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Nathalie Puche, Giuseppe Querques, Nathanel Benhamou, Sarah Tick, Gerard Mimoun, et al.. High-resolution spectral-domain optical coherence tomography (SD OCT) features in adult onset foveomacular vitelliform dystrophy. British Journal of Ophthalmology, 2010, 94 (9), pp.1190. 10.1136/bjo.2009.175075 . hal-00557353

HAL Id: hal-00557353

<https://hal.science/hal-00557353>

Submitted on 19 Jan 2011

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**High-resolution spectral-domain optical coherence tomography (SD OCT)
features in adult onset foveomacular vitelliform dystrophy**

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The authors have no proprietary interest in the materials used in this study.

Keywords: Adult onset foveomacular vitelliform dystrophy; Best disease; high
resolution; spectral domain optical coherence tomography; vitelliform macular
dystrophy.

Abstract

Purpose: To describe the different morphological features in adult onset foveomacular vitelliform dystrophy (AOFVD) using high-resolution spectral-domain optical coherence tomography (SD OCT).

Design: Prospective observational cases series.

Methods: Complete ophthalmologic examination, including SD OCT, was performed in 49 consecutive AOFVD patients (60 eyes).

Results: In 28/60 eyes, SD OCT showed hyperreflective clumps within the outer plexiform and outer nuclear layers. In 9/60 eyes, the photoreceptors inner /outer segments (IS/OS) interface appeared highly reflective like a shell all around the vitelliform material, and appeared irregular and discontinued in 27/60 eyes. The Verhoeff membrane (VM) was clearly visible at the border of the lesion, disappeared over the vitelliform lesion in 20/60 eyes, became thickened and less defined on the outer aspect of the lesion in 11/60 eyes, appeared without noticeable alterations in 10/60 eyes, and not well defined in 19/60 eyes. The vitelliform material appeared as a highly reflective dome-shaped lesion (homogeneous in 14/60 eyes and heterogeneous in 36/60 eyes) located between the photoreceptor layer and the retinal pigment epithelium (RPE). In 10/60 eyes the macular lesion appeared hypo/a-reflective. The RPE appeared irregular in 14/60 eyes, with hyperreflective mottling on its inner aspect. We observed discrete RPE detachments in 29/60 eyes.

Conclusions: We hypothesize that early changes involve the layer between RPE and IS/OS interface, first with vitelliform material accumulation beneath the sensory retina, and then with IS/OS alterations, pigments migration towards inner layers, and

fluid accumulation. These changes come with RPE alterations such as hypertrophy or sub-RPE deposits.

Introduction

Adult-onset foveomacular vitelliform dystrophy (AOFVD) is a relatively uncommon macular disease first described by Gass in 1974¹⁻². The disease in its classic presentation starts between the fourth and sixth decade. Fundus examination shows a subretinal oval or round elevated deposit of yellowish material, located in the macular area, and often centered by a pigmented spot. Transmission is autosomal dominant with variable penetrance resulting in highly variable phenotypic expressions³.

The exact location of the vitelliform material in AOFVD has not been fully elucidated yet neither by clinical or histological descriptions¹⁻⁷. Using different generations of optical coherence tomography (OCT), several authors have tried to answer this question but studies vary in their interpretations of the abnormal lipofuscin deposit location⁸⁻¹¹. Using the first generation OCT, Benhamou et al⁸ suggested that the vitelliform material was located between the sensory retina and the retinal pigment epithelium (RPE). Recently, these findings were confirmed using the third generation time-domain OCT, locating the vitelliform accumulation between the junction of the photoreceptor inner and outer segments (IS/OS interface) and the RPE/choriocapillaris complex¹¹. Conversely, Pierro et al showed, using time-domain OCT, a sub-RPE vitelliform deposit in AOFVD and vitelliform macular dystrophy (VMD).

Compared to time-domain optical coherence tomography, spectral-domain OCT (SD OCT) technology improves resolution. Combination of scanning laser ophtalmoscopy and SD OCT with real-time eye tracking technology allows orientating

precisely the scan towards the region of interest¹². Our purpose was to analyze AOFVD morphologic features using high-resolution SD OCT.

Patients and Methods

All consecutive patients evaluated in our Department with AOFVD diagnosis were prospectively included in this study from May 2008 through April 2009. Diagnosis of AOFVD was based on the clinical appearance and fundus autofluorescence (AF) findings; no genetic testing was performed on this population. Informed consent was obtained according to a Paris XII University Institutional Review Board–approved protocol, in agreement with the Declaration of Helsinki. All patients underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA) at 4 m with standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts, fundus biomicroscopy, color photography of the fundus (Canon 60 fundus camera, Tokyo, Japan; Topcon TRC-50 retinal camera, Tokyo, Japan), infrared (IR) reflectance images, FAF images, and fluorescein angiography (FA). The minimal criteria for AOFVD diagnosis were the presence of a macular round, yellowish, more or less homogeneous lesion at fundus examination, showing hyperautofluorescence, associated or not with a central spot of hyperpigmentation. Exclusion criteria were signs of CNV or subretinal fibrosis, or any other retinal disease in the study eye such as diabetic retinopathy, epiretinal membrane, or macular hole. Patients presenting a central spot of hyperpigmentation surrounded by a depigmentation halo without hyperautofluorescence were not included in this study. Simultaneous recording of SD OCT and digital infrared imaging (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) was performed for each included eye. Examination field size was 30x30 degrees and frequency of image acquisition was up to 9 images/second. At least 3 horizontal lines

scans were placed into the lesion area (superior, middle and inferior). Additional 3 vertical lines scans were performed in case of a large lesion (superior than 0,5 disc diameters). SD OCT scans were proportionally magnified for a better visualization of intraretinal changes. The retinal layer structure observed in OCT images were described, analyzed and interpreted, by NP, GQ and ES.

SD OCT examination highlights reflectivity differences within the human retina layers. SD OCT scans of the retina show bands that seem to correspond to the anatomic layers of the human retina, but no strict correlation with histology have been demonstrated so far. However, to describe SD OCT images, the following correspondence has been applied to the outer retinal layers (FIGURE 1): the innermost band reflects the external limiting membrane (ELM); a second band corresponds to photoreceptor inner /outer segments (IS/OS) interface; a third band represents the Verhoeff membrane (VM); and the most external band, corresponds to RPE/Bruch's membrane complex.

Statistical calculations were performed using STATA 10 MP for MacOs X. In this cross sectional study we analyzed the functional and SD OCT characteristics in all consecutive patients that presented in our Department with AOFVD diagnosis, over a 12-month period. The analysis of variance test (ANOVA) was used to assess the influence of patient's demographic factors and type of SD OCT lesions on BCVA converted to the logarithm of the minimum angle of resolution (logMAR) units. Comparisons of specific SD OCT features were performed using the χ^2 test. The chosen level of statistical significance was $p < .05$.

Results

Patient demographics and fundoscopic/FA macular characteristics

Four of the 64 eyes originally examined were excluded: 3 because of CNVs (one harboured an active CNV, one showed an atrophic scar after photocoagulation, and one had undergone intravitreal injections of ranibuzimab), and 1 had an epiretinal membrane; therefore, a total of 60 eyes from 49 consecutive patients (29 male and 20 female) were finally included in this study (table 1). Age at presentation ranged from 44 to 91 years. Macular lesions were bilateral in 11 patients. BCVA ranged from 20/20 to 20/400 (mean 20/50). Lesions were centered in the fovea in 56/60 eyes, and were extrafoveolar in 4/60 eyes. AOFVD lesions were associated with soft drusen in 19 cases and basal laminar drusen in two. Pigmented spots were observed in 19/60 eyes. On early phases of FA, we observed in all eyes, an early hypofluorescence corresponding to the vitelliform lesion area; late FA phases showed a central staining of variable intensity, without leakage.

Spectral-domain optical coherence tomography

We analyzed macular SD OCT scans passing by and at the borders of the vitelliform lesions. No abnormality on SD OCT scans was found outside the vitelliform lesions for all of the 60 eyes. By analyzing OCT scans, layer by layer, we observed the following features:

1) In 28/60 eyes, SD OCT showed hyperreflective clumps within the outer plexiform and outer nuclear layers (FIGURE 2). In 3 / 28 eyes, large lesions within the outer plexiform and outer nuclear layers were associated with pigmented spots on fundus biomicroscopy and FA (FIGURE 2 C). In 4 / 28 eyes, the hyperelective clumps disrupted the external limiting membrane continuity (FIGURE 2 D).

2) In 9/60 eyes, the IS/OS interface appeared highly reflective like a shell all around the vitelliform material (FIGURE 3 A). The IS/OS interface appeared irregular and discontinued in 27/60 eyes (FIGURE 3 B).

3) The VM, the optical layer between the RPE and the photoreceptor IS/OS interface¹², was clearly visible at the border of the lesion. It disappeared over the vitelliform deposit in 20/60 eyes (FIGURE 4 A), or became thickened and less defined on the outer aspect of the lesion in 11/60 eyes (FIGURE 4 B). The VM appeared without noticeable alterations in 10/60 eyes, and was not well defined in 19/60 eyes.

4) SD OCT showed the vitelliform material as a highly reflective dome-shaped lesion located between the photoreceptor layer and RPE. The vitelliform material appeared homogeneous in 14/60 eyes (FIGURE 5 A) and heterogeneous in 36/60 eyes (FIGURE 5 B and C). In 10/60 eyes, the macular lesion was hypo/a-reflective, and no hyperreflective material was observed within the macula. The interface between the vitelliform material and photoreceptor layer seemed well defined, with a vitelliform material located beneath the hyperreflective IS/OS interface (FIGURE 6 A). In addition, we observed an optically empty zone between the photoreceptor layer and the material and/or the RPE layer, within the hyperreflective vitelliform lesion in 29/60 eyes (FIGURE 6 B).

5) The RPE appeared irregular in 14/60 eyes, with hyperreflective mottling on its inner aspect (FIGURE 5B). We observed discrete RPE detachments harboring a “wave” shape in 29/60 eyes. The sub-RPE space appeared hyporefective in all eyes (FIGURE 7).

No association existed between patients demographics, BCVA and the type of SD OCT lesion ($p>.05$). Comparisons (cross sectional analysis) of specific SD OCT features (table 1) were not statistically significant ($p>.05$).

Discussion

The goal of this study was to describe the spectrum of morphological changes in AOFVD using high- resolution SD OCT. Analysis of high-resolution images provided new informations on location and reflectivity of the vitelliform lesions. This prospective study brought new data on OCT features in AOFVD.

First, we described hyperreflective clumps within the inner retinal layers in 28/60 eyes and we could hypothesize that these clumps have probably migrated from the outer retinal layers. Retinal changes in SD OCT scans may be correlated with findings reported in histological studies in AOFVD eyes⁷. In our study, the hyperreflective clumps within the outer plexiform and outer nuclear layers seem to disrupt the external limiting membrane. Dubovy et al⁶ in a clinic-pathological description reported that pigment-laden cells migrate into the outer retina by breaking the external limiting membrane. In our cases, hyperelective clumps within the outer retina could correspond to migrated pigment-laden cells into the outer retina.

Secondly, IS/OS interface appeared highly reflective, showing a shell-like aspect all around the vitelliform material in 27/60 eyes. The highly reflective IS/OS interface, which gives the aspect of a shell all around the vitelliform material, is more difficult to interpret and may even represent an optical artifact due to the elevated dome-shaped lesions. Alternatively, as reported by Arnold et al⁷ in a clinico-pathological study of AOFVD eyes showing stunted IS, it may represent a sign of photoreceptor cells dysfunction.

Thirdly, VM was well defined at the lesion border, but over the vitelliform lesion it disappeared in 20/60 eyes or became thickened and less defined on the outer aspect of the lesion in 11/60 eyes. VM granularity or disappearance may be explained by the clinico-pathological report by Arnold et al⁷ showing, in 3 AOFVD cases, the RPE cells that progressively lose their microvilli, as well as the progressive photoreceptor disintegration responsible for subretinal debris accumulation.

Fourthly, the vitelliform material appeared heterogeneous in 36/60 eyes, showing an optically empty zone between the RPE and PR layer in 29/60 eyes. The vitelliform material seems to lie between the photoreceptor layer and RPE, as suggested by previous histological and OCT studies⁹⁻¹¹. In most cases the vitelliform material appeared, on SD OCT, heterogeneous showing two different reflectivity aspects in 19/36 (the innermost being hyperreflective, and the outermost being hyporefective). Arnold et al⁷ showed that there may be OS and RPE contribution in the deposit: the vitelliform material probably derives from OS, while pigment granules derive from degenerated RPE cells. Therefore, we propose that the reflectivity difference within the lesion seen in our series, may be related to the difference in the vitelliform material origin. The optically empty zone seen on SD OCT in some vitelliform lesions could correspond to the serous retinal detachment noted by Jaffe et al⁵. The accumulation of subretinal fluid separating directly or indirectly the material from the RPE may be due to the decreased ability of RPE cells to pump fluid from the subretinal space like in vitelliform macular dystrophy. In vitelliform macular dystrophy, subretinal fluid appears to be caused by underlying defect of VMD2, which involves bestrophin, a calcium sensitive chloride channel protein found in the basolateral membrane of RPE cells^{13 14}. Proteins mutations lead to a reduced or abolished membrane current and may alter the RPE cells ability to pump fluid¹⁵.

Fifthly, the RPE was found to be irregular with hyperreflective mottling in 14/60 eyes. This SD OCT feature could be correlated with RPE hypertrophy described by Arnold⁷ et al. In addition, the RPE showed discrete detachments in 29/60 eyes, harboring a “wave” shape. It could be due to coincident presence of sub-RPE deposits, such as soft drusen, in these eyes. Of note, some authors have previously described discrete RPE detachments and hypothesized that the vitelliform material was localized under the RPE¹⁻⁴⁻⁵.

We previously defined a correlation between the neuroepithelium thickness at the foveola, BVCA and stage of the disease, and we suggested a 4-stage classification for AOFVD based on the one established for Best vitelliform macular dystrophy: vitelliform, pseudohypopion, vitelliruptive and atrophic stage¹⁵. This classification is in accordance with our SD OCT findings. Here we described an SD OCT aspect showing the vitelliform material as a dome like in the vitelliform stage of Best vitelliform macular dystrophy. Another SD OCT aspect is characterized by an optically empty zone localized in the upper zone of the lesions with vitelliform material accumulation underneath like in the pseudohypopion stage of Best vitelliform macular dystrophy (eyes with heterogeneous vitelliform material showing two different reflectivity aspects, the innermost being hyperreflective, and the outermost being hyporefective). Other SD OCT aspects were characterized by an heterogeneous vitelliform material with hyperreflective clumps within the inner retina like in vitelliruptive stage of Best vitelliform macular dystrophy. We speculate that during the disease progression, pigments migrate into the inner retina.

SD OCT findings in our series seem to suggest that the earliest alteration in the subretinal ionic environment involves first the layer between the RPE and the IS/OS interface (extracellular accumulation of vitelliform material). Interestingly, the

RPE seems to be also involved in the disease process, as it presents hypertrophy or sub-RPE deposits.

Our study has several limitations: first, the different OCT layers have not yet been correlated with physiological anatomic layers in normal eyes and therefore this could be responsible for misinterpretations of hyperreflective bands especially in outer retinal layers. Secondly, longitudinal observations over longer period of time would help understanding the disease natural course.

In conclusion, in this study SD OCT provided new informations in AOFVD. We hypothesize that early changes in AOFVD involve the layer between RPE and IS/OS interface, first with vitelliform material accumulation beneath the sensory retina, and then with IS/OS alterations, pigments migration towards inner layers, and fluid accumulation. These changes come with EPR alterations such as hypertrophy or sub-RPE deposits.

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Legends

Figure 1. Spectral domain coherence (SD OCT) scan through the fovea of a healthy subject. Different hyperreflective bands can be defined which seem to correlate with the anatomical layers of the retina. The following correspondence has been used to discuss morphologic alterations: 1= external limiting membrane (ELM), 2= interface of the inner and outer segments (IS/OS) of the photoreceptors, 3 = verhoeff membrane (VM), 4 = RPE/Bruch's membrane complex.

Figure 2. Combined infrared reflectance and spectral domain optical coherence (SD OCT) images (A and B, case 25 and case 44, respectively) and, combined fluorescein angiography and SD OCT images (C and D, case 18 and case 24, respectively), showing, at the level of the vitelliform lesions, the presence of hyperreflective clumps localized within the outer plexiform and nuclear layers (arrows). The OCT scan centered on the vitelliform lesion associated with a hypofluorescent (pigmented) spot on fluorescein angiography (C) shows large hyperreflective clumps within the inner retinal layers (asterisk). Combined fluorescein angiography and SD OCT images (D), showing the hyperreflective clumps (arrowheads) that seem to disrupt the continuity of external limiting membrane.

Figure 3. Combined infrared reflectance and spectral domain optical coherence images (A, case 4; B, case 28). In A, the IS/OS interface appears highly reflective like a shell all around the vitelliform material (arrows). In B, IS/OS interface is irregular and discontinued (arrowheads).

Figure 4. Combined infrared reflectance and spectral domain optical coherence images (A, case 47; B, case 36). The Verhoeff membrane (VM) is clearly visible at the border of the lesion (arrow) and disappears over the lesion (dotted arrow) in A.

The VM appears thickened (asterisk) and less defined on the outer aspect of the lesion (arrowhead) in B.

Figure 5. Combined infrared reflectance and spectral domain optical coherence images (A, case 16; B, case 42; C, case 7). In A, the vitelliform material appears as an homogeneous hyperreflective lesion (asterisks), despite the presence of an optical empty zone (arrowhead) between the photoreceptor layer and the vitelliform material. In B, the vitelliform material appears as a heterogeneous lesion showing two different reflectivity aspects, the innermost aspect being less hyperreflective (open arrows), compared to the outermost one (thick arrow). Note, the retinal pigment epithelium appears irregular, with hyperreflective mottling on its inner aspect (dotted arrows). In C, the vitelliform material appears as a heterogeneous lesion showing a snow-balls aspect (thin arrows).

Figure 6. Combined infrared reflectance and spectral domain optical coherence (SD OCT) images (A, case 21; B, case 3).

In A, arrow 1 shows the aspect of a shell all around the vitelliform material; arrow 2 shows the vitelliform material located beneath the hyperreflective layer corresponding to the IS/OS interface; arrow 3 shows discrete retinal pigments detachments; arrow 4 shows the disappearance of Verhoeff membrane.

In B, arrow 1 shows the heterogeneous vitelliform material; arrow 2 shows the optically empty zone; arrow 3 shows the hyperreflective clumps.

Figure 7. Combined infrared reflectance and spectral domain optical coherence (SD OCT) images (A, case 1; B, case 31; C, case 39) showing discrete retinal pigment detachments (arrows).

Acknowledgements

The authors have no proprietary interest in the materials used in this study.

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Table 1. Patients demographics and main spectral-domain optical coherence tomography characteristics.

Best corrected visual acuity: BCVA; inner segment/outer segment interface: IS/OS; Verhoeff membrane: VM; retinal pigmented epithelium: RPE.

	STUDY EYE	AGE	GENDER	BCVA	hyperreflective clumps	IS/OS irregularities	disappearance of VM	heterogeneous material	RPE detachments
Case 1	RE	69	F	20/32	N	Y	Y	N	Y
Case 2	LE	69	M	20/25	N	Y	N	N	N
Case 3	RE	76	F	20/40	Y	Y	N	Y	Y
Case 4	RE	88	F	20/40	N	N	Y	Y	Y
Case 5	RE	89	F	20/62	N	Y	N	N	N
Case 6	LE	81	M	20/50	N	N	Y	Y	Y
Case 7	LE	68	M	20/20	Y	Y	N	Y	N
Case 8	RE	65	M	20/32	N	N	N	N	Y
Case 9	RE	91	F	20/32	N	Y	N	N	N
Case 10	RE	77	M	20/40	Y	N	N	N	N
Case 11	RE	46	M	20/32	N	N	N	N	Y
Case 12	RE	68	M	20/50	Y	N	N	Y	N
Case 13	RE	67	M	20/20	Y	Y	Y	Y	Y
Case 14	RE	88	M	20/32	N	Y	N	N	N
Case 15	RE	66	M	20/32	Y	N	Y	Y	N

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Case 16	RE	70	M	20/40	Y	Y	Y	Y	Y
Case 16	LE	70	M	20/32	Y	Y	N	N	Y
Case 17	LE	45	F	20/32	N	Y	N	Y	Y
Case 18	RE	65	M	20/25	Y	N	N	Y	Y
Case 19	RE	78	F	20/32	Y	Y	Y	Y	Y
Case 20	LE	73	F	20/50	N	Y	Y	N	N
Case 21	RE	73	M	20/32	N	N	Y	N	N
Case 21	LE	73	M	20/25	N	Y	Y	Y	Y
Case 22	RE	80	F	20/40	N	N	N	Y	N
Case 22	LE	80	F	20/40	N	N	N	Y	N
Case 23	LE	76	F	20/40	Y	N	N	Y	Y
Case 24	RE	83	M	20/400	Y	Y	N	Y	N
Case 25	RE	77	M	20/32	Y	N	N	Y	N
Case 25	LE	77	M	20/50	Y	Y	Y	Y	N
Case 26	RE	80	F	20/80	Y	N	N	Y	N
Case 27	RE	79	F	20/50	Y	N	N	N	Y
Case 28	RE	73	M	20/25	Y	Y	N	Y	N
Case 29	RE	79	M	20/80	N	N	Y	N	Y
Case 30	RE	89	M	20/32	N	N	N	N	N
Case 31	LE	69	M	20/62	N	Y	N	Y	Y
Case 32	RE	45	F	20/62	N	Y	N	Y	N

Case 32	LE	45	F	20/62	N	Y	N	Y	N
Case 33	RE	75	M	20/25	Y	N	Y	Y	Y
Case 34	RE	80	M	20/32	N	Y	N	N	N
Case 35	LE	69	M	20/25	N	N	N	N	Y
Case 36	RE	44	M	20/40	Y	N	N	Y	N
Case 37	RE	77	F	20/25	N	N	N	N	Y
Case 38	RE	83	F	20/80	Y	N	N	Y	N
Case 38	LE	83	F	20/100	Y	Y	N	Y	Y
Case 39	RE	82	F	20/62	N	N	N	Y	Y
Case 39	LE	82	F	20/62	N	N	N	Y	Y
Case 40	LE	82	M	20/50	N	Y	N	Y	Y
Case 41	RE	62	F	20/50	Y	N	N	N	N
Case 41	LE	62	F	20/20	Y	N	Y	N	Y
Case 42	RE	80	M	20/40	N	N	Y	N	N
Case 42	LE	80	M	20/100	N	N	Y	Y	N
Case 43	LE	44	M	20/25	N	N	N	N	Y
Case 44	LE	78	M	20/32	Y	N	Y	Y	Y
Case 45	LE	69	M	20/20	Y	N	Y	N	N
Case 46	LE	82	F	20/62	N	Y	N	N	N
Case 47	RE	64	M	20/32	N	N	N	Y	N
Case 47	LE	64	M	20/32	N	N	Y	Y	N

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Case 48	RE	57	F	20/32	Y	Y	Y	Y	N
Case 48	LE	57	F	20/400	Y	Y	N	Y	Y
Case 49	RE	52	F	20/40	Y	Y	N	N	Y