MARTINIQUE (WEST INDIES) CRINKLED RETINAL PIGMENT EPITHELIOPATHY

Clinical Description

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Purpose: To report a previously undescribed pattern of crinkled retinal pigment epithelium (RPE), observed in a family of black patients originating from Martinique, an island in the French West Indies.

Methods: Three generations were examined by visual acuity measurement and fundus photography. Autofluorescence photography, fluorescein and indocyanine green angiography, visual field testing, electrophysiology, and spectral domain optical coherence tomography were performed in certain patients.

Results: One 86-year-old grandmother, her 7 children, her nephew, and 18 of her 22 grandchildren were examined. Nine patients were affected: five children, one nephew, and three grandchildren. An unrelated patient originating from the same area was also affected. In the third generation, fundus findings were whitish deep lines located in the posterior pole. Optical coherence tomography showed a crinkled pattern of a slightly elevated RPE. In the second generation, a scalloped crinkled RPE was observed in the posterior pole and midperiphery, giving an image of dry desert land in fluorescein and indocyanine green angiography. Optical coherence tomography showed that the RPE formed ripples, giving it a crinkled appearance. Complications were observed in six cases: they included RPE atrophy (one case), subretinal and sub-RPE hemorrhages because of polypoidal choroidal vasculopathy (four cases), and fibrovascular scarring (one case). The grandmother's fundi were characterized by peripheral pigmentary changes, with severe visual loss.

Conclusion: The observed pattern appeared different from previously described dystrophies and could be referred to as Martinique crinkled retinal pigment epitheliopathy.

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A curious pattern of the fundus was observed in one brother and two sisters living in Martinique, an island in the French West Indies. The same pattern was concurrently observed in two patients living in metropolitan France, originating from Martinique, one of whom was a cousin of the family cited above. We report here the unique clinical findings and the angiographic and optical coherence tomography (OCT) images observed from these patients. As far as we know, these images do not correspond to any known type of dystrophy.

Methods

The family living in Martinique was examined by two of us (A.J.C. and H.M.), and the patients living in metropolitan France were examined by three of us (S.Y.C., G.Q., and A.G.). All patients underwent refraction, best-corrected visual acuity, and fundus color photography (TRC-NW8 Non-Mydriatic Retinal Camera, NW 6 S, or TRC-50X; Topcon, Tokyo, Japan). Most of the patients were examined with Spectral Domain OCT (Cirrus SD-OCT; Carl Zeiss Meditec, Dublin, CA, or Nidek RS 3000, Tokyo, Japan). Certain patients were explored with autofluorescence pictures, fluorescein and indocyanine green angiography (Topcon), visual field testing (Goldmann

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visual field, Humphrey field analyzer [Carl Zeiss Meditec]), and electrophysiology consisting of an electrooculogram, electroretinogram (ERG), multifocal ERG, and pattern ERG (Metrovision, Perenchies, France). The protocols used were consistent with the standards defined by the International Society for Clinical Electrophysiology of Vision.

Each patient gave informed consent to participate in the study, which was carried out in accordance with Health Insurance Portability and Accountability Act guidelines and was approved by the IRB and Ethics Committee of the *Société Française d'Ophtalmologie* (French Society of Ophthalmology).

Results

The pedigree of the family is shown in Figure 1. The 86-year-old grandmother, her 7 children, her nephew, and 18 of her 22 grandchildren were examined. One additional patient presented with a similar pattern of the fundus. To our knowledge, she is not related to the affected family, but her mother originated from the same area of Martinique. The clinical findings are reported in Table 1.

The disease seems to progress with age. Potentially, severe complications were observed in six patients. One was aged 30 years, but all the others were aged 50 years and older. The findings were different in each of the three affected generations.

1. In the third generation (Patients III 2, 3, and 5), the disease was characterized by a network of deep whitish lines observed in the posterior pole, temporally to the fovea for Patient III 2 (Figure 2) or in the juxtapapillary area for other patients (Figure 3). Corresponding OCT scans showed minor changes, with a diffuse scalloped shallow elevation of the retinal pigment epithelium (RPE; Figure 2B).
2. In the second generation (one or both eyes of Patients II 1, 2, 4, 5, 6, and 8), the disease was

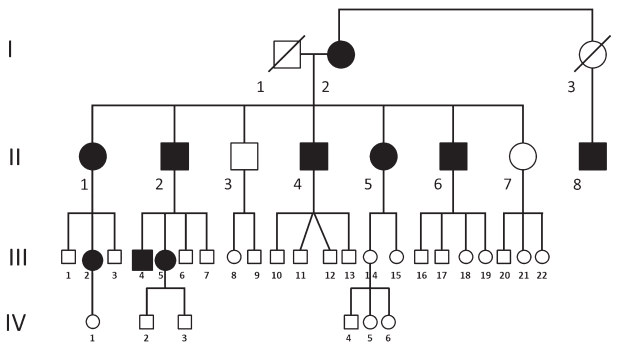

Fig. 1. Pedigree of the family. Affected members were the grandmother, 5 of her 7 children, 1 nephew, and 3 of the 18 grandchildren.

Table 1. Clinical findings in affected patients

Patient	Gender	Age	Refraction OD/OS (Spherical Equivalent)	Visual Acuity OD–OS (Snellen Equivalent)	Clinical Findings	Complications
I 2	Female	86	−4.00/−2.25	LP–LP	Midperipheral osteoblastic changes	
II 1	Female	59	+1.75/+0.75	20/2,000–20/400	Large foveal atrophy	Foveal atrophy
II 2	Male	58	−0.75/+0.25	20/25–20/25	Typical crinkled fundus	
II 4	Male	54	+0.00/+0.00	20/25–20/25	Typical crinkled fundus	
II 5	Female	51	−0.50/−0.50	20/20–20/400	Typical crinkled fundus	Severe bleeding—PCV OD
II 6	Male	50	+0.00/+0.00	20/25–20/1,000	Typical crinkled fundus	Fibrovascular scar OD
II 8	Male	63	+1.50/+1.25	20/20–20/20	Typical crinkled fundus	PCV OD
III 2	Female	30	+0.75/+0.75	20/63–20/20	Tiny juxtafoveal whitish deep network	PCV OD
III 4	Male	37	−1.00/−0.75	20/20–20/20	Whitish lines located temporally to the fovea	
III 5	Female	20	−0.50/−0.50	20/20–20/20	Tiny juxtafoveal whitish deep network	
Unrelated	Female	43	+1.50/+1.75	20/400–20/30	Whitish juxtafoveal deep network	Fibrovascular scar OD, PCV OS

Age, at presentation; visual acuity, as measured at last visit; LP, light perception.

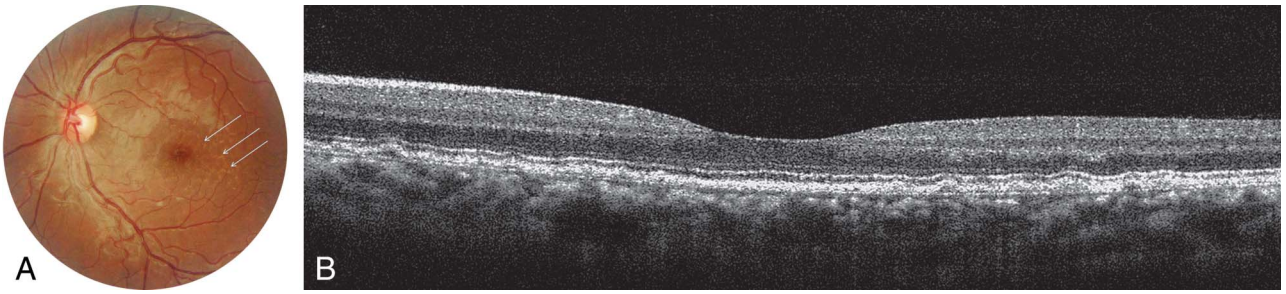

Fig. 2. Patient III 5, aged 20 years. Martinique crinkled retinal pigment epitheliopathy, left eye. **A.** Fundus photograph showing deep whitish lines temporal to the fovea. **B.** A horizontal spectral domain OCT scan of the corresponding area passing through the fovea revealed a scalloped RPE.

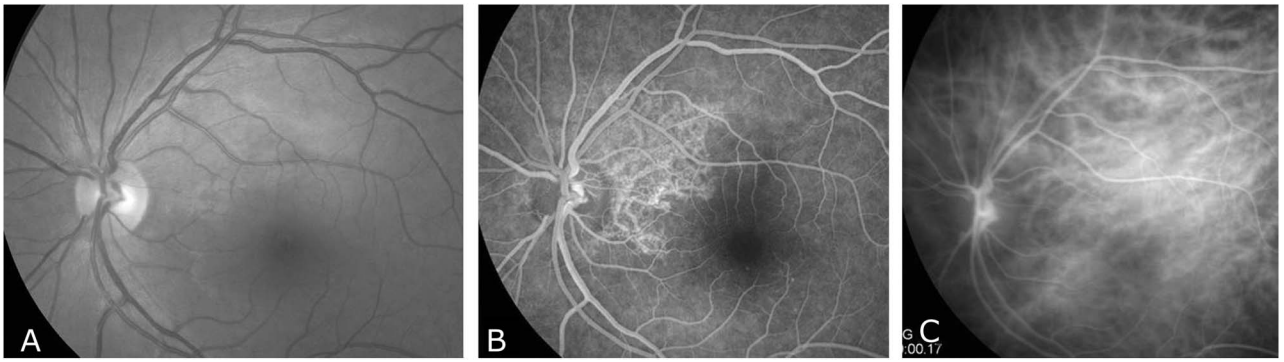

Fig. 3. Patient III 2, aged 30 years. **A.** Unremarkable red-free fundus photograph. **B.** Fluorescein angiography showed an irregular hyperfluorescent network located between the disk and the fovea. **C.** The corresponding early phase of indocyanine green angiography did not exhibit a similar pattern. The network could correspond to proliferation of small blood vessels located in the inner choroid, with a caliber too small to be visible with indocyanine green.

characterized by a whitish deep reticular pattern at the level of the RPE, located not only in the posterior pole but also in the midperiphery (Figure 4). This network of white lines displayed hyperautofluorescence associated with a few dark polycyclic dots (Figure 5A). Fluorescein angiography showed a crinkled pattern of the fundus resembling crocodile skin that was clearer in the late frames of the sequence (Figure 5B). Indocyanine green angiography also showed this crinkled pattern, but less clearly, and only in the late phase of the sequence (Figure 6). The OCT RPE map confirmed that the crinkled pattern of white lines was indeed located in the RPE. There were no folds in the inner retina, but the thickness of the outer nuclear layer was irregular because of the scalloped elevation of the RPE (Figure 7). Complications were mainly observed in the second generation, except for Patient III 2. One patient (II 1) exhibited marked atrophy of the macular RPE, choriocapillaris, and outer retina (Figure 8). Another patient (II 2) had a subretinal fibrous scar at the posterior pole, which might correspond to a scarring process after macular hemorrhages (Figure 9). Four patients (II 5, II 8, III 2, and the unrelated

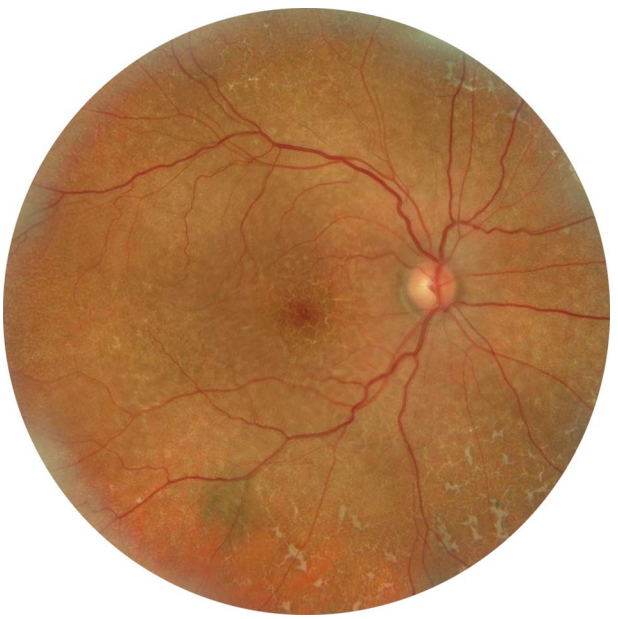

Fig. 4. Patient II 5, aged 51 years. Typical pattern of Martinique crinkled retinal pigment epitheliopathy. This photographic montage of the right fundus showed a deep reticular pattern of whitish lines extending from the posterior pole to the midperiphery, very characteristic of the disorder.

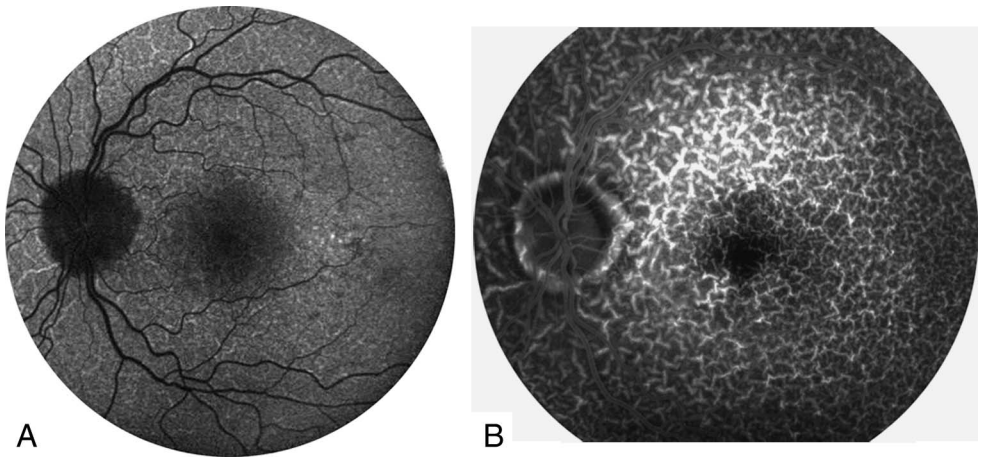

Fig. 5. Patient II 8, aged 63 years. **A.** Autofluorescence photograph of the fundus showing a whitish hyperfluorescent network, with areas of dark dots in left eye. **B.** Fluorescein angiography (late phase) shows the pattern of a reticular elevation of the RPE stained by fluorescein, giving a crinkled pattern resembling crocodile skin in left eye.

patient) displayed evidence of polypoidal choroidal vasculopathy (PCV), with subretinal and/or sub-RPE bleeding (Figure 10).

3. In the 86-year-old grandmother, the disease was characterized by severe visual loss combined with pigmentary clumping in the periphery and a focal area of deep whitish network (Figure 11).

The unrelated patient has now been followed up for 20 years. In this patient, the clinical changes were initially located in the peripapillary area. Severe subretinal bleeding occurred, because of lesions initially attributed to choroidal neovascularization but later diagnosed as PCV, and achieved fibrovascular scarring of the fundus. When last measured, visual acuity was 20/400 in the right eye and 20/30 in the left eye.

The visual field test (Goldman wide-field and Humphrey 30°) was normal in all uncomplicated eyes. This test could not be done in Patient I 2, aged 86 years. However, this patient had very poor vision limited to light perception, suggesting a deep visual field defect.

Electroretinography was performed in Patients II 8 and the unrelated patient. Each patient underwent a full electrophysiologic exploration, including an electrooculogram, ERG, multifocal ERG, and pattern ERG (Figure 12). The baseline amplitude of the electrooculogram was lower than the normal. The variation in the amplitude of the responses during the different states of adaptation was also lower than the normal. The amplitudes of the ERG responses elicited by flashes were below normal for the rod and the cone responses. Oscillatory potentials were indistinguishable from the electrical background noise. Assessment of the macular area with multifocal ERG revealed that the amplitude of the responses was very small or close to normal. The results of the electrophysiologic tests therefore suggested major dysfunction of the RPE, which may have induced a dysfunction of the photoreceptors that was greater for rods than for cones.

Samples of blood were obtained from affected and nonaffected patients belonging to the three generations. Gene testing is under way.

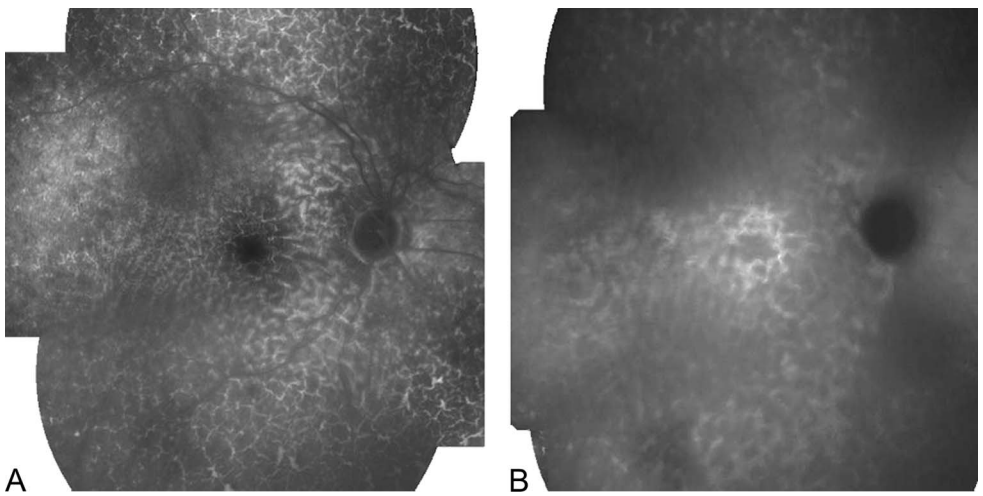

Fig. 6. Patient II 5, aged 51 years. Fluorescein and indocyanine green (ICG) angiography. **A.** Montage of the late phases of the angiography showing the fluorescent pattern of the RPE. **B.** Montage of the late phase of the ICG angiography. The RPE network is also fluorescent in ICG angiography but less than in the fluorescein angiography.

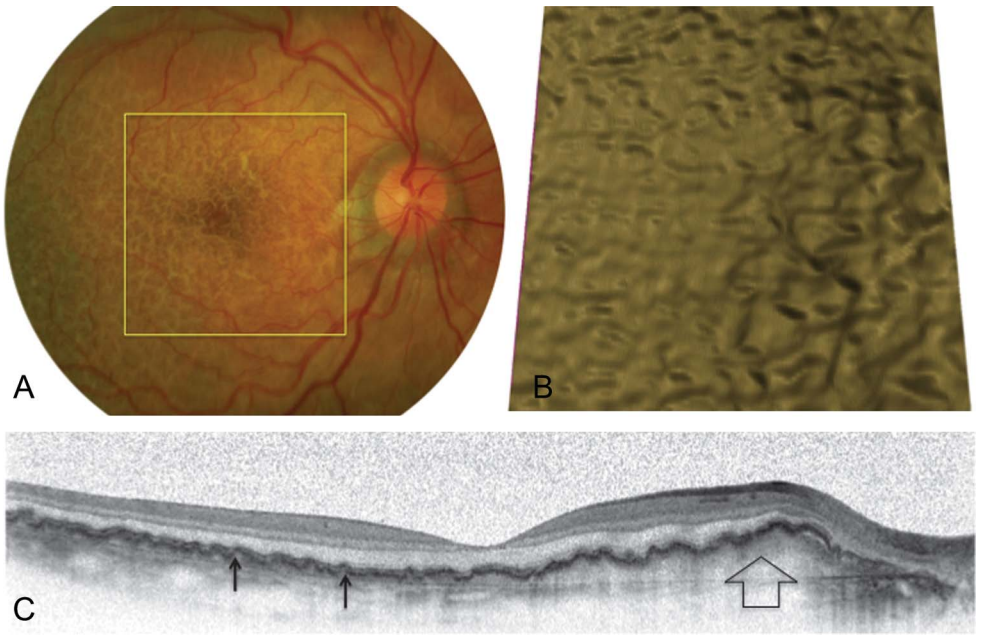

Fig. 7. Patient II 8, aged 63 years. **A.** Fundus photograph showing the typical network of white RPE lines (the yellow square corresponds to the area of the RPE map on OCT) in the right eye. **B.** Retinal pigment epithelium map showing the crinkled pattern of the RPE in the right eye. **C.** High-resolution 9-mm horizontal OCT scan showing irregular elevation of the RPE, with some sub-RPE deposits near the optic disk (large arrow) corresponding to the crinkled pattern shown in (**B**).

Discussion

The present report concerns a family with a crinkled pattern of the RPE and a probable autosomal dominant inheritance. As far as we know, the angiographic and OCT patterns observed here do not correspond to any previously reported patterns. This is the first description of the family in question, except for some pictures contributed by the present authors to the fifth edition of Gass' stereoscopic Atlas under the title of West Indies Crinkled Retinal Pigment Epitheliopathy.[1] Because no similar cases have been observed in West Indian islands other than Martinique, we now refer to the disease as Martinique Crinkled Retinal Pigment Epitheliopathy.

The phenotypic abnormalities were more obvious and severe in aged patients than in younger ones. It

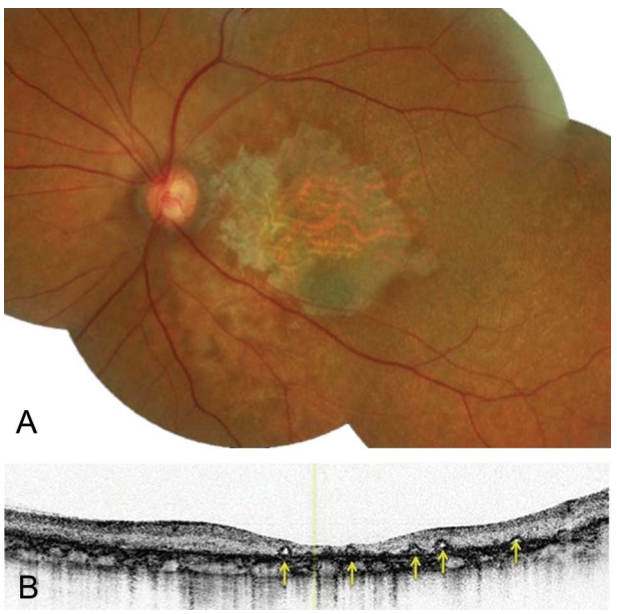

Fig. 8. Patient II 1, aged 59 years. Evolution to geographic atrophy. **A.** Color photomontage of the left fundus showing a large area of geographic atrophy in the macula. **B.** Optical coherence tomography 6-mm horizontal scan showing retinal atrophy in the macula with outer retinal cavitations (arrows).

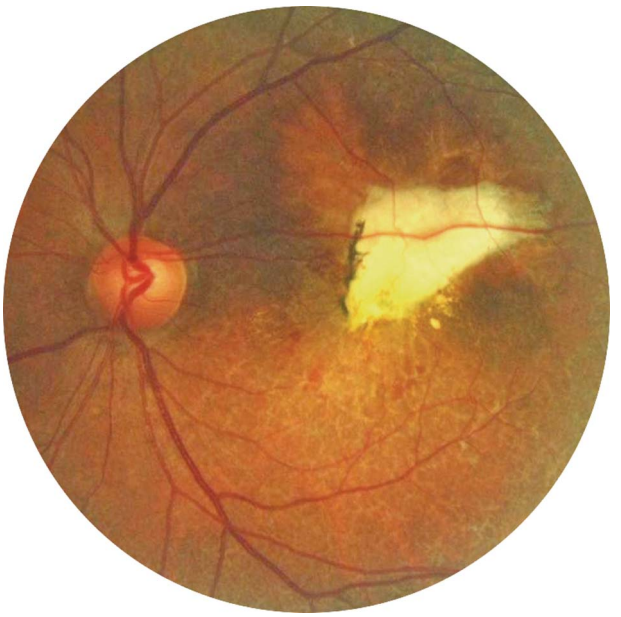

Fig. 9. Patient II 2, aged 58 years. Subretinal fibrosis. Fundus color photograph showing extensive subretinal fibrosis in the superotemporal part of the posterior pole, associated with the typical pattern of a white RPE network.

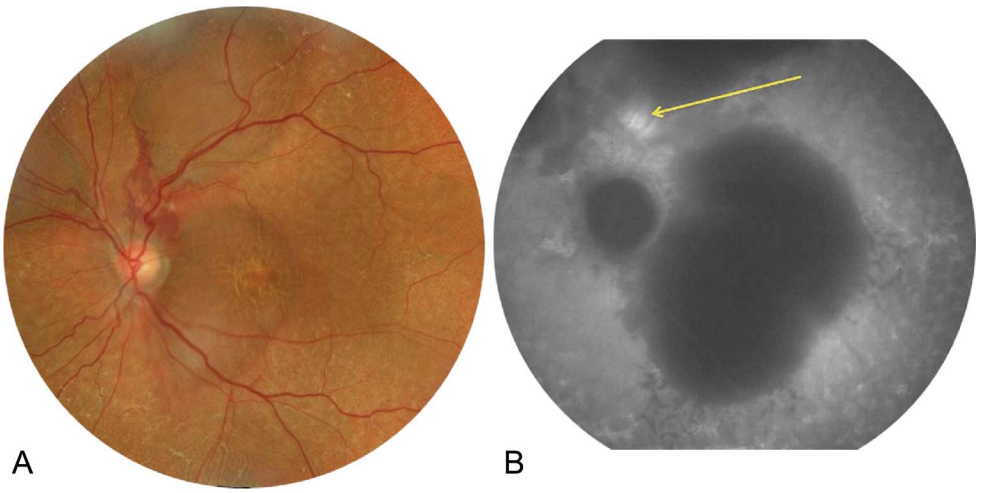

Fig. 10. Patient II 5, aged 51 years. **A.** Fundus photograph showing large areas of subretinal and sub-RPE bleeding in left eye. **B.** Indocyanine green angiography, late phase, showing PCV (arrow) as the cause of the bleeding in left eye.

may suggest an evolution of the disease characterized by different stages, from asymptomatic tiny abnormalities observed in young patients to the end-stage severe disease observed in the grandmother. However, description of stages is questionable in absence of longitudinal studies.

Its pattern seems unique. However, certain rare conditions may have some clinical features close to the ones reported here.

Cone–rod dystrophy with serpentine-like retinal deposits has been described in a German family with a probable autosomal inheritance. It was characterized by gray serpentine-like deposits in the RPE. However, the fluorescence pattern indicated faint local blockage of the background, very different from the present findings.[2]

In dominantly inherited Müller cell sheen dystrophy, prominent glistening light reflections may result in a whitish reticular pattern of the fundus,[3] but the pattern of railroad track-like folds is superficial, very different from the one reported here, as are the fluorescein angiography pictures.

Chorioretinal wrinkling caused by hypotony may give a fluorescein image close to the one reported here.[4] The appearance of the fundus, however, is very different, and in all the patients reported here, intraocular pressure was in the normal range. Furthermore, the OCT pattern was not one of chorioretinal folds, but rather corresponded to uneven elevations of the RPE, as if it had been crinkled.

The Alagille syndrome may be associated with chorioretinal folds that may cause streaky depigmentation of the RPE; however, the syndrome is associated with characteristic facies, arteriohepatic dysplasia, and ocular findings that include pseudopapilledema, which was not present here.[5]

The origin of the present complaint remains unknown. Electroretinography was performed in two patients, according to the ISCEV protocol.[6] The results did not

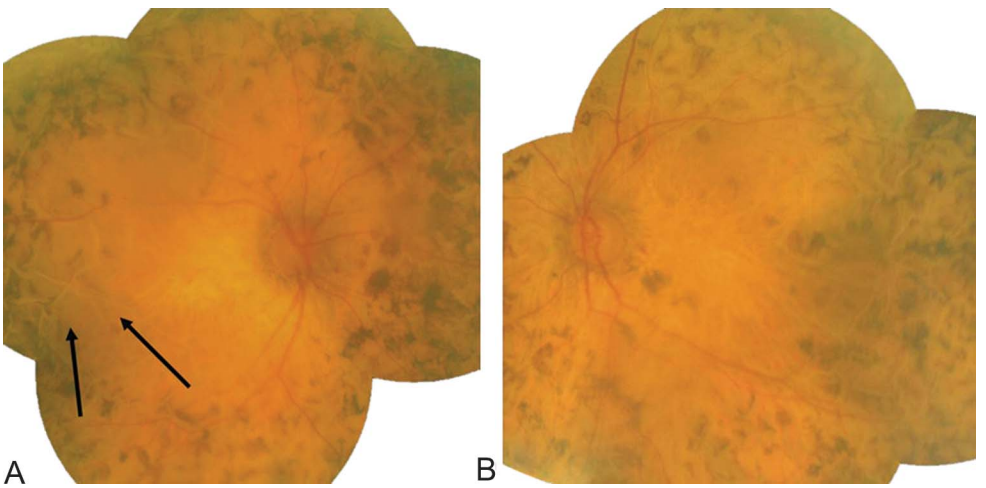

Fig. 11. Patient I 2, **A**. Right (**A**) and left (**B**) fundus photography of the 86-year-old grandmother. She had severe visual impairment associated with pigmentary changes in the periphery. Some whitish deep lines temporal to the fovea are visible (arrows).

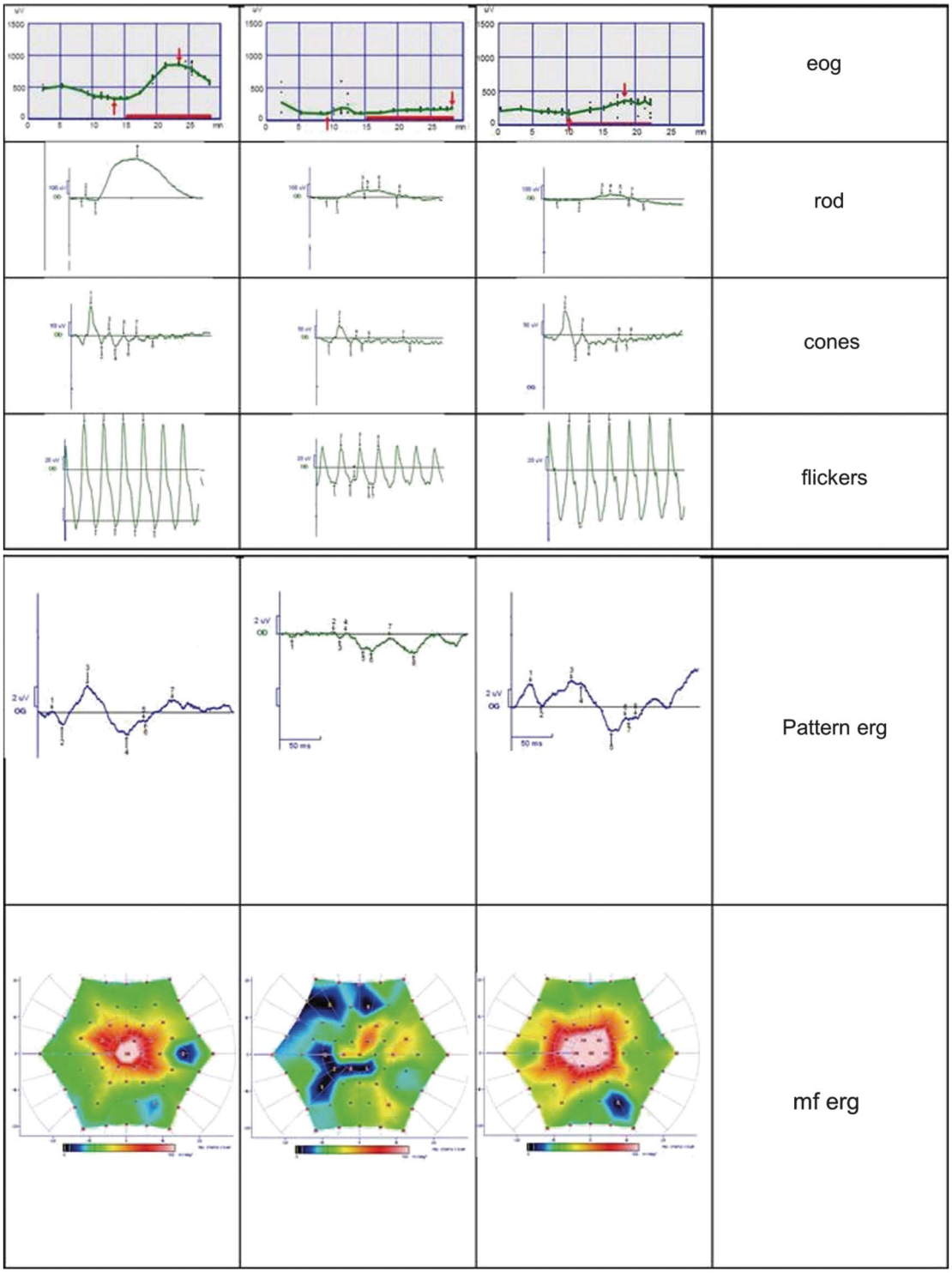

Fig. 12. Electrophysiologic testing of the unrelated patient aged 59 years and Patient II 8 aged 62 years. In both cases, the baseline amplitude of the electrooculogram (EOG) was lower than the normal. The amplitude of the variation in the responses during the different states of adaptation was also smaller than the normal, suggesting deterioration of the RPE. The amplitudes of the ERG responses elicited by flashes were below normal values for both the rod and cone responses. Oscillatory potentials were indistinguishable from the electrical background noise. Assessment of the macular area by multifocal ERG (mfERG) produced responses of very small amplitude or close to normal. These results show that macular function was relatively well preserved. Electroretinogram, tested by the alternating checkerboard pattern did not elicit any response.

suggest primary photoreceptor dysfunction. In contrast, the present results for electrooculogram disclosed deterioration of the RPE, even in Patient II 8 whose fundi showed no RPE changes except for the crinkled pattern. Retinal pigment epithelium dysfunction may be at the origin of relative ERG deterioration. Additional tests may be necessary to draw any conclusions about the involvement of photoreceptors in the pathogenesis of the disorder.

Optical coherence tomography findings showed anomalies of the RPE or below it. Deterioration of the elastic layer of the Bruch membrane, such as that occurring in pseudoxanthoma elasticum, may also cause uneven elevation of the RPE.[7] However, none of our patients had angioid streaks, *peau d'orange*, or the associated fundus findings. Skin biopsies were not performed, but the diagnosis of atypical pseudoxanthoma elasticum seems unlikely. The gene testing now under way will probably exclude the possible presence of pseudoxanthoma elasticum and will no doubt also help to understand the origin of the disorder.

Polypoidal choroidal vasculopathy complicated the disorder in four patients and another patient presented with a foveal fibrovascular scar, which might correspond to the natural history of a PCV lesion.[8,9] In PCV, vascular networks emerging from the choroid may extend from the Bruch membrane to the RPE and cause serohemorrhagic detachments of the RPE.[10] This condition was first described in American patients of African origin[11]; it is more frequent in black patients[12] and is common in the French West Indies.[13] The patients described here are French patients of African origin living in the French West Indies. The association of crinkled retinal pigment epitheliopathy with PCV may be coincidental. However, PCV seems to be frequently observed in this disorder, and the preexisting lesions located in the RPE or below probably enhance the risk of PCV lesions. It is not known whether in the present cases the PCV consisted of nonspecific vascular lesions complicating the disorder or whether it was part of the spectrum of the disorder. All patients related to the family examined here were informed about the symptoms that might necessitate an urgent visual examination.

Key words: retinal pigment epithelium, dystrophy, spectral domain optical coherence tomography.

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