrophy and the 8 eyes of the 4 patients with a subclinical form). All 10 eyes had a BCVA of 20/20, a normal anterior segment, and normal fundus appearance (Table 1).

Three *BEST1* sequence variants were identified in patients affected by subclinical Best vitelliform macular dystrophy, including c.73C>T (p.Arg25Trp), c.28G>A (p.Ala10Thr), and c.652C>G (p.Arg218Gly). Mean age was 42 ± 19, and 3 patients were female.

The control group included 10 patients (mean age of 41 ± 18, 3 female), showing mean BCVA of 20/20, normal short-wavelength FAF, normal near-infrared FAF, normal OCT, normal EOG, and normal microperimetric responses.

The examination of the 10 eyes with subclinical Best vitelliform macular dystrophy revealed a normal response on short-wavelength FAF in all eyes, whereas near-infrared FAF detected a specific pattern characterized by a central hypo-autofluorescence surrounded by a circular area of hyper-autofluorescence (Figures 1 and 2). The 2 examiners were in perfect agreement in all cases in their assessments of the short-wavelength FAF and the near-infrared FAF. EOG response was within the normal range in all eyes with subclinical Best vitelliform macular dystrophy, except 2 eyes of a single patient (2 out of 10 eyes, 20%), which had a light peak–to–dark trough ratio of 1.12. SD OCT revealed that 4 eyes of 2 patients (4 out of 10 eyes, 40%) had a thicker, well-defined, and more reflective interdigitation zone, corresponding to the hyperreflective zone lying anterior to the retinal pigment epithelium complex (Figure 2).

Microperimetry of the central 10 degrees revealed a slight but diffuse reduction of retinal sensitivity in the eyes affected by subclinical Best vitelliform macular dystrophy compared with the control group (Table 2). Mean