Comparison of Macular Choroidal Thickness in Adult Onset Foveomacular Vitelliform Dystrophy and Age-Related Macular Degeneration

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Purpose. To compare macular choroidal thickness (MCT) in eyes with adult onset foveomacular vitelliform dystrophy (AOFVD) and eyes with AMD.

Methods. Five groups of 38 eyes each were included in a prospective, observational, comparative study: AOFVD eyes with fluid accumulation; AOFVD fellow eyes without fluid (early stage); advanced exudative (wet) AMD; advanced dry AMD; and healthy normal eyes. All study eyes underwent a comprehensive ophthalmologic examination. Macular choroidal thickness was measured using enhanced depth imaging optical coherence tomography (EDI-OCT).

Results. Subfoveal choroidal thickness (SFCT) in AOFVD with subretinal fluid (325.66 ± 85.98 μm) was significantly ($P < 0.001$) thicker compared with that in exudative AMD (158.55 ± 57.87 μm) and in dry AMD (157.53 ± 67.08 μm). Also, in AOFVD, the choroid was significantly ($P = 0.001$) thicker than that in the normal group (255.87 ± 87.46 μm). However, in AOFVD, there was no significant difference ($P = 0.69$) between the SFCT in the study eye and in the fellow eye (317.66 ± 90.04 μm). The choroidal thickness at each of the other 12 measured points showed similar results.

Conclusions. This study demonstrates choroidal thickening in AOFVD in contrast with the choroidal thinning observed in advanced AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in exudative AMD. Choroidal thickness measurement could help differentiate the challenging diagnosis between exudative AMD and the advanced stage of AOFVD (with fluid accumulation but without choroidal neovascularization).

Keywords: adult onset foveomacular vitelliform dystrophy, age-related macular degeneration (AMD), choroidal neovascularization (CNV), choroidal thickness, enhanced depth imaging (EDI), optical coherence tomography (OCT), pigment epithelial detachment (PED)

The choroid plays an important role in ocular physiology by providing metabolic support to the RPE and outer retina. The choroid may be affected in several diseases such as AMD, polypoidal choroidal vasculopathy, central serous chorioretinopathy, pathologic myopia, choroidal melanoma, as well as microvascular arteriosclerotic disease and inflammatory processes.[1–14] Advances in ocular imaging technology—for example, spectral domain optical coherence tomography (SD-OCT)—have enabled clinicians to visualize in detail the various structures within the retina and choroid using the enhanced depth imaging (EDI) technique.[15,16]

In 1974, Gass described adult-onset foveomacular vitelliform dystrophy (AOFVD) as acquired vitelliform, near-best vitelliform macular dystrophy (VMD).[17,18] This condition typically occurs between the fourth and sixth decades of life and involves the accumulation of yellowish, heterogeneous subretinal material located between the photoreceptor layer and the RPE in the macular area.[19–23] The histopathologic features of adult-onset foveomacular dystrophy are not clearly established.[24,25] It has recently been suggested that accumulations of yellowish subretinal material demonstrated in various macular diseases could be named as an acquired vitelliform lesion (AVL).[26,27]

Our objectives were to describe and to compare macular choroidal thickness (MCT) in AOFVD and advanced AMD. We also evaluated the different patterns of morphological choroidal changes in AOFVD and in AMD.

Materials and Methods

This was a prospective study of a consecutive series of patients who were being followed-up for their ocular condition and were invited to come back for EDI-OCT examination of the choroid. This study was performed during a 5-month period, ending February 2012, in the Hospital of Créteil, University of Paris-Est (12 patients with AOFVD) and at the Centre Ophtalmologique de l'Odéon, Paris (140 patients).

Patients

The study subjects were divided into five groups of 38 eyes each: AOFVD eyes with fluid accumulation; AOFVD fellow eyes without fluid (early stage); advanced exudative (wet) AMD; advanced dry AMD; and healthy eyes (normal without any

TABLE. Study Eye Baseline Characteristics

	AOFVD	AOFVD Fellow Eye	Exudative AMD	Dry AMD	Normal
Eyes, *n*	38	38	38	38	38
Age, y; mean ± SD	74.47 ± 11.59	74.47 ± 11.59	80.71 ± 8.3	80.18 ± 7.2	62.0 ± 9.9
Visual acuity, mean (range)	20/63 (20/32–20/250)	20/40 (20/25–20/100)	20/80 (20/32–20/250)	20/80 (20/32–20/250)	20/20 (range: none)
SFCT, μm; mean ± SD	325.66 ± 85.98	317.66 ± 90.04	158.55 ± 57.87	157.53 ± 67.08	255.87 ± 87.46 (adjusted for age)
P value (AOFVD vs. other groups)	NA	$P = 0.693$	$P = 0.001$	$P = 0.001$	$P = 0.001$
P value (AOFVD fellow eye vs. other groups)	$P = 0.693$	NA	$P = 0.001$	$P = 0.001$	$P = 0.001$

study-inclusion criteria). All the study subjects were aged older than 60 years. The study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the patients after explanation of the nature and possible consequences of the study. This study was performed in accordance with French legislation and our local ethical committee regulations. All AMD and AOFVD subjects underwent a comprehensive ophthalmologic examination including EDI-OCT, fundus fluorescein (FA), and indocyanine green angiography (ICGA) with commercial EDI-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). The normal group underwent EDI-OCT.

Inclusion Criteria

All the study subjects were aged older than 60 years for the diagnosis of AMD. The diagnosis of exudative AMD was based on hyperfluorescence and late leakage associated with serous retinal detachment (SRD), subretinal exudation, and hyperfluorescent leaking choroidal neovascularization (CNVs) on FA and/or vascularized pigment epithelial detachment (V-PED) confirmed on ICGA. The diagnosis of dry AMD was based on the presence of drusen, RPE changes, and geographic atrophy on FA.

The criteria used for the diagnosis of AOFVD was: aged older than 60 years; macular yellowish deposits on fundus examination; hyper-autofluorescent spots in the autofluorescent (AF) pictures; late staining, without leakage, on fluorescein angiography; no CNV detectable on ICGA; hyperreflective material located between the photoreceptor layer and the RPE in the macular area. Adult onset foveomacular vitelliform dystrophy, at the vitelliruptive stage, was diagnosed using the presence of partial resorption of the material, based on EDI-OCT and autofluorescence imaging and the absence of CNVs on ICGA.

Exclusion Criteria

In the study eye, presence of epiretinal membrane, amblyopia, refractive error (spherical equivalence of < -2.00 or $> +2.00$), significant cataract, thick subfoveal hemorrhage, history of previous vitrectomy, intraocular surgery for retinal detachment, ocular trauma, ocular inflammation, tapeto-retinal dystrophy, history of photodynamic therapy, focal laser, anti-VEGF treatment or use of any corticoids, history of glaucoma, angioid streaks, and history and diagnosis of polypoidal choroidal vasculopathy and central serous chorioretinopathy. In the series of cases with AOFVD, patients with history or diagnosis of CNV were excluded. The absence of CNV in AOFVD was confirmed on ICGA by two retinal specialists (FC, NP).

EDI-OCT Protocol

The method of obtaining EDI-OCT (Heidelberg Engineering) images has been previously reported.[15,16] The software update version (5.4) automatically produced inverted capturing images; and the eye tracking technology improves image quality and acquisition times, but no automatic measuring software is present. These methods showed a high inter- and intraobserver reproducibility of choroidal thickness measurements with EDI-OCT analysis.[28–30]

Choroidal thickness (CT) is defined as the distance from the outer border of the RPE to the hyperreflective line of the choroid/sclera boundary at predefined intervals of inner surface of the sclera on the two eyes of each study participant and without pupil dilatation. The quality of the scans was assessed prior to analysis and poor quality scans were rejected and repeated until acceptable quality was obtained.

Cross line scans of 30°, composed of 100 averaged images, across the fovea were obtained automatically. Choroidal thickness measurements were performed subfoveally and at 1500-, 1000-, and 500-μm intervals from center to nasal and to temporal and from superior to inferior. All subjects underwent choroidal imaging and thickness measurements by EDI-OCT. EDI-OCT scans were performed by two retinal physicians (FC, NP).

Statistical Analysis

Statistical calculations were performed using standard statistical software (Statistical Package for Social Sciences, version 20.00; SPSS, Inc., Chicago, IL). The difference between the AOFVD, unaffected fellow eye AOFVD, dry AMD, wet AMD, and the normal group (healthy subjects) was evaluated by conducting repeated measures: ANOVA followed by Dunnet's post hoc test for each individual axial choroidal thickness over the horizontal and vertical line scans (at each 500-μm interval from the fovea to nasal, temporal, superior, and inferior from the center of the fovea). *P* values lower than 0.05 (paired-samples correlation and "Pearson" test) were considered statistically significant.

RESULTS

A series of 190 eyes (from 152 patients; 32 men and 120 women; mean age ± SD: 76 ± 10.8 years) were included. The mean ages and visual acuities of the study patients are shown in the Table.

Subfoveal choroidal thickness (SFCT) in AOFVD was significantly ($P = 0.001$) thicker than in wet and dry AMD. Also, SFCT in AOFVD was significantly ($P = 0.001$) thicker than in the normal control group. The choroidal thickness in the normal group was calculated after adjusting for age-related changes.[28] All the statistical results were adjusted for age-related changes.

There was no significant difference in SFCT between eyes with AOFVD and their fellow eyes ($P = 0.693$). Also, the SFCT in AOFVD fellow eyes was significantly different from the SFCT in dry AMD, wet AMD, and normal groups. The choroidal

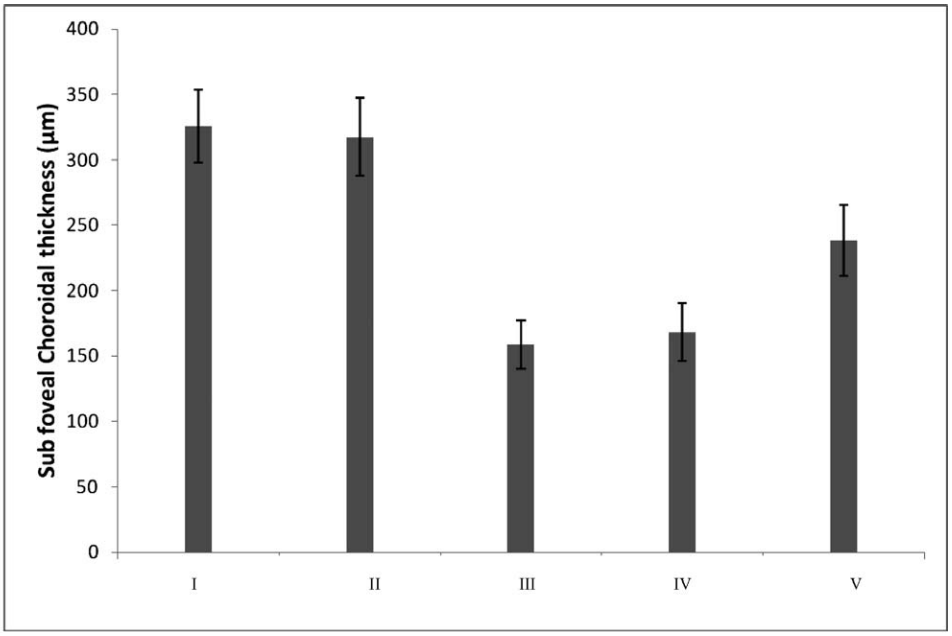

Figure 1. Bar graph (with SD and 95% confidence intervals) showing mean SFCT in the study groups. Subfoveal choroidal thickness in AOFVD is significantly ($P = 0.001$) thicker than in wet and dry AMD. Also, SFCT in AOFVD was significantly ($P = 0.001$) thicker than in the normal control group. There was no significant difference in SFCT between eyes with AOFVD and their fellow eyes ($P = 0.693$).

thickness at each of the other measured points showed similar results (Fig. 1).

Clinically, the subretinal deposit of yellowish material in AOFVD was located in the macular area with a highly variable phenotypic expression. The vitelliform material was mostly heterogeneous and associated with an optically empty zone between the IS/OS layer and the material, suggesting fluid accumulation. In many cases, the IS/OS interface appeared irregular and discontinued. The heterogeneous vitelliform material was sometimes associated with serous pigment epithelium detachment (PED) and subretinal fluid masquerading as exudative AMD.

In our study, mean CT in AOFVD was thicker than normal. The Haller and Sattler's layers were present but the caliber of blood vessels was enlarged and dilated (mainly the outermost layer) with very limited intervascular tissue (Figs. 2, 3). This pattern was very different from the choroid layer observed in AMD, where the choroidal vessels appear smaller and irregular with substantial intervascular tissue (Figs. 4, 5).

Discussion

Recent advances in SD-OCT enable detailed visualization of the choroid. Using image averaging and particularly EDI, improved imaging of the choroidal structures and more accurate measurement of its thickness have been reported. In a pilot study of 30 normal subjects, Margolis and Spaide reported that the mean subfoveal choroidal thickness was 287 ± 75.5 µm decreasing on both sides of the fovea, more nasally, with high correlation in both eyes. They also found that MCT decreased with age by 1.87 µm/year and 15.6 µm per decade of life.[15,16]

The exact location of the subretinal deposit of yellowish material in AOFVD has been identified, using high definition SD-OCT, between the inner/outer segment (IS/OS) interface and the RPE band. Adult onset foveomacular vitelliform dystrophy progression is characterized by fragmentation and regression of this vitelliform material accompanied by fluid accumulation and disruption of the RPE layer.[31]

We have shown in our study, for the first time, that in all cases of AOFVD, subfoveal CT (in both AOFVD eyes with fluid

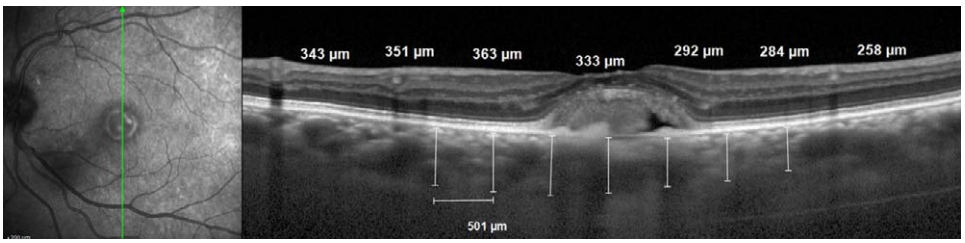

Figure 2. Optical coherence tomography in advanced AOFVD shows partial regression of the vitelliform material and fluid accumulation. Subfoveal choroidal thickness was analyzed with measurement of the vertical distance from the Bruch's membrane to the innermost choroid/sclera junction, at 500-µm intervals up to 1500 µm, from temporal to nasal. The choroid is thick; the Haller and Sattler's layers are present, but the caliber of blood vessels is enlarged and dilated (mainly the most outer layer) with very limited intervascular tissue.

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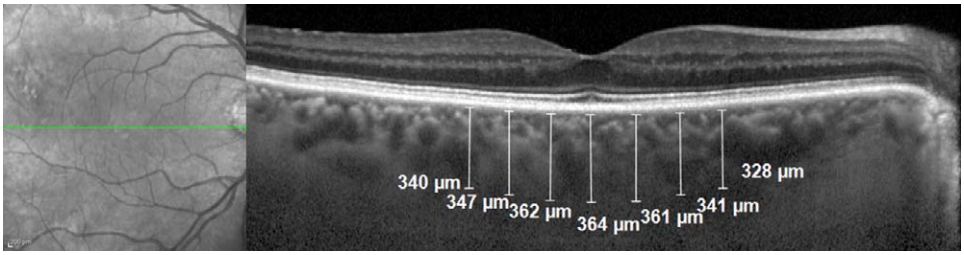

FIGURE 3. Optical coherence tomography in the fellow eye of the patient in Figure 2. The choroid is thick; the Haller and Sattler's layers are present, but the caliber of blood vessels is enlarged and dilated (mainly the outermost layer) with very limited intervascular tissue.

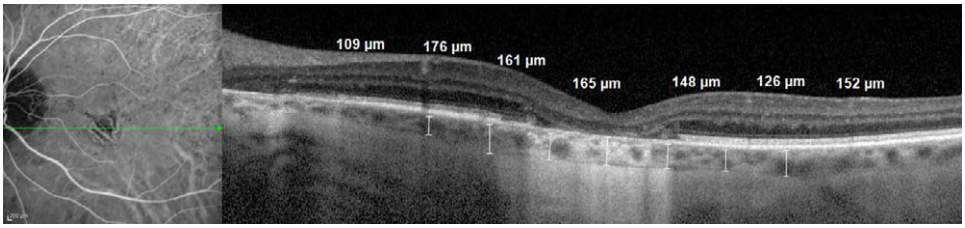

FIGURE 4. Optical coherence tomography in dry AMD. The choroid is thin; the choroidal vessels appear small and irregular with substantial intervascular tissue.

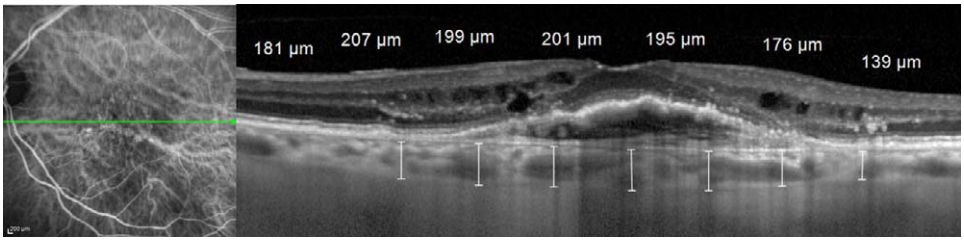

FIGURE 5. Optical coherence tomography in wet AMD. The choroid is thin; the choroidal vessels appear small and irregular with substantial intervascular tissue.

accumulation and AOFVD fellow eyes without fluid) was statistically thicker than in wet and dry AMD and in the healthy normal control group. Also, the choroidal thickness at each of the 12 other measured points showed similar results.

Various reports have suggested that the choroid may be involved in the pathogenesis of a variety of ocular diseases, including thinning of the choroid in age-related choroidal atrophy,[2] in wet and dry AMD[1,7,8,11] and in reticular pseudodrusen.[22]

In our study, we found that the mean CT in wet and in dry AMD was significantly thinned in comparison with both AOFVD and AOFVD fellow eyes. This thinning remained consistent even after adjustment for age. Notably, this thinning was similar in both wet and dry AMD.

Choroidal thickness was also found severely reduced in pathologic myopia[4,10,13] with a mean SFCT of 93.2 ± 62.5 µm and an 8.7-µm decrease for each diopter of myopia.[4] Therefore, all cases of myopia were excluded from our study to avoid any bias.

In a study related to choroidal imaging in inherited retinal disease, Yeoh et al.[32] showed that choroid thinning was dependent on the stage of the disease but was not observed in the vitelliruptive stage (in one case of Best disease). In our study, on the contrary, a statistically significant increase in choroidal thickness was observed in all cases of AOFVD (both affected and fellow eye), suggesting a clinical pattern differentiating exudative AMD from AOFVD, even when both conditions may be associated with fluid accumulation. Additionally, SLO-ICG angiography performed in all our study patients did not show any neovascular network in AOFVD. Anti-VEGF treatment was reported to be useful only in AOFVD cases with evidence of CNV complication.[33]

A significant increase in choroidal thickness has been reported in many diseases with fluid accumulation associated with venous dilatation and hyperpermeability as in central serous chorioretinopathy (CSC)[3,12] and polypoidal choroidal vasculopathy (PCV).[6,8] Increased choroidal thickness is thought to be due to increased circulation and vascular dilatation. This view is consistent with ICGA studies that show diffuse ICG leakage in both choroids, even when only one eye has a clinically demonstrable vitelliform deposit. Such venous dilatation may occasionally be associated with or induced by dilatation and congestion of the vortex vein.[14] Combined with our findings, these studies suggest that this CT increase could be observed in three macular diseases (CSC, PCV, and AOFVD) as in some clinical continuum in this group of diseases with subretinal fluid accumulation and deposits of lipofuschsin material.

Adult onset foveomacular vitelliform dystrophy is a bilateral condition even though it may present as an asymmetrical lesion. This could explain the observation that the SFCT of the affected and fellow eyes in AOFVD were similar, without any statistically significant difference. A recent study has shown that in eyes with PCV, the I62V polymorphism in the CFH gene is associated with choroidal thickness.[9] Future studies on genetic polymorphism could become useful in AOFVD. Inflammatory infiltration but also increased exudation could

be involved in the increase in choroidal thickness observed in patients with active Vogt-Koyanagi-Harada disease.[5]

Finally, in these different diseases, it is possible that noninvasive EDI-OCT measurements of choroidal thickness and its variations could become useful not only for more accurate diagnosis, but also for evaluating prognosis and providing indications for active treatment.

Our study has several limitations. First, our sample is limited as the studied disease is relatively rare. Second, as ocular biometry was not always available, we excluded cases with unusual changes in optical axial length and large refractive errors.[34] Third, comparing our measurements with published literature was difficult since these studies involved either one single location or several points or even volume measurements to provide information on sectorial choroidal thickness.[15,16,31,34–36] Fourth, our study was performed with manual measurements as the used EDI-OCT software did not have automated measurements.

In conclusion, our study demonstrates choroidal thickening in AOFVD, in contrast with the choroidal thinning observed in advanced dry and exudative AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in exudative AMD. Choroidal thickness measurement could help differentiate the diagnosis between exudative AMD and AOFVD (with fluid accumulation but without choroidal neovascularization). This would be particularly useful in helping decide appropriate treatment with intravitreal anti-VEGF injections.

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