Original article

Retinal autofluorescence imaging in patients with pseudoxanthoma elasticum

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ABSTRACT

Purpose: To evaluate the autofluorescence findings in patients diagnosed with pseudoxanthoma elasticum.

Material and methods: A prospective study was conducted on 18 eyes of 9 patients who had ocular pathology and followed up in the pseudoxanthoma elasticum (PSX) unit of our hospital. We evaluated the best corrected visual acuity (BCVA), colour and autofluorescence photography (AF), and fluorescein angiography (FA) in patients with choroidal neovascularization.

Results: Of the 9 patients, 7 were women and 2 were men. The mean age was 40 +/- 14 years. The BCVA ranged from 1 to 0.01 (Mean 0.65 +/- 0.4). All patients showed PSX injuries. Angioid streaks (AS) 18 (100%), peau d’orange 16 (87.5%) and pigmented fibrotic plates 5 (31.5%). We observed different hypoautofluorescence patterns (RPE atrophy), of which 2 of them were AS patterns (irregular lines with hyperautofluorescence speckled in its interior and edges, or bands with lobulated lesions inside and hyperautofluorescence at the edges), and finally widespread areas of hypoautofluorescence, larger than observed by ophthalmoscope.

Conclusions: Autofluorescence in patients with PSX is an easy method to evaluate the initial level of ophthalmoscopic involvement and its subsequent progression. The extensive changes in the retinal pigment epithelium (RPE) suggests the important role of this in the pathophysiology of the disease.

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Introduction

Pseudoxanthoma elasticum (PXE) or Gronblad-Stranberg syndrome is a rare multisystemic hereditary disease characterized by progressive calcification and fragmentation of soft connective tissue elastic fibers. Patients develop typical dermatological, ophthalmological and cardiovascular expressions. There is a broad range of genetic mutations and inter- and intra-family phenotype variety, enhancing the importance of early diagnostic to minimize systemic complication risks.1-4

The prevalence of PXE is estimated as 1 out of 25,000-100,000, with a prevalence of 2:1 in females. Its inheritance is autosomic (AR), with some cases of pseudo-dominance.1-4 The disease is due to mutations in the ABCC6 gene of chromosome 16p13.1, which encodes a carrier of the multidrug resistant protein (MRP-6) family, involved in cellular extrusion of molecules, hydrolyzing ATP.1-4

Ocular expressions are very frequent, including pigmentary changes in “orange skin”, optic nerve drusen, crystalline bodies, dystrophy in pattern. The most typical and frequent injuries, exhibited by 85% of PXE patients, are angioid striations (AS), which may remain stable or give rise to choroidal neovascularization (CNV), which affects 72-86% of these patients.2-5

The fundus photographs with autofluorescence (FA) is a new easy and non-invasive imaging technique that provides a topographic map of the lipofuscin pigment distribution in the retinal pigment epithelium (RPE) as well as other fluorospheres that may appear in other diseases affecting the external retina or the subretinal space. The excessive accumulation of lipofuscin granules in the RPE liposomes represents a descending pathway in the pathogenesis of many diseases, thus making this technique useful for a better understanding of the physiological mechanisms, the diagnostic, the phenotype – genotype correlation, predictive markers of the disease progression as well as for monitoring future therapies.6,7

Material and method

A prospective study comprising nine patients (18 eyes) diagnosed with PSX, followed up by the Pseudoxanthoma unit (considered as “a rare disease”) in our hospital. This unit comprises Internal Medicine, Dermatology, Physiology and Ophthalmology.

The study included all the patients diagnosed with PSX who exhibited ocular disease. The data included in the study were age, sex, years of follow-up after diagnostic and the presence of systemic involvement.

The ophthalmological assessment included best corrected visual acuity (BCVA) measured with the Snellen optotype, color and autofluorescence retinographies as well as fluorescein angiographies for the cases that presented neovascularization coroidea (NVC).

Results: De los 9 pacientes, 7 eran mujeres y 2 hombres. Edad media de 40,5 +/- 14, MAVC desde la 1 a 0,01 (media = 0,65 +/- 0,4). Todos los pacientes (18 ojos) presentaban lesiones del PSX: estrías angioides (EA) en 18 (100%), fondo en “piel de naranja” en 16 (87,5%) y placas fibrogliales pigmentadas en 5 ojos (31,5%). Observamos diferentes patrones de hipoautofluorescencias (atrofia de epitelio pigmentario), dos que se corresponderían a EA (líneas anfractuosas con moteado hiperautofluorescente en su seno y bordes, o bien bandas con lesiones lobuladas en su seno e hiperautofluorescencia en sus bordes) y por último grandes placas hipoautofluorescentes, de mayor tamaño que las observadas funduscópicamente.

Conclusions: La autofluorescencia en los pacientes con PSX es un método fácil para valorar el grado de afectación funduscópica inicial y su posterior evolución. La gran afectación del epitelio pigmentario retiniano (EPR), que hemos observado, nos sugiere el importante papel que juega este, en la fisiopatología de esta enfermedad.

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Results

Of the nine patients, 7 were female and 2 male, with ages comprised between 26 and 63 years (mean=40.5 +/- 14). BCVA ranged between 1 and 0.01. (Mean=0.65 +/- 0.4). All our patients exhibited ocular alterations, a necessary condition for inclusion in the study.

The autofluorescence of each funduscopic lesion was assessed separately: «orange skin» fundus, EA, crystalloid and colloidal bodies, optic nerve drusen, association to "pattern" retinal dystrophy and finally the development of CNV.

The "orange skin" fondness was exhibited by 16 eyes (87.5% of cases) and was defined as a small granular speckling, with similar translation in funduscopy and fluorescein angiography (fig. 1). The two remaining eyes (12.5%) exhibited large atrophic plates which made observation impossible.

In one eye (6.25%), optic nerve drusen were identified and the FA confirmed what we had already observed with funduscoppy (fig. 2).

The crystalloid and colloidal bodies are small subretinal peri-papillary peripheral rounded lesions which were found in 2 eyes (12.5%) and in FA they performed as hypoaautosfluorescent, with slightly hyperautopfluorescent edges (crystalloid bodies); or hyperautopfluorescent (colloidal bodies) (figs. 3 and 4).

Only one eye (6.25%) of one patient exhibited grid-type pattern retinal dystrophy. In FA it performed as the negative of FAG (hyperautopfluorescent grid, with hypoaautosfluorescent edges) (fig. 5).

The most typical lesions, but not pathognomonic of PSX, are EA which appeared in 100% of our cases. FA revealed hypofluorescent linear lesions (RPE atrophy), with

Figure 1 – Orange skin» background (brownish spots in funduscopy and slight autofluorescence in FA).

Figure 2 – Optic nerve drusen. Intense hyperautopfluorescence.
Figure 3 – More peripapillary colloidal bodies are observed than in funduscopy. Behavior is hyperautofluorescence, with hypoautofluorescent edges.

Figure 4 – Crystalline (hypoautofluorescent) bodies. “Comet tail” image.

Figure 5 – Grid pattern dystrophy. Hyperautofluorescent images surrounded by hypoautofluorescent area. FAG performs as negative.
hyperautofluorescent granules at the bottom and diffuse hyperautofluorescence along the edges, (parastriatal phenomenon), due to RPE carrying lipofuscin (figs. 6 and 7).

Of the 18 eyes, 5 exhibited large glyotic-atrophic plates in the posterior pole. Three (18.7%) exhibited CNV, which had been previously treated by our service, 2 eyes with photodynamic therapy (PDT) and one with anti-VEGF intravitreal injections (ranibizumab) (fig. 8). One patient (2 eyes) has been treated 10 years ago with argon laser in another hospital.

**Discussion**

The main goal of this paper is to make a descriptive and comparative study of funduscopic lesions by means of color photographs, with autofluorescence and fluorescein angiography of patients diagnosed with PSX.

The brownish spots ("orange skin" background) which can be seen in the mean periphery, more frequently temporal to the fovea, the first lesions to appear as a hypofluorescent spotted surface, with hyperfluorescent edges in FAG (which can be explained as a choroidal disease or due to an obstruction

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**Figure 6** – HypoFA linear lesions. Lobe-shaped hupoFA lesions in the path of EA.

**Figure 7** – Poorly defined hypoFA lesions bigger than those observed in funduscopy. Parastriation phenomenon.
of a dense RPE burdened with pigment), while in FA the lesions exhibit a slightly autofluorescent spotted pattern without clear topographic correlation with funduscopy. The electrophysiological tests provided normal results.²⁻¹⁴

In one of our patients we observed optic nerve drusen, described with a frequency of 5% in patients with PSX.²⁻⁴ In FA, they appeared with intense hyperautofluorescence and could be observed easier than in funduscopy.⁶⁻¹⁴ However, this was not our case.

Peripapillary and peripheral colloidal and crystalloid bodies are described. In the FA we observed to difference behavior, one as if they were crystalloid drusen (hypoautofluorescent with hyperautofluorescent halo) while others exhibited intense hyperautofluorescence (similar to optic disc drusen). These lesions extends to the periphery yielding a “comet tail” image.²⁻⁹ Shiraki et al prompted us to reflect on the material accumulated in the colloidal bodies, exhibiting intense hyperautofluorescence, most similar to those found in retinal dystrophies then into the drusen in the course of age related macular degeneration (ARMD).¹⁰

PSX is associated to pattern shaped retinal dystrophies in 10-15% of cases. The most frequent patterns are the dusty background and the grid. Agarwal et al¹¹ found a high prevalence of dystrophies: 73% (22 patients). As with Finder et al (10), our prevalence (6.25%) is lower.⁸ We believe that the large fibroglyal plates exhibited by some patients in the posterior pole could conceal these lesions. The patient who exhibited the grid pattern dystrophy in our work had a large pigmented glyotic plate in the other eye, secondary to CNV treated with anti-VEGF intravitreal injections. We postulate a greater and faster progression to the development of CNV in patients exhibiting pattern retinal dystrophies on the basis of a genotypical variety of PSX.⁸⁻¹¹

The angioid striations are described as uneven orange, dark red or brown radial lines which extend from the peripapillary area (as this is the point where the extrinsic ocular muscles exert more traction) to the periphery. There are color depends on the pigmentary characteristics of the choroids, which beginning to be seen with the thinning of the RPE over the linear defects of Bruch’s membrane. They usually appear in the second or third decade of life.²⁻⁴

We observed that the EA exhibit different FA patterns: I) The EA well defined in funduscopy appeared as hypoautofluorescent anfractuous lines with small hyperautofluorescent rounded lesions in their path, which correspond to RPE cells charged with lipofuscine. D) The EA with atrophic bed edges with paired reddish spots on the edges, shown in FA as hypoautofluorescent strips sometimes with oval-shaped images in their course and small hyperautofluorescent points or areas in their bed or edges (parastriation phenomenon). This phenomenon could be the result of the proliferation of RPE cells carrying lipofuscine or other fluorosphoric materials). The lesions are always shown in greater extension in FA than in funduscopy.

Sawa et al⁹ described three hypoautofluorescence patterns due to RPE atrophy (cracks, multi-lobule areas and poorly defined broad regions). While assessing our cases we thought that these patterns are an evolution of the disease because the large plates described by said authors were observed in advanced cases exhibiting treated or untreated CNV evolving to fibroglyal’s cause with large aggregates of pigment. It is true that said terminal lesions are more extended in FA, leading us to think that they follow a progressive growth in time.⁸⁻¹⁴ On the basis of the work of Schmitz-Valckenberg et al in which they relate hyperautofluorescence along the edges of the geographic atrophy of ARMD, with a greater prevalence of growth thereof, we could believe that the hyperautofluorescent strips (the parastriation phenomenon) and the hyperautofluorescence around the macular atrophic extended plates, would predict the evolution of the disease.¹⁵

The increased aggressiveness of CNV would be related to the EA (Bruch membrane fracture lines) which facilitates the invasion of choroidal vessels. The atrophic changes in RPE observed in FA could lead us to think that RPE also plays an important role in the behavior of the disease involving greater risk, aggressiveness and subsequent scarring of the CNV.⁴⁻⁵,⁸⁻¹⁰ With the exception of the three patients who had exhibited
CNV, the remaining six were young and their disease was in the early stages.

The gene responsible for PSX (ABCC6) encodes protein MPR6, a member of the ABC family of membrane carriers. Even though the physiological function of MPR6 is as yet unknown, at present there are two theories that endeavor to explain the phenotypic variation of PSX: one is the “metabolic hypothesis” which suggests that the lack of MPR6 prevents hepatocytes from releasing essential substances for preventing an ectopic and aberrant mineralization. The other is the “PSX cellular hypothesis” which postulates that the inactivity of MPR6 gives rise to abnormalities in the sand of the tissues affected by PSX, such as dermic fibroblasts. The majority of their alterations are attributed to the degeneration of elastic fibers which involve a progressive mineralization and fragmentation. Other studies demonstrate a severe involvement of the extracellular matrix components (collagen, proteoglycans, fibroblasts and others).

Gheduzzi et al carried out a histological study of the eyes of two cadavers that exhibited PSX, observing that the Bruch membrane was always very altered and almost entirely calcified. Abundant collagen and elastin fibers were found in all the layers of the choroids and vessel walls.

Even though the MPR6 carrier does not seem to express in any ocular cell, this cannot be stated with full certainty. Histological studies carried out in mutated mice observed dense calcified materials in the elastic sheet of Bruch’s membrane, similar to that found in humans with ARMD. As we know, with aging the digestion of the external segments of photoreceptors by RPE is altered, producing waste products (basal laminar deposits - plasmatic and basal membrane of the RPE- and basal linear deposits - basal RPE membrane and internal sheet of Bruch’s membrane).

Even though the metabolic hypothesis is increasing in relevance on the grounds of «in vitro» and mutated mice studies, we could think that both hypothesis are valid to determine the pathogenesis of the ocular lesions: the «metabolic pathway» would involve aberrant calcifications with an ensuing deterioration of RPE cells. Alternatively, with the «PSX-cellular pathway», the inactivity of MPR6 could also be expressed in the RPE cells just like in the liver and kidney, altering their function. Accordingly, these cells would not be able to evacuate their waste products which would accumulate inside them causing their destruction, or would eliminate substances involved in the calcification of Bruch’s membrane. This would be similar to the pathogenesis of Stargardt’s disease (aggregation of a lipofuscin-like material in the RPE), in which the defective ABCA4 gene is also encoded by a protein carrier.

We will conclude indicating that FA is an easy method for diagnosing and following up the disease of this paper, observing the large involvement of RPE. Subsequent studies with a higher number of patients and longer evolution times will assist in confirming these hypotheses, namely whether there are phenotypes other than PSX which are more related to the development of CNV and its visual evolution, and whether or not RPE plays a leading role in the physiopathology of this disease (fig. 8).

Conflict of interest

None of the authors have declared any conflict of interest.

References
