Title: PACHYCHOROID: an inherited condition?

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PACHYCHOROID

An Inherited condition?

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Purpose: Thick choroid (pachychoroid) is associated with central serous chorioretinop- athy (CSC), but whether pachychoroid is inherited is unknown.

Methods: In a prospective observational study, first- or second-degree relatives (16 individuals) of 5 patients with CSC had refraction and visual acuity measurement, fundus examination, nonmydriatic photography, and autofluorescence photography. Eyes were graded using the following criteria: 0: normal fundus and autofluorescence photography, 1: focal retinal pigment epithelium hyperfluorescence and/or hypofluorescence and/or retinal pigment epithelial detachment, 2: CSC or diffuse retinal epitheliopathy. Choroid thickness was measured by enhanced depth imaging mode on optical coherence tomography.

Results: Considering 395 mm as the threshold limit for normal subfoveal choroidal thickness, 50% of the eyes from relatives had a thick choroid. Nine eyes of Grade 0 (28%) with an isolated pachychoroid would thus have been considered normal, if cho- roidal thickness was not included as a screening sign predisposing for CSC.

Conclusion: Our observation suggests that pachychoroid could be an inherited condition with potentially a dominant transmission mode. Its inclusion in the phenotype of CSC for genetic studies should be considered.

Choroid imaging, using optical coherence tomogra- phy enhanced depth imaging function, wasfirst described by Margolis and Spaide in 2008.1,2Multiple studies have measured choroidal thickness as a func- tion of age, axial length,3,4 and circadian rhythm,5 thus defining the normality limits. Table 1 summarizes cho- roid measurements performed on normal subjects and reported in different studies. With the emergence of this new imaging modality, the range o retinal pathol- ogies associated with increased choroid thickness or “pachychoroid” is increasing.

Central serous chorioretinopathy (CSC) belongs to this spectrum of diseases associated with enlarged choroid. In 30 patiemts with CSC, choroidal thickness was found significantly increased not only in the affected eye (445.58 ± 100.25) but also in the contralateral unaffected eye (378.35 ± 117.44), and choroid was sig- nificantly larger in the affected eyes.6 In another study, 36 patients with CSC had retrofoveal choroid thickening (459.16 ± 77.50 mm) during the acute phase, regression after spontaneous resolution, and normalization after photodynamic therapy (349.50 ± 88.99 mm).7 Other studies have confirmed that one possible mechanisms of photodynamic therapy in CSC could be related to the reduction of permeability and dilation of choroidal vessels.8–10

However, not all patients with CSC have enlarged choroids, and whether this choroidal vessels dilation is causative of the disease or only a favoring factor remains controversial. The fact that only one eye could ever show serous detachment, whereas both eyes have enlarged choroid, favors consider choroidal thickening as a "susceptibility factor for CSC" rather than as a triggering event.

Sporadic familial cases of CSC have been re-ported11–13 until Weenink et al14 reported that 44% among 80 relatives of 27 patients with CSC had sub- clinical signs of CSC, suggesting a potential autosomal transmission of the disease. Several cases of CSC in two families with anxious profiles have raised the hypothesis that the inheritance could rather be related to specific psychological profile15 rather than CSC inheritance per se. In a larger study including 30 rel- atives of patients with CSC, signs of CSC were found in 92% of the cases, while no familial history was reported, suggesting that nonsymptomatic forms of the disease could mask inheritance character.16 To date, no clear transmission pattern and no specific genotype have been associated with CSC. One of the difficulties of such genetic studies resides in the iden- tification of a well-defined phenotype. Indeed, with advanced imaging systems, a larger spectrum of clinical entities are being recognized from isolated choroidal enlargement (pachychoroid), pachychoroid pigment epitheliopathy recently described by Warrow et al,17 acute CSC, diffuse retinal epitheliopathy, andage-related macular degeneration–like CSC associated to choroidal neovascularization or pseudo polypoidal vasculopathy, having all in common a thick choroid. Whether a common physiopathogenic mechanism drives all these clinical manifestations remains to be clarified. Because choroidal thickness is now recognized as a "sign" in the diagnosis of

CSC, we have questioned whether choroidal thickness could be a sus- ceptibility inherited factor for CSC.

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Table 1. Choroid Measurements Performed on Normal Subjects in the Literature

	Eyes	SFCT (mm)
Hirata et al, IOVS 2011	31	191
Shao et al, IOVS 2013	3233	254
Branchini et al, Ophthalmology 2013	42	256
Chhablani et al, IOVS 2012	64	264
Kim et al, Eye 2011	30	266
Manjunath et al, AJO 2010	34	272
Yamashita et al, IOVS 2012	39	272
Margolis and Spaide, AJO 2008	54	287
Yang et al, Acta Opth 2013	15	289
Ikuno et al, IOVS 2011	24	292
Ouyang et al, IOVS 2011	55	297
Spaide et al, AJO 2008	34	335
Tan et al, IOVS 2012	24	340
Qiang Li et al, IOVS 2011	93	342
Branchini et al, Ophthalmology 2012	28	347
Ikuno et al, IOVS 2010	79	354

Patients and Methods

This is a prospective observational noncomparative study. Patients were included after informed consent. Five patients with CSC were prospectively included at Hôtel-Dieu of Paris hospital from September 2012 to April 2013. All 5 patients had at least 1 eye with serous detachment for .3 months and retinal pigment

	Sex: M/F	Age	Clinical Grade: OD/OS	Use of Steroids	Allergy	Stress/Emotional Shock
Family 1						
Father	M	67	2/2	No	Yes	Burnout, 1976
Index	M	43	2/2	Inhaled	No	Burnout, 2008
Son	M	15	0/0	No	No	No
Sister	F	38	0/1	Oral, 2012	No	Depression, 2010
Nephew	M	14	0/0	Intravenous	Yes	No

Family 2						
Index	M	62	0/2	Intraarticular, 2011	No	No
Brother	M	61	0	No	No	No
Brother	M	57	0	Intraarticular, 2004	No	No
Brother	M	56	1/1	No	No	No
Family 3						
Index	F	56	2/2	Intraarticular	Yes	Stress at work
Sister	F	57	0	No	No	Stress at work
Daughter	F	31	0	No	No	Stress at work
Son	M	28	0	No	No	Stress at work
Family 4						
Index	M	64	2/2	Inhaled until 2010	No	Depression, 2008
Sister	F	60	0/1	Intraarticular, 1994	No	Stress at work
Sister	F	66	0/0	Intraarticular, 2003	Yes	Stress at work
Daughter	F	24	0/0	Inhaled	Yes	No
Son	M	18	0/0	No	No	No
Family 5						
Index	M	59	0/2	No	No	No
Brother	M	61	1/0	No	No	No
Brother	M	51	1/1	Inhaled	No	No

Index, index case in the family.

Clinical grade, 0 normal fundus and autofluorescence; 1, focal retinal pigment epithelium hyperfluorescence and/or hypofluorescence and/or retinal pigment epithelial detachment in favor of previous asymptomatic CSR; 2, clinically obvious CSR or diffuse retinal epitheliopathy.

epithelium alterations in at least 1 eye. Exclusion crite- ria were: myopia or hyperopia . 3 diopter (D), ambly- opia, any form of choroidal neovascularization, diabetes mellitus, and hypertension. All their first- or second- degree relatives (36 individuals) were invited to the clinic for a free ophthalmologic examination. We could examine 16 relatives of the 5 patients. All individuals had refraction and visual acuity measurement, slit-lampand fundus examination, nonmydriatic photography, and a 55° autofluorescence photography (Spectralis; Heidel- berg Engineering, Heidelberg, Germany). We assessed choroid thickness by enhanced depth imaging images performed with 6 linear horizontal scan of 100 averaged images: centered on the fovea, horizontal at 750 mm superior and inferior to the fovea, vertical at 750 mm temporal and nasal from the fovea. Manual measure- ment of choroid thickness was performed by two ophthalmologists (M.L. and E.B.) using caliper place- ment between the hyperreflective band corresponding to the retinal pigment epithelium Bruch layer and the outer hyperreflective band at thesclera–choroid interface. Measures were performed at the fovea, and every 500 mm up to 1,500 mm nasal and temporal from the fovea. Patients were then classified from Grade 0 to 2, using the following criteria: 0: normal fundus and

autofluorescence photography; 1: focal retinal pigment epithelium hyperfluorescence and/or hypofluorescence and/or retinal pigment epithelial detachment (in favor of previous asymptomatic CSC); 2: clinically obvious CSC or diffuse retinal epitheliopathy. Figure 1 shows example of this classification.

Results

Subject Characteristics

Twenty-one subjects (5 patients with CSC and 16 relatives), 14 men and 7 women, were included. Mean age was 47 years (14–67 years), 10 of 21 subjects (47.6%) had history of emotional stress or depression, and 11 of 21 (52.3%) had taken corticosteroids by any route in their medical history. History of allergy was recorded in 5 of 21 (24%) of the subjects (Table 2). Mean spherical equivalent (SE) of both eyes of index cases was 0.47 ± 0.49 D. The mean SE in eyes of relatives was−0.46 ± 1.93 D. The mean SE in Grade 0 eyes was −0.70 ± 1.79, and it was 0.01 ± 2.1 in Grade 2 or 3 eyes. Subfoveal choroidal thickness (SFCT) was significantly correlated with SE in the studied

Fundus, Autofluorescence Photography, and Optical Coherence Tomography Findings

Among the 5 index cases, 3 had a bilateral disease (of Grade 2) (Figure 2). Six of the relatives had at least 1 eye

showing a grade .0 (37.5%), and 9 of 32 eyes (28%) of the relatives were graded 1 or 2. The mean SFCT (42 eyes) was 396.64 ± 113.3 mm, with a median of 404 mm (range, 179–800 mm). There was a significant difference

Table 3. Subfoveolar Choroidal Thickness, Nasal (N), Temporal (T), and Fundus Autofluorescence With 55° SD-OCT

	SD-OCT Combined With EDI							
	OD			OS			Autofluorescence	
	N	SFCT	T	N	SFCT	T	OD	OS
Family 1								

Father	166	295	249	259	337	255	DRE	DRE
Index	616	800	648	550	591	615	DRE	DRE
Son	155	264	284	124	325	300	N	N
Sister	339	372	394	471	481	504	N	RPE anomaly + PED
Nephew	331	393	305	384	418	382	N	N
Family 2								
Index	181	278	248	336	449	346	N	DRE
Brother	171	265	160	191	325	274	N	N
Brother	264	—	289	310	410	367	Macular toxoplasmosis scar	N
Brother	382	428	346	320	398	269	RPE anomaly + PED	RPE anomaly + PED
Family 3								
Index	347	403	516	532	599	470	RPE anomaly + PED	DRE
Sister	315	429	418	431	466	408	N	N
Daughter	215	405	306	253	289	311	N	N
Son	490	340	382	542	490	398	N	N
Family 4								
Index	315	284	282	274	444	523	DRE	RPE anomaly + PEDs
Sister	232	315	387	217	310	326	N	PED
Sister	105	193	222	151	179	188	Temporal toxoplasmosis scar	N
Daughter	387	470	496	382	490	476	N	N
Son	150	341	341	145	346	398	N	N
Family 5								
Index	383	352	429	490	444	476	N	DRE
Brother	424	448	439	346	496	346	RPE anomaly + PED	Past inferior BRVO
Brother	419	485	451	—	423	—	PED	RPE anomaly + PED

Index, index case in the family.

BRVO, branch retinal vein occlusion; DRE, diffuse retinal epitheliopathy; N, normal; OD, right eye; OS, left eye; PED, pigment epithelium detachment; RPE, retinal pigment epithelium.

in SFCT in Grade 1 or 2 eyes (448.1 ± 126.7 mm) as compared with Grade 0 eyes (3,616 ± 89.8 mm [P = 0.038]). Mean SFCT was not statistically different in the fellow eyes and in the affected eyes (362.6 ± 82.79 mm and 426.4 ± 66.74 mm in the affected eye [P = 0.41]). It was also not statistically different between fellow eyes and healthy eyes (362.6 ± 82.7 mm vs. 361.35 ± 93.5mm [P . 0.99]). Subfoveal choroidal thickness $395 mm was found in 76.4% of affected eyes (Grade 1 or 2, and SFCT was ,395 mm in 60% of Grade 0 eyes).

As shown in Table 3, mean choroidal thickness nasal to the fovea was 319.39 ± 131.85 mm as com- pared with 371.31 ± 108.82 mm temporal to the fovea (P = 0.067), and the mean SFCT was statistically high- er than that the nasal choroidal thickness (319.39 vs. 396.64, P = 0.0065).

Subfoveal Choroidal Thickness as a Potential Inherited Sign, Predisposing to Central Serous Chorioretinopathy

If we consider the SFCT as a screening sign for CSC, we obtain an ROC curve (Figure 3) with the best

threshold measure at 395 mm, giving a sensitivity of 76.47% and a specificity of 60%. Area under the curve is 0.6894 ± 0.0835 with a confidence interval at 95% from 0.5257 to 0.8532. The mean SFCT of the rela- tives was 375.46 ± 87 mm (vs. 464.4 ± 160.3mm in the patients) with a median of 395.5 mm. When con- sidering 395 mm as the threshold limit for“normal” SFCT, 50% of the eyes from relatives have an increased SFCT, and among those, 9 eyes (28%) were graded 0. These eyes would have been considered “normal” if choroidal thickness was not included as a screening sign predisposing for CSC.

Figure 2 represents the different family members with their grading and shows the eyes with SFCT.395 mm. Figure 4 shows the 4 brothers of the same family, their fundus autofluorescence, and their spectral domain opti- cal coherence tomography.

Discussion

To date, no clear inheritance has been identified for CSC, even if description of family cases has been recognized. Inherited signs of the disease have not been yet well established, and whether pachychoroid should be considered as an inherited sign of the disease has not yet been questioned. Enhanced depth imaging mode of optical coherence tomography has allowed to measure choroidal thickness with increased precision. Normal

subjects have variable SFCT depending on their age, axial length, and the time of the day. Subfoveal choroidal thickness was measured between 191.5 ± 74.218 and 354 ± 111 mm19 in normal subjects and between 345 ± 127 mm20 and 505 ± 124 mm2patients with CSC, depending on the studies.

In our limited group of subjects, the mean SFCT was 448.1 ± 126.7 mm in eyes with signs of CSC and it was 361.6 ± 89.8 mm in Grade 0 eyes (P = 0.038), which is higher than the SFCT measured in emetropic eyes, suggesting that relatives of patients with CSC may have enlarged choroids. Indeed, the SE (−0.70 ± 1.79) in this group could not explain the larger choroidal thickness.

Other studies evaluating inheritance of CSC have classified eyes depending on their fundus finding: normal fundus, retinal pigment epithelium atrophy and/or pig- ment epithelial detachment, or chronic CSC.14 Eyes pre- senting classic signs of CSC or suspected CSC are thus considered as affected. Taken the same classification criteria, we designed an ROC curve with affected and healthy patients, considering their SFCT as a screening test. The best sensibility was 76.47%, for a specificity of sample ($r = 0.53$, $P = 0.01$, Pearson's correlation).

Fig. 1. Example of clinical grad- ing. A and B. Grade 0 defined as normal fundus and auto-fluorescence (A). In that case, the eye had an increased SFCT (B). Cand D. Grade 1 is defined as focal retinal pigment epithelium hyper-autofluorescence (C) and/or hy- poautofluorescence and/or retinal pigment epithelial detachment (D). In this case, it is associated with increased SFCT (D). E and F.Grade 2 is defined as clinically obvious CSC or diffuse retinal epitheliopathy. Hypoauto-fluorescence and hyper- autofluorescence (F) associated with irregular retinal pigment epi-thelium, SFR, and elongated outer segments, witnessing chronic CSC.

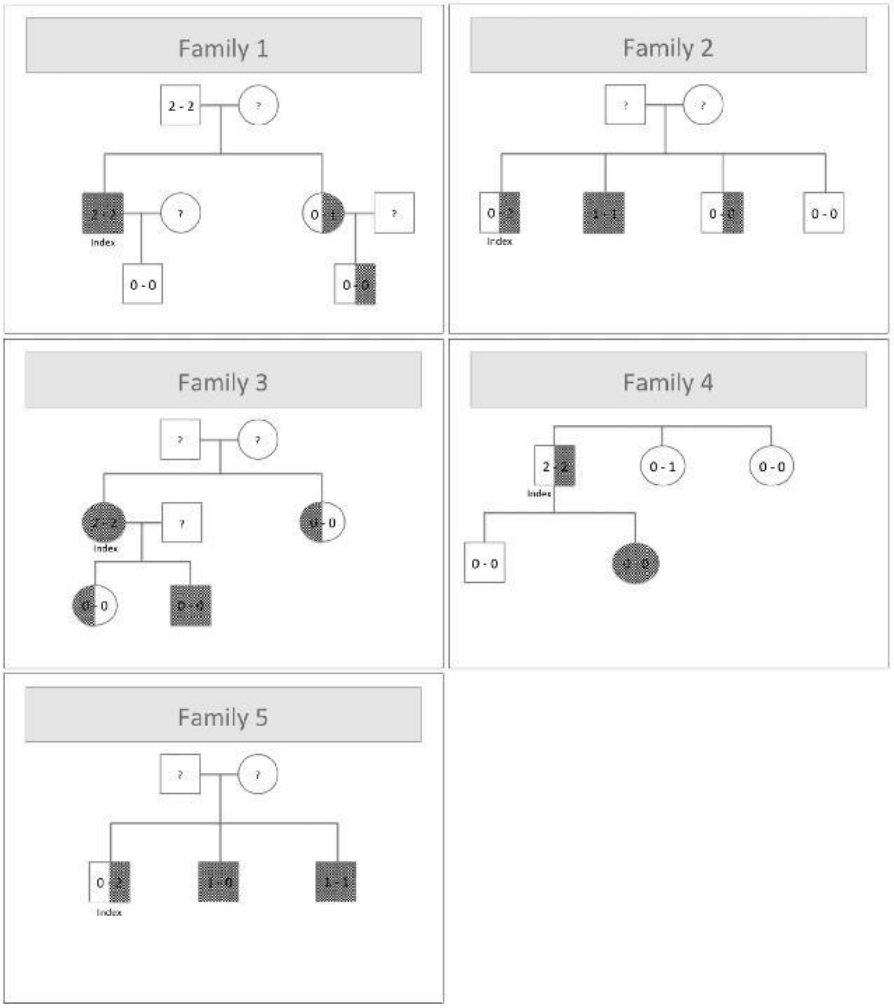

Fig. 2. Family trees of the 5 families: 0: normal fundus autofluorescence; 1: focal retinal pigment epithelium hyperfluorescence and/or hypofluor- escence and/or retinal pigment epithelial detachment in favor of previous asymptomatic CSC; 2: clinically obvious CSC or diffuse retinal epitheli- opathy. Gray color indicates SFCT .395 mm.

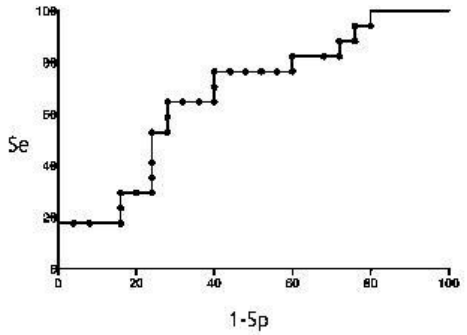

Fig. 3. ROC curve of SFCT as a screening tool for CSC. Se, sensibility; Sp, specificity.

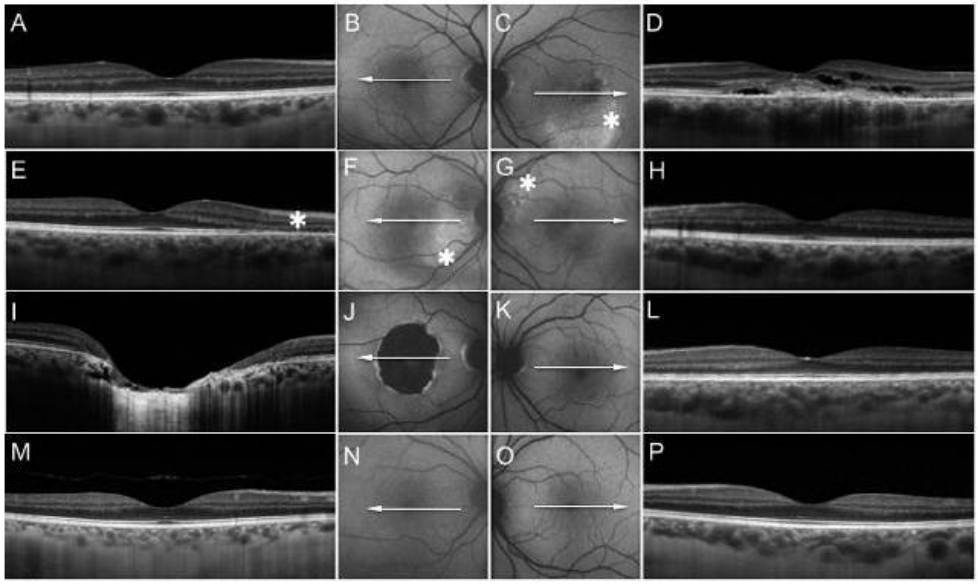

Fig. 4. Spectral domain optical coherence tomography and autofluorescence images of members of family N° 2 patient index. The fellow eye has a normal fundus autofluorescence (B) and a normal SFCT (A). The pathologic eye shows a chronic CSC (C) and a SFCT of 449mm (D). One of his brothers with enlarged choroids (428 and 398 mm [E and H]) shows fundus autofluorescence alterations in the interpapillomacular area on both eyes (white arrow, F and G). Another brother with a normal nasal and temporal choroidal thickness (I) and a toxoplasmosis scar on the right eye fundus associated with subfoveal thinning. The choroidal thickness at the border of the scar is 299 mm (J). His left eye shows normal fundus autofluorescence (K) and a thickened subfoveolar choroid (410 mm [L]). The last brother has a strictly normal fundus autofluorescence in both eyes (N and O) and a normal SFCT (M and P