ORIGINAL ARTICLE

Macular pigment distribution in Stargardt macular disease

Densité du pigment maculaire dans la maladie de Stargardt

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KEYWORDS
Autofluorescence; Macular pigment; Macular pigment optic density; Stargardt disease

Summary
Purpose. — To investigate macular pigment optical density (MPOD) and distribution in patients with Stargardt disease.
Methods. — Prospective observational case series. The study included 13 eyes of 13 consecutive patients. A modified confocal scanning laser ophthalmoscope (SLO, Heidelberg, Germany) was used for MPOD measurement. It calculated the MPOD at 0.5° of the center of the fovea, and MPOD in the 0.5° and 2° areas.
Results. — Two different MPOD profile patterns were observed: group 1 was composed of patients with a flat profile, i.e., with very low MPOD in all locations, and group 2 presented a normal profile. In group 2, all eyes but one had good visual acuity (VA); in group 1, some displayed poor VA, but others had good VA. All patients in group 1 displayed a thinning of the macular area on OCT.
Conclusions. — These results suggest that the flat MPOD profile, even if the visual acuity is good, could be associated with poor prognosis. The two different patterns of MPOD distribution described could reflect two different stages in the course of Stargardt disease. No strong correlations were found between MPOD profiles and visual acuity or macular thickness, but a straight trend was brought out that may indicate that the flat MPOD profile has a poor functional prognosis. Long follow-up is required to confirm this hypothesis.

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Purpose

Stargardt dystrophy is an hereditary sight-threatening disease that affects both retinal pigment epithelium and photoreceptor layers. General course of Stargardt disease consists in a slow loss of central vision associated, in the late stages, with central atrophy [1]. Before final atrophy occurs, there is a time period during which foveal structure and function are both relatively preserved as compared to the surrounding parafoveal region. It has been hypothesized that macular pigment, the yellowish carotenoid concentrated in the foveal area, contributes — at least for part — to the preservation of this region [2,3]. Hence, measuring macular pigment density (MPD) could help to improve our understanding of the course of the disease.

Recently, heterochromatic flicker photometry has been used to determine MPD [2] in Stargardt disease, but this method has the disadvantage to be a psychophysical test requiring a reliable participation of the patient. Fundus autofluorescence was generally considered as the most effective method to ascertain Stargardt disease and to evaluate its evolution [4–6]. This technique has also been used to perform a functional approach in Stargardt disease, like establishing correlation with the scotomas or with the retinal function [7,8], but it could only give an indirect evaluation of MPD. Zhang et al. [3] analyzed macular pigment in Stargardt disease comparing the appearance of the macula with a four wavelengths illumination (reflectance method), but the results were only qualitative.

All these techniques do not need any elaborate participation of the patient, but they were unable to give quantified data as heterochromatic flicker photometry or Raman do. Our study was aimed at evaluating MPD and macular pigment spatial distribution in Stargardt disease using an objective method.

Methods

Patients

This study is a prospective observational case series. Thirteen consecutive patients seen between 2007 and 2008 presenting Stargardt disease with macular involvement were included. The diagnosis was based on clinical evaluation, ascertained by fundus autofluorescence and fluorescein angiography. All patients were informed of the purpose of the analysis and provided their signed consent to be measured. They were recruited in compliance with French regulation, and this research adhered to the tenets of the Declaration of Helsinki.

All patients had at least a visual acuity (VA) of 20/200 which is the minimum required for fixation during examination; therefore no eye with a late stage of the disease was included. When both eyes were eligible, only the one with the highest MP density at the 0.5° radius was included in the analysis. Normal data for MPD were recorded from a group of subjects without ocular disease. These subjects were matched to our patients for age and sex (n = 13).

Macular evaluation

Inclusion criteria were age over 18 years, fundus with loss of the foveal reflex, pigmentary maculopathy or retinal flecks. All patients had a complete ophthalmic examination, including best-corrected Snellen visual acuity (BCVA),

Résumé

But. — Mesurer la densité du pigment maculaire (PM) chez des patients porteurs de maladie de Stargardt.

Méthodes. — Étude observationnelle prospective portant sur 13 yeux de 13 patients consécutifs. Une acuité visuelle minimale était requise afin d’obtenir une bonne fixation au cours de l’examen. Dans tous les cas il y avait des lésions maculaires. La densité du PM a été mesurée à l’aide du scanning Laser Ophtalmoscope (Heidelberg®) utilisant la méthode d’autofluorescence. La densité du PM était mesurée à 0.5° d’excentricité et dans l’aire des 0.5 et 2° centraux. Une mesure de l’épaisseur maculaire centrale à l’aide du Stratus OCT (Zeiss®) a également été effectuée.

Résultats. — Deux types de profil de densité de PM ont été mis en évidence : un type de profil plat (groupe 1) dans lequel la densité de PM est très basse quelque soit le degré d’excentricité, et un type avec pic central (groupe 2) dans lequel la densité de PM est normale à 0.5° et décroît très rapidement pour des valeurs basses à 2°. Tous les patients du groupe 2 sauf un présentent une bonne acuité visuelle. Ceux du groupe 1 ont des acuités visuelles très variables. Enfin tous les patients du groupe 1 ont une épaisseur maculaire diminuée sur l’OCT.

Conclusions. — Nos résultats suggèrent qu’un profil de répartition plat du PM, même si l’acuité visuelle reste bonne, pourrait être associé avec un moins bon pronostic. Les deux types de profil de densité de PM décrits pourraient correspondre à des stades évolutifs différents de la maladie. Aucune corrélation n’a pu être établie entre les types de profil de PM et l’acuité visuelle d’une part, ni avec l’épaisseur maculaire d’autre part. Il serait intéressant de confirmer cette hypothèse sur une série plus importante, et avec un suivi plus long.

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Results

Results are presented in Table 1. The patients with Stargardt’s disease were 5 men and 8 women. Mean age was 37 ± 16.3 years (range 18–61).

Autofluorescence

Autofluorescence images demonstrated typical lesions of Stargardt macular dystrophy or fundus flavimaculatus [6,8,13]: reduced signal of autofluorescence in the fovea, and/or small disseminated spots of reduced and increased intensity, and/or retinal flecks, and/or an elevated background autofluorescence signal. In all patients but two, images showed a diffuse high level of autofluorescence. Eleven among the thirteen included eyes presented macular dystrophy. The pattern of this dystrophy is represented by small spots with high and low signal of autofluorescence and/or hyperfluorescent flecks. Only three patients presented an area with intense loss of autofluorescence corresponding to area of atrophy, but this atrophy was located in para-macular zone.

Macular pigment density

Findings are presented in Tables 1 and 2. MPOD in normal subjects (control group) was 0.48 (± 0.16) at 0.5° radius, 0.54 (± 0.16) within the 0.5° area, and 0.36 (± 0.10) within the 2° area. Normal subjects demonstrated typical distribution of MPOD as previously described with a central peak and decline with eccentricity.

In Stargardt patients, mean MPOD at 0.5° radius was 0.29 (± 0.18). Mean MPOD within the 0.5° area and the 2° area were 0.30 (± 0.22) and 0.21 (± 0.11) respectively. These results show that Stargardt patients of our study have a lower MPOD than the control population. Furthermore, patients with Stargardt disease presented two different patterns of MPOD:

- a first group (group 1; n = 6) was composed of eyes with low MPOD at 0.5° (≤ 0.22) and very low MPOD in the eccentric locations, showing a flat profile. In this group, mean MPOD at 0.5° radius was 0.13 ± 0.07, and within the 0.5° and 2° areas 0.11 ± 0.08 and 0.12 ± 0.04 respectively (Fig. 1);
- a second group (group 2; n = 7) was composed of eyes with normal MPOD at 0.5° (≥ 0.32) and with a normal profile, i.e. a central peak with a decrease of MPOD at 2°. In this group 2, mean MPOD at 0.5° radius was 0.43 ± 0.11. Within 0.5° and 2° areas, it was 0.45 ± 0.14 and 0.28 ± 0.08 respectively (Fig. 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Data of the 13 eyes of the 13 Stargardt patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>MPOD 0.5° radius</td>
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<tr>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
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<tr>
<td>2</td>
<td>39</td>
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<tr>
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<td>24</td>
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<td>18</td>
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<td>6</td>
<td>35</td>
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<td>Group 2</td>
<td></td>
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<td>1</td>
<td>51</td>
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<td>2</td>
<td>52</td>
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<td>50</td>
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<td>6</td>
<td>48</td>
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<td>7</td>
<td>17</td>
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</tbody>
</table>

MPOD: macular pigment optical density; BCVA: best-corrected visual acuity; OCT: optical coherence tomography.
Table 2  Mean Macular Pigment Density (MPD) measured at the 0.5° radius, within the 0.5° and the 2° areas in controls, Stargardt’s eyes, group 1 and group 2.

<table>
<thead>
<tr>
<th></th>
<th>0.5° radius (± SD)</th>
<th>0.5° area (± SD)</th>
<th>2° area (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control eyes (n = 13)</td>
<td>0.48 (0.16)</td>
<td>0.54 (0.16)</td>
<td>0.36 (0.10)</td>
</tr>
<tr>
<td>Stargardt’s eyes (n = 13)</td>
<td>0.29 (0.18)</td>
<td>0.30 (0.22)</td>
<td>0.21 (0.11)</td>
</tr>
<tr>
<td>Group 1 (n = 6)</td>
<td>0.13 (0.07)</td>
<td>0.11 (0.08)</td>
<td>0.12 (0.04)</td>
</tr>
<tr>
<td>Group 2 (n = 7)</td>
<td>0.43 (0.11)</td>
<td>0.45 (0.14)</td>
<td>0.28 (0.08)</td>
</tr>
</tbody>
</table>

DS: standard deviation.

Figure 1.  Left eye of patient 6 from group 1. BCVA = 20/100 and central retinal thickness = 121 μm. Autofluorescence images (A) depict retinal flecks with pigment clusters and a reduced central signal of autofluorescence. MPD map with the diagram on the left side displaying the radial distribution of macular pigment (B): there is an area of macular pigment (in drab greyish) with a very low density either at 0.5° from the fovea (MPD = 0.14) or into the 2° area where density is almost the same (MPD = 0.12).

Figure 2.  Left eye of patient 5 from group 2. BCVA = 20/20 and central retinal thickness = 209 μm. Autofluorescence images (A) demonstrate retinal flecks and spots of reduced and increased intensity on the macula. MPD map with the diagram on the left side displaying the radial distribution of macular pigment (B): there is an area of macular pigment (in bright white) with a normal peak either at 0.5° from the fovea (MPD = 0.64), and into the 2° area (MPD = 0.38).
The autofluorescence patterns were similar in the two groups. One patient with para-macular atrophy was in group 1, and the two others in group 2.

Central Macular Thickness

Central macular thickness was 150.1 μm (± 44.8) on average. Patients with a normal MPOD profile (group 2) had also normal macular thickness (182 ± 36 μm) on average, whereas those with a flat MPOD profile displayed decreased macular thickness (113 ± 13 μm) on average. In group 1 all patients had a decreased thickness. But in group 2, three patients had a decreased thickness: one with atrophy and the two others with a low level of central autofluorescence without atrophy.

Visual Acuity

BCVA ranged from 20/20 to 20/200. BCVA tends to be better in group 2 than in group 1 (visual acuity was 20/20 in 4/7 eyes), but no correlations between VA and MPOD at 0.5°, neither between VA and central macular thickness were observed.

Discussion

Numerous studies have tended to demonstrate that macular pigments, lutein and zeaxanthin, have a protective role against macular degeneration [14,15]. The major topic of interest is represented by age-related macular degeneration, because of the high number of patients concerned [16—18]. Stargardt disease, on the contrary, is far less frequent, but threatens the vision of younger patients, sometimes in the childhood. The course of the disease is not homogenous, and two different forms can be distinguished: Stargardt dystrophy, on the one side, in which macula is mostly altered, and fundus flavimaculatus, on the other side, characterized by yellowish fish tails lesions scattered through the posterior pole and extending out to the midperiphery [1]. However, it has been demonstrated that these two well-defined clinical forms correspond to a same disease, characterized by mutations on the ABCR gene [19].

Macular pigment optical density has already been evaluated in patients presenting ABCA4 gene mutation (which encodes the ABCR protein) by Aleman et al. [2]. In their study, they measured MPOD using heterochromic flicker photometry, which is the most widely used method validated by numerous previous studies [20—22]. But, despite consistent advantages (inexpensive, no pupil dilatation required, non influence of absorption or scattering in the optic media), it remains a subjective method, requiring training of subjects. The scanning laser ophthalmoscope (SLO) modified autofluorescence technique, on the contrary, appears to be more objective and reproducible [23], and is now well validated [10—12].

In our study, as the number of patients is low, it is difficult to establish any statistical analyses. Nevertheless, we observed that the mean MPOD in Stargardt patients was lower than in control group, such results being relevant with those published by Aleman et al. [2]. If we consider MPOD measurements at 0.5° radius, Stargardt eyes showed 60% of the MPOD measured in the control population. Within the 2° area the difference of MPOD between patients and control subjects was quite the same (58%).

More interestingly is the analysis of the spatial distribution of the MP displayed by the MP profiles curves. Two profiles of MP distribution can be identified. The first one corresponds to a flat profile, in which MPOD is low in all locations. The second one displays a normal profile with a central peak at 0.5° of eccentricity, and a decrease of MPOD at 2°. On the Fig. 3 we can see that the curves of the control group and of the group 2 are parallel, when the group 1 is strongly flat and low. Zhang et al. [3], using another HRA method, also found different amounts of mean macular pigment in the fovea of Stargardt eyes, however they did not define any profile of macular pigment distribution [3]. Moreover, in our study no correlations between presence of flecks or small spots around the fovea on the autofluorescence images and MPOD were observed. For instance, some eyes with normal MPOD profile presented advanced dystrophic lesions while others presented very subtle lesions associated with poor MPOD. MPOD did not seem to be related to the severity of funduscopic lesions, but mainly to the level of autofluorescence intensity emitted by the macula. This finding is consistent with the fact that MPOD is calculated from the subtraction between two autofluorescence images taken at two different wavelengths.

A correlation between VA and macular pigment has been already suggested by Zhang et al. [3]. They indeed described a strong link between mean macular pigment level and VA as none of their patients presenting low MP amount had a good visual acuity, and proposed that macular pigment could be related to foveal cone acuity. Our results are different as no strong correlation between level of MPOD and visual acuity could be found. Even if most of the patients of group 2 had a good visual acuity (all but one had VA > 20/40 and 4/7 had 20/20) some patients of group 1 could have a low MPOD with a good BCVA (patients 3 and 4, Fig. 4). We are not able to establish a strong correlation between MPOD and VA prognosis, but our data suggest that low MPOD may be correlated to a poor visual prognosis, as low MPOD may precede RPE atrophy and decreased VA. The natural history of both macular dystrophy and VA loss in Stargardt disease has been well described [1,24], demonstrating over the time a functional deterioration related to the progression of the macular dystrophy. The two different patterns of MPOD distribution we
described could represent two different stages of the course of Stargardt disease: first a normal profile and then a flat one. With this hypothesis, a patient with a good visual acuity but a flat profile would have more risk to progress towards a more severe stage. And the flat profile could represent a more severe form of Stargardt disease. Further studies with repeated MPOD measurements during follow-up are required to confirm such hypothesis.

Finally, central foveal thickness on OCT is lower than normal on average. If all patients with a flat profile had a thinning of the macula, some patients in group 2 had normal central thickness. This result could be related to the presence of less severe forms of the disease in this group. No correlations between central thickness and BCVA could be established. This result is different from those published either with a spectral OCT [25] or a Stratus OCT [26] where poor visual acuity was associated with low macular thickness. This difference could be related to the absence of late stages of Stargardt disease in our study, as minimal VA was required for a good fixation during MPOD measurement.

**Conclusion**

Stargardt disease is a clinical heterogeneous disease. Even if an eye presents characteristic fundoscopic lesions, it remains difficult to establish an early prognosis regarding to the severity of these lesions. Macular pigment density and distribution pattern could help to establish a prognosis. Our series contributes to the description of the macular pigment distribution in Stargardt dystrophy. The observation of two different macular pigment profiles, flat and normal, could represent two different stages of the disease. Flat MPOD profile with a good visual acuity could be associated with poor prognosis, as it could precede the loss of visual acuity. Long follow-up is required in order to confirm this hypothesis.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


