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# Distribution of pigment epithelium autofluorescence in retinal disease state recorded in vivo and its change over time

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**Abstract** ● Background: Recently a technique of imaging the retinal pigment epithelium (RPE) has been developed that takes advantages of its intrinsic fluorescence derived from lipofuscin. The purpose of this study was to document the distribution of fundus autofluorescence in patients with various retinal diseases and its change over time. ● Methods: The intensity and spatial distribution of fundus autofluorescence was documented in 318 eyes from 159 patients with various retinal diseases using a confocal Laser Scanning Ophthalmoscope. Thirty patients with macular dystrophies and 30 with age-related macular disease underwent serial examinations over a period of 1–3 years in order to monitor the changes over time of fundus autofluorescence. ● Results: Absent autofluorescence corresponded well spatially with outer retinal atrophy in eyes with retinitis pigmentosa and rod-cone dystrophy. Abnormally high background autofluorescence was seen in the macular region in some patients with dominant and recessive retinitis pigmentosa and rod-cone dystrophies. In areas of macular edema fundus autofluorescence was abnormal. Fundus autofluorescence showed changes over time in most of the eyes with retinal diseases studied. ● Conclusion: Fundus autofluorescence allows documentation of areas of photoreceptor cell loss in eyes with retinitis pigmentosa and rod-cone dystrophies. If abnormal high background autofluorescence in the surviving areas occurs only in some patients with retinitis pigmentosa, the technique may serve to distinguish the regional from the diffuse type of disease. Over time, fundus autofluorescence may demonstrate change or may remain stable.

## Introduction

Recent advances in opthalmoscopic imaging have resulted in a new technique of visualising the retinal pigment epithelium (RPE), taking advantage of its autofluorescence derived from lipofuscin [14–16]. Autofluorescence imaging with a confocal Laser Scanning Ophthalmoscope (cLSO) can prodive highly detailed information about the levels and distribution of lipofuscin of the RPE within the living eye, revealing a previously invisible structure. In vivo recording of pigment epithelial autofluorescence as an index of lipofuscin accumulation allows analysis of the sequence of pigment epithelial changes and gives indirect information on the level of metabolic activity of the RPE.

It is expected that accurate imaging of the distribution of autofluorescence in the RPE, quantitative measurements under direct viewing in specific areas and studies of the dynamics of accumulation, degradation and clearance of lipofuscin would add a great deal of information regarding the relation between the pigment epithelial autofluorescence and retinal disease.

In this paper we document the intensity and distribution of fundus autofluorescence in eyes with various retinal diseases and demonstrate its change over time.

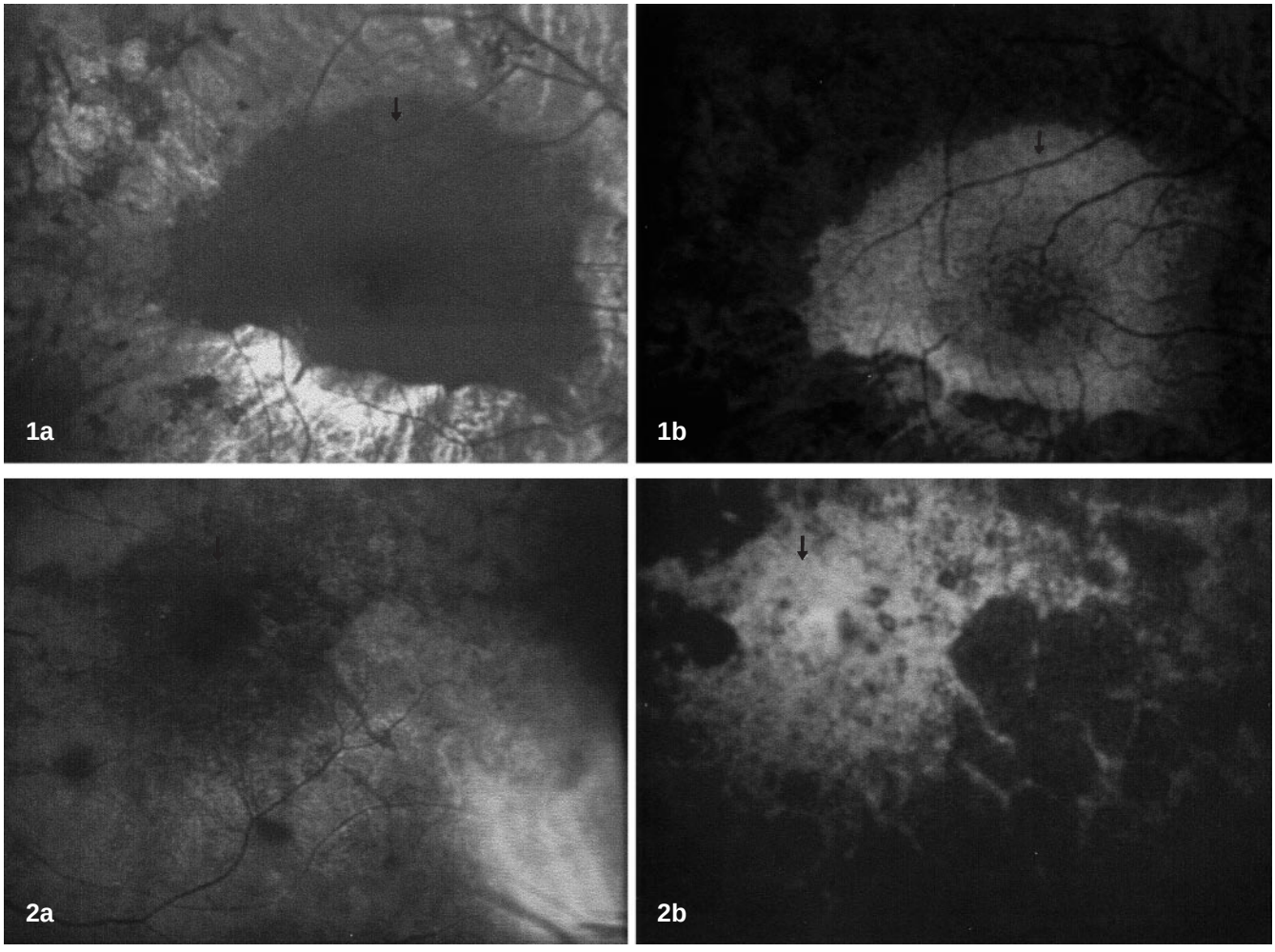



**Fig. 1** **a** Reflectance image of a 36-year-old woman with autosomal recessive retinitis pigmentosa with atrophy of the outer retina, RPE and inner choroid except at the macula (*arrow*). Visual acuity in the left eye was 20/20. **b** Fundus autofluorescence image showed decreased fluorescence at the sites of atrophy. Autofluorescence is present in the surviving area (*arrow*)

**Fig. 2** **a** Reflectance image of a 38-year-old man with autosomal dominant retinitis pigmentosa with well-defined profound atrophy of the outer retina, RPE and inner choroid except at the macula (*arrow*). Visual acuity in the right eye was 20/30. **b** Fundus autofluorescence image showed decreased fluorescence at the sites of atrophy. Autofluorescence is abnormally high in the surviving central area (*arrow*)

## Subjects and methods

A total of 318 eyes from 159 patients with various retinal diseases were examined. The study group consisted of 28 patients with dominant retinitis pigmentosa, 35 patients with recessive retinitis pigmentosa, 36 patients with rod-cone dystrophies, 30 patients with inherited macular dystrophies (7 with adult vitelliform macular dystrophy, 6 with Best disease, 12 with fundus flavimaculatus and 5 with pattern dystrophy) and 30 patients with age-related macular disease. The patients with macular dystrophy and age-related macular disease underwent repeated examinations for a period of 1–3 years in order to monitor the changes over time of fundus autofluorescence. The age range of the patients was 17–78 years (mean 46 years). All patients had clear lenses or minimal nuclear sclerosis as determined by slit-lamp examination. The pupil was dilated with phenylephrine 2.5% before imaging to a size of at least 6 mm (at which pupil size has a negligible effect).

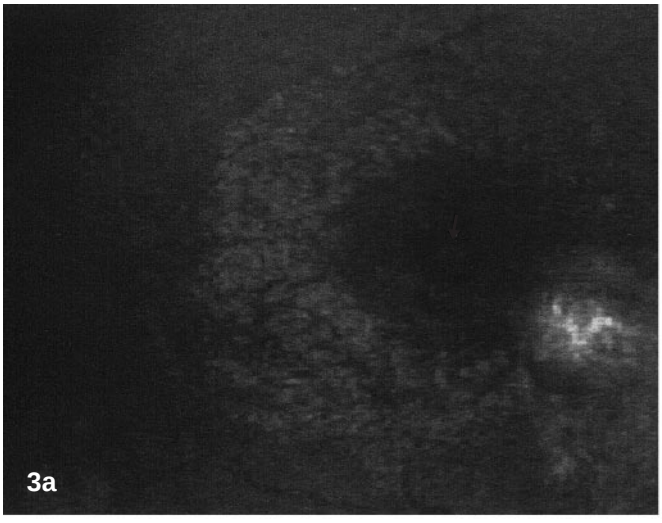
The cLSO was a prototype SM 30-4024, Zeiss, Oberkochen, Germany. Argon laser light was used for illumination and to record autofluorescence, a wide band-pass filter with a cut-off at 521 nm was inserted in front of the detector. The 40° field-of-view mode and the confocal aperture 3, providing a depth resolution of less than 200 μm, were used to produce reflectance (standard red-free) and autofluorescence images. After focusing on the structure of interest, a series of images (reflectance images) was recorded. The barrier filter was then moved into place in front of the detector in the cLSO and a series of images (autofluorescence images) was recorded again [14–16]. The images were recorded at standard video scanning rates on SVHS video type and digitized. Thirty-two images were aligned and averaged automatically to reduce noise. The image resolution is 768×572 pixel.

The autofluorescence images were compared with reflectance images and color slides obtained using a fundus camera.

The intensity of autofluorescence was measured in gray-scale arbitrary units from 0 to 255. The levels of autofluorescence were compared with normal values established previously [15, 16] (Table 2b). Abnormally high (low) autofluorescence was defined as that

**Table 1** Frequency of normal, increased and decreased autofluorescence in patients with retinitis pigmentosa and rod-cone dystrophy measured in the central and peripheral fundus of the right eye. *n*, total numbers of subjects

| Category | Location of autofluorescence measurement | Normal autofluorescence | Increased autofluorescence | Decreased autofluorescence |
|---|---|---|---|---|
| Dominant retinitis pigmentosa (*n*=28) | Center | 10 (36%) | 7 (25%) | 8 (29%) |
| | Periphery | 0 (0%) | 0 (0%) | 28 (100%) |
| Recessive retinitis pigmentosa (*n*=35) | Center | 14 (40%) | 8 (23%) | 13 (37%) |
| | Periphery | 0 (0%) | 0 (0%) | 35 (100%) |
| Rod-cone dystrophy (*n*=36) | Center | 2 (6%) | 11 (31%) | 8 (22%) |
| | Periphery | 0 (0%) | 0 (0%) | 36 (100%) |



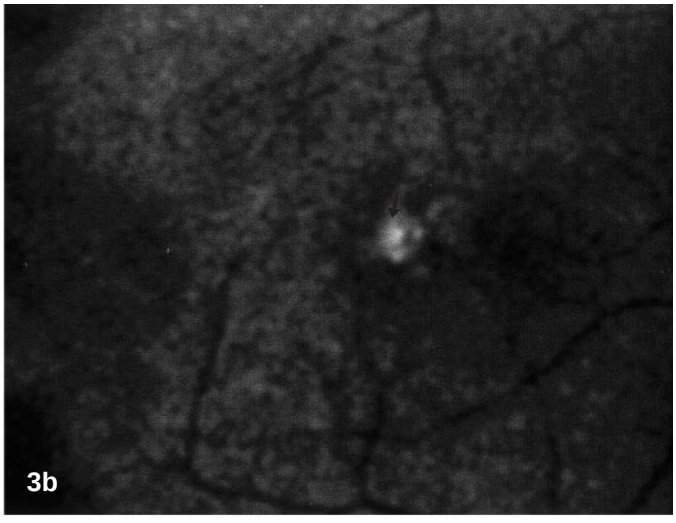
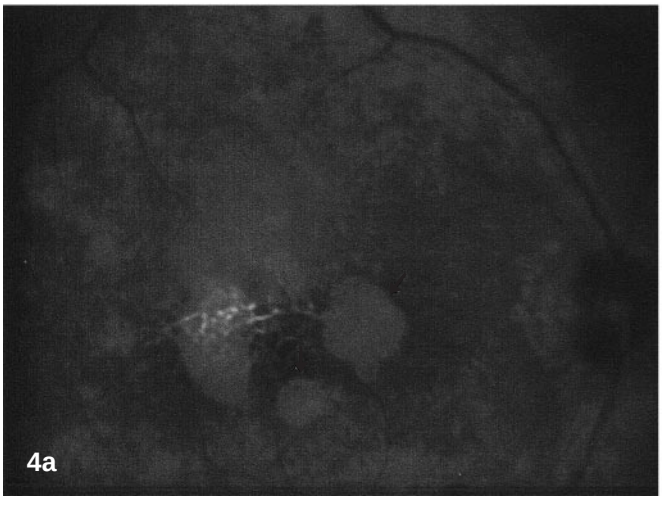




**Fig. 3** **a** Reflectance image and **b** autofluorescence image of a 51-year-old woman with autosomal dominant retinitis pigmentosa and macular edema of 9 months duration reducing visual acuity to 20/100 (**a**). The focal central area of abnormal high autofluorescence corresponds to the area of macular edema (*arrow*, **b**)



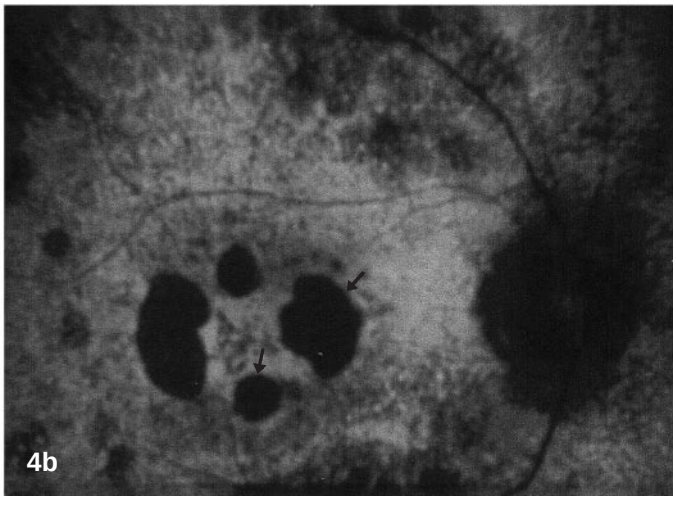




**Fig. 4** **a** Reflectance image and **b** autofluorescence image of a 63-year-old man with autosomal recessive retinitis pigmentosa and macular edema (*arrows*) of 5 years duration reducing visual acuity to 20/200 (**a**). Fundus autofluorescence was absent in the area of macular edema (*arrows*, **b**)

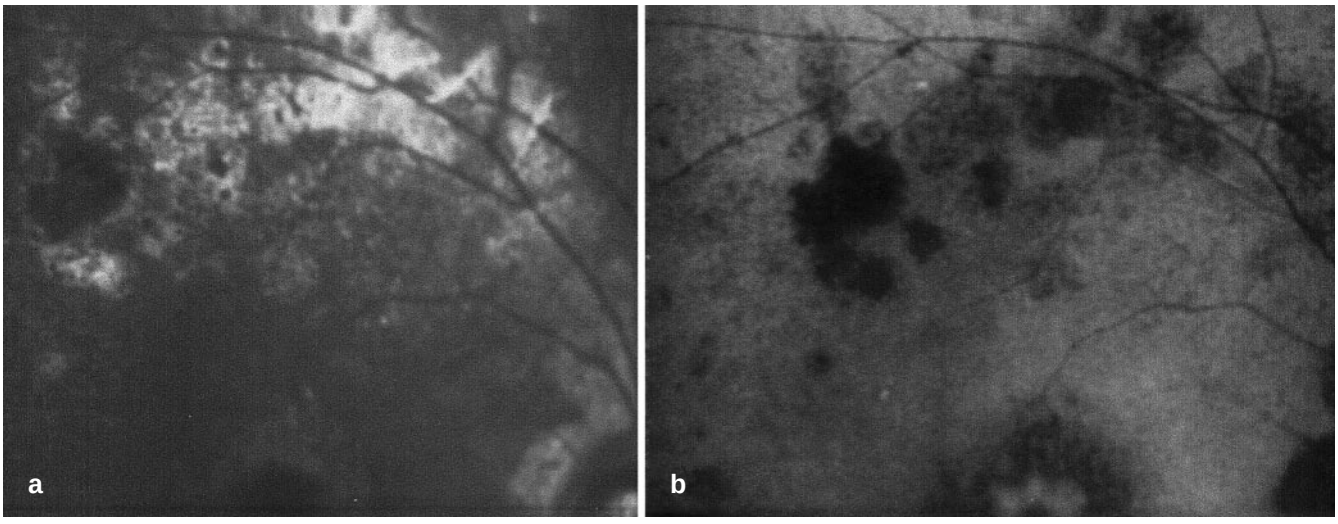



**Fig. 5** **a** Reflectance image of a 42-year-old woman with rod-cone dystrophy with retinal atrophy in the near periphery and at the fovea reducing visual acuity in the right eye to 20/400. **b** Fundus autofluorescence image showed decreased fluorescence at the sites of atrophy. Autofluorescence is present in the surviving retinal areas

greater (lesser) than the mean autofluorescence intensity of the age group concerned by 2 standard deviations or more.

The research followed the tenets of Declaration of Helsinki and was approved by the hospital ethics committee. Informed consent was obtained from subjects involved in the study.

## Results

Absent autofluorescence corresponded well spatially with outer retinal atrophy in eyes with dominant and recessive retinitis pigmentosa (Figs. 1, 2, Table 1). Fundus autofluorescence was present in the adjacent regions where there was surviving retina. Abnormally high levels of autofluorescence were seen in the surviving retinal areas in some cases of dominant and recessive retinitis pigmentosa (Fig. 2, Table 1).

Areas of macular edema of more than 4 months duration associated with retinitis pigmentosa showed increased autofluorescence (Fig. 3). In some eyes with macular edema of more than 3 years duration fundus autofluorescence was very irregular, there being regions of greater and lesser autofluorescence intensity than in corresponding areas in age-matched normal controls, whereas in other eyes absent autofluorescence corresponded well with the area of edema (Fig. 4).

Absent autofluorescence corresponded well spatially with outer retinal atrophy in eyes with rod-cone dystrophy. Fundus autofluorescence was abnormally high, low, or within normal limitis in the adjacent regions where there was surviving retina (Fig. 5, Table 1).

Changes in the intensity and spatial distribution of fundus autofluorescence over time occurred in most of the studied eyes. In macular dystrophies characterized by pale deposits at the level of the RPE, the shape, size and number of deposits, as well as the levels of background autofluorescence, changed over a period of at least 6 months (Fig. 6, Table 2a, b).

Fundus autofluorescence over age-related drusen was within normal limits. In 31% of eyes with drusen there were focal hyperfluorescent areas that did not correspond with drusen. During the study period such focal hyperfluorescent areas occurred in eyes with previously normal fundus autofluorescence (Table 3).

In areas of geograpic atrophy, absent autofluorescence corresponded well with the atrophy but was present in the adjacent regions where there was surviving retina (Table 3). In five eyes (62%) with geographic atrophy the areas of absent autofluorescence increased in size during follow-up.

In most of the patients with choroidal neovascularization due to age-related macular disease, fundus autofluorescence was irregular; hyper- and hypofluorescent regions alternated (Table 3). Areas with previously abnormally high levels of autofluorescence showed a decrease in autofluorescence intensity after at least 6 months (Fig. 7).

The levels of background autofluorescence remained within normal limits in all patients with age-related macular disease during the study period.

## Discussion

There is evidence supporting the concept that the images of fundus autofluorescence recorded in vivo are derived from lipofuscin in the RPE [3, 5, 14–17].

Until recently, data on retinitis pigmentosa have been limited, since observations have been made on a small number of specimens, of which all except two describe the most advanced stages of these disorders, where the histological appearance was similar regardless of the gen-

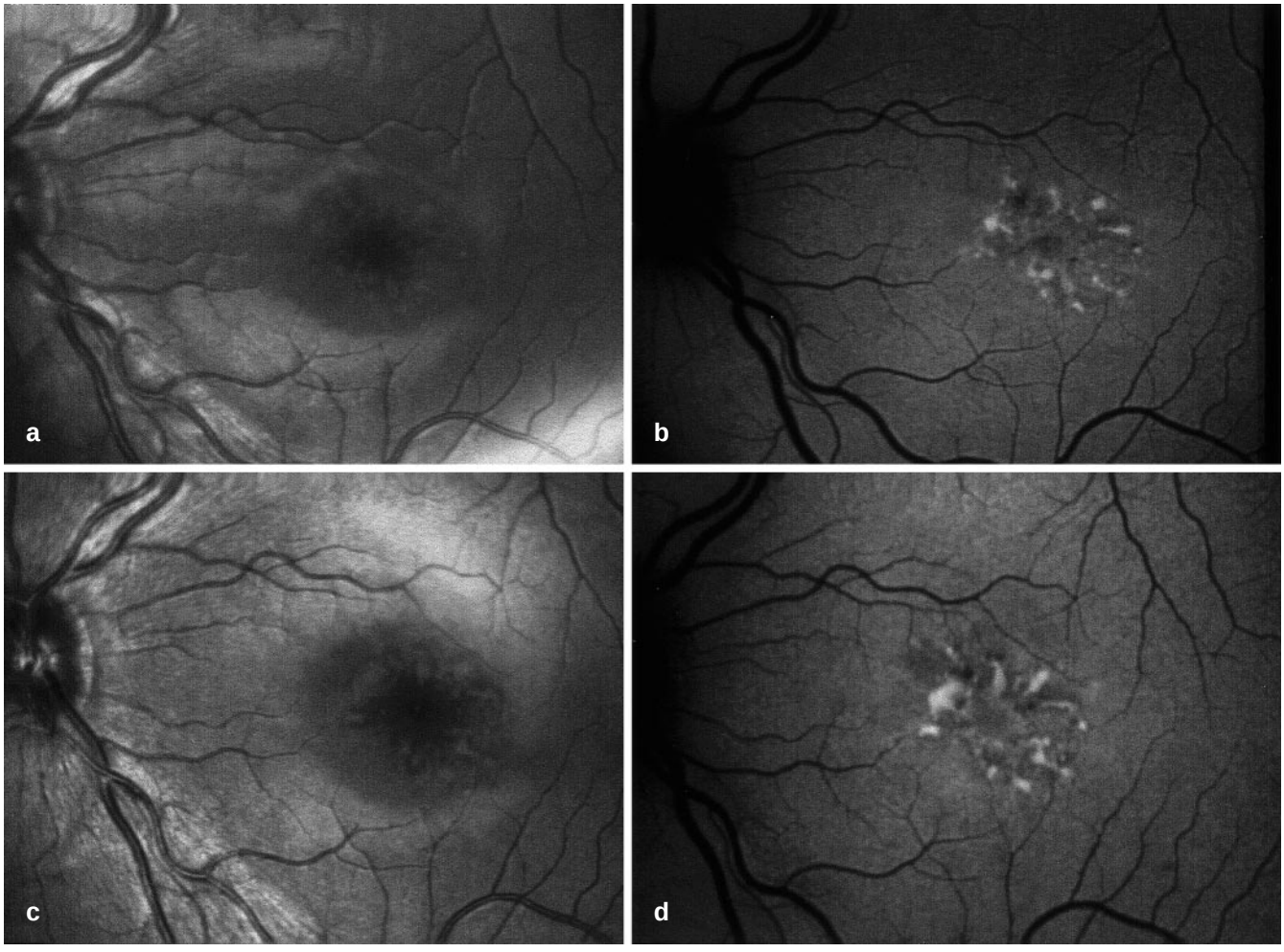



**Fig. 6** **a** Reflectance image and **b** autofluorescence image of a 28-year-old woman with pattern dystrophy with well-defined yellowish deposits at the level of the RPE which show abnormal high autofluorescence. Visual acuity in the left eye was 20/30. **c** Reflectance image and **d** autofluorescence image of the same fundus 18 months later. The size and shape of the focal autofluorescent deposits seen on the autofluorescence image have changed

otype [8, 10]. This is not surprising since the retina has a limited spectrum of response to injurious agents. Examination of material 20 years or more after the onset of severe visual loss gives little information about the underlying pathological mechanism. It is not known whether the finding of increased quantities of autofluorescent material in the central RPE is consistent from one condition to another. Also, the time course of the acquisition of autofluorencent material has not been documented. Given that many disorders are involved, all of which have different basic pathogeneses, some variation might be expected from one condition to another. In vivo analysis of RPE autofluorescence would allow many more observations to be made, and recording lipofuscin accumulation may give important clues as to the pathogenesis and progress of retinitis pigmentosa.

The peripheral fundus appearance on autofluorescence imaging was similar in patients with retinitis pigmentosa, regardless of the type of inheritance. Lipofuscin accumulates in the RPE with age, and its presence is thought to reflect the metabolic activity which is largely determined by the rate of turnover of photoreceptor outer segments. There is evidence of continuous degradation of autofluorescent material in the RPE [7, 13]. Thus progressive loss of lipofuscin would occur in the case of reduced metabolic demand due to photoreceptor cell loss. This explains the finding that decreased autofluorescence corresponded well with areas of photoreceptor cell loss in eyes with retinitis pigmentosa and rod-cone dystrophies.

Using histopathologic techniques on a specimen of dominant retinitis pigmentosa, Kolb described the peripheral RPE as being constituted of highly melanin-containing RPE cells arranged in a bone-corpuscle-like pattern interspersed between areas of atrophic lipofuscin-containing epithelium and areas in which the RPE layer had completely disappeared [10]. This corresponds with the in vi-

**Table 2a** Background autofluorescence of the right eye in different macular dystrophies and its change over time (arbitrary units, 0–255). The background autofluorescence was measured in an area where there was no abnormal appearance on opthalmoscopy and where there were no focal changes on autofluorescence imaging. *n*, number of subjects. For comparison, fundus autofluorescence levels in normal subjects established previously [14] are shown in Table 2b

| Category | Age group (years) | First examination | 1 year examination | 2 year examination | 3 year examination |
|---|---|---|---|---|---|
| Adult vitelliform dystrophy (*n*=7) | 10–19 | 104 | 111 | 108 | 105 |
| | | 111 | 142 | | |
| | 20–29 | 45[a] | 98 | 103 | |
| | 30–39 | 116 | 143 | | |
| | | 123 | 108 | | |
| | 40–49 | 117 | 115 | 118 | 112 |
| | | 154 | 161 | | |
| | 50–59 | | | | |
| Best disease (*n*=6) | 10–19 | 48 | 52 | 59 | 55 |
| | | 51 | 46[a] | | |
| | 20–29 | 52 | 64 | | |
| | | 61 | 81 | | |
| | 30–39 | 59[a] | 82 | | |
| | 40–49 | 74[a] | 61[a] | | |
| | 50–59 | | | | |
| Fundus flavimaculatus (*n*=12) | 10–19 | 102 | 114 | | |
| | | 117 | 131 | 154 | 151 |
| | 20–29 | 146 | 132 | 138 | |
| | | 148 | 157 | | |
| | | 157 | | | |
| | 30–39 | 96 | 117 | | |
| | | 104 | 118 | | |
| | | 143 | 166 | | |
| | | 154 | 167 | | |
| | 40–49 | 114 | 109 | | |
| | | 125 | 126 | 92 | |
| | 50–59 | 149 | 152 | | |
| Pattern dystrophy (*n*=5) | 10–19 | 122 | 116 | 132 | 149 |
| | 20–29 | 109 | 122 | 126 | |
| | 30–39 | 131 | 133 | 129 | 153 |
| | | 158 | 141 | | |
| | 40–49 | 126 | 98 | | |
| | 50–59 | | | | |

[a] Within normal limits

**Table 2b** Fundus autofluorescence levels in normal subjects obtained in the area of maximal intensity of the right eye: mean±2 standard deviations in arbitary units

| | Age group (years) | | | | |
|---|---|---|---|---|---|
| Normal subjects (*n*=28) | 10–19 | 20–29 | 30–39 | 40–49 | 50-59 |
| | 24±22 | 33±14 | 43±20 | 56±22 | 67±20 |

vo distribution of autofluorescence and is shown in Figs. 1 and 2.

Some of the eyes with retinitis pigmentosa studied showed abnormally high levels of fundus autofluorescence in the surviving areas, while others did not. This appears to correlate with histopathologic studies demonstrating normal or excessive lipofuscin content in the RPE [8, 10]. Long-term longitudinal studies will clarify whether accumulation of autofluorescent material in the RPE occurs in all patients with retinitis pigmentosa at some stage of evolution of disease. If this phenomenon occurs only in some of the patients with retinitis pigmentosa, imaging of fundus autofluorescence might serve to distinguish type I (diffuse) retinitis pigmentosa, in which the photoreceptors have a near-normal compliment of rhodopsin after loss of scotopic sensitivity, from type II

**Table 3** Frequency of normal, increased, decreased and irregular autofluorescence in the macula in eyes with age-related macular degeneration. *n*, total numbers of eyes. Results are shown for the group of patients with 3 years follow-up

| Category | Normal autofluorescence | | | | Increased Autofluorescence | | | | Decreased autofluorescence | | | | Irregular autofluorescence | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First exam | 1 year | 2 years | 3 years | First exam | 1 year | 2 years | 3 years | First exam | 1 year | 2 years | 3 years | First exam | 1 year | 2 years | 3 years |
| Drusen (*n*=13) | 9 (69%) | 9 (69%) | 7 (54%) | 6 (46%) | 4[a] (31%) | 4[a] (31%) | 6[a] (46%) | 7[a] (54%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Geographic atrophy (*n*=8) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 (100%) | 8 (100%) | 8 (100%) | 8 (100%) | 0 | 0 | 0 | 0 |
| Choroidal neovascularisation (*n*=11) | 2 (18%) | 0 | 0 | 0 | 3 (27%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 (55%) | 11 (100%) | 11 (100%) | 11 (100%) |

[a] Focal hyperfluorescent areas that did not correspond with drusen

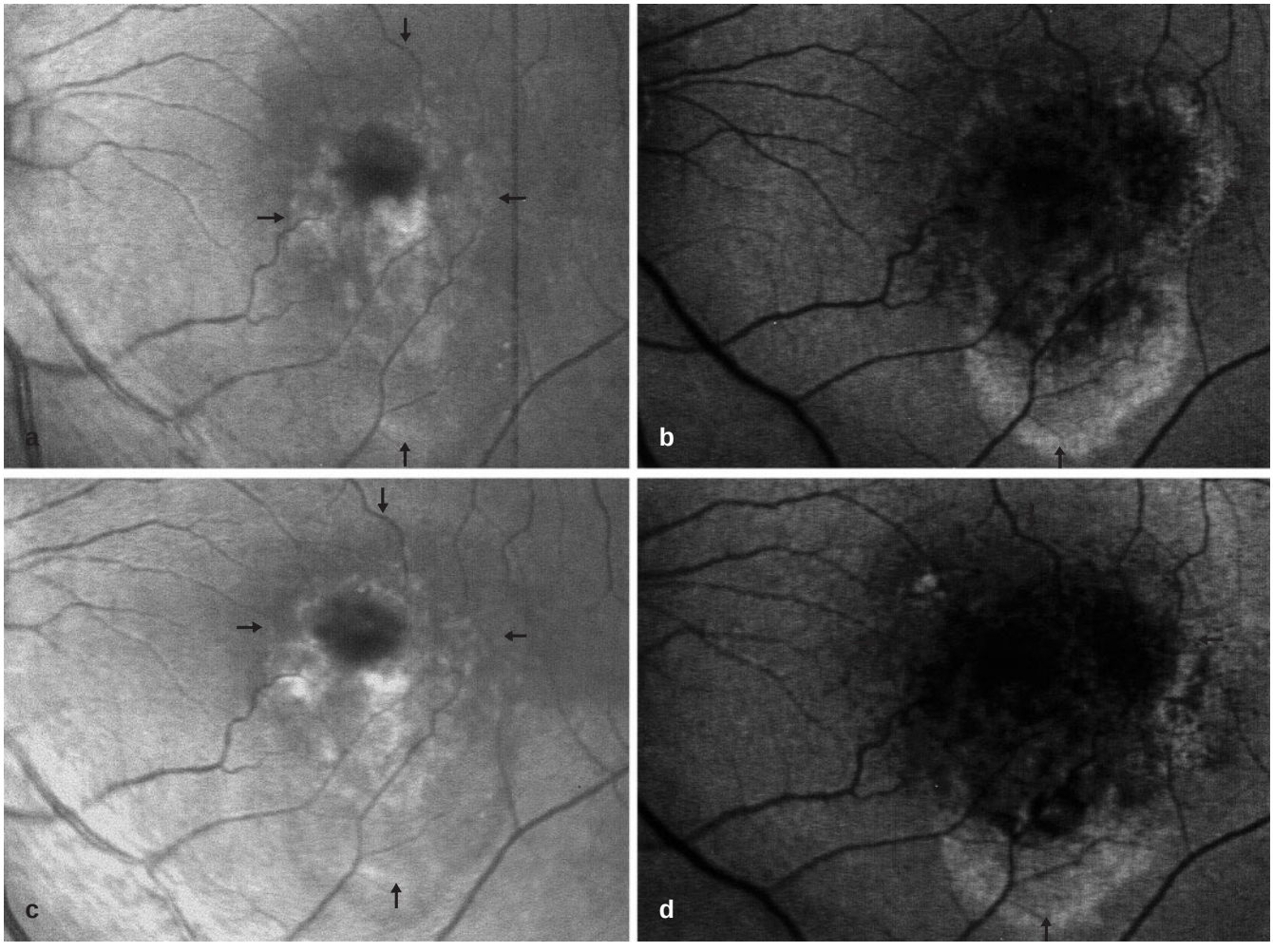



**Fig. 7** **a** Reflectance image and **b** autofluorescence image of a 71-year-old man with occult neovascularization due to age-related macular degeneration reducing visual acuity to 20/100. Autofluorescence imaging shows irregular fundus autofluorescence centrally and increased autofluorescence in the inferior part of the lesion. **c** Reflectance image and **d** autofluorescence image of the same fundus 21 months later. Autofluorescence intensity has decreased markedly in the area of subretinal neovascularization. *Arrows* mark edges of subretinal lesion on reflectance and autofluorescence images

(regional) disease, in which there is outer segment loss early in disease [1, 9, 11, 12]. Type I retinitis pigmentosa would be expected to have normal or excessive quantities of lipofuscin, whereas type II would have reduced leels.

Increased quantities of autofluorescent material may occur in the case of abnormally high metabolic activity and if degradation of waste material of metabolic activity is defective. Thus, increased fundus autofluorescence in areas of macular edema of more than 4 months duration is not surprising. Phagocytosis of material derived from the subretinal space may be greater than normal in areas with macular edema. This material may origin from photoreceptor outer segment components shed into the subretinal space, expecially if outer segment half-life is shortened, as may be the case given the loss of physical support from the extracellular structures in the interphotoreceptor matrix. The observation that the number of photoreceptor cells is reduced in the presence of increased lipofuscin content in the RPE led to the hypothesis that increased accumulation of autofluorescent material may occur prior to cell loss [6]. The decreased autofluorescence seen in areas of longstanding macular edema in eyes with retinitis pigmentosa may reflect photoreceptor cell loss before the condition becomes clinically evident.

The entire fundus of patients with adult vitelliform macular dystrophy, Best disease, fundus flavimaculatus and pattern dystrophy showed abnormally high autofluorescence, confirming previous results derived from in vivo studies [3, 14, 16]. This suggests that the abnormality of the RPE is generalized, even though on biomicroscopy the visible lesions are focal.

Changes in the intensity and spatial distribution of fundus autofluorescence over time occurred in most of the studied eyes with macular dystrophies. The background autofluorescence leels showed variation during the follow-up period. This confirms the hypothesis that the autofluorescent pigment content in the RPE varies over time as a function of disease stage [16]. Only four of the patients with macular dystrophies had normal background autofluorescence. This may indicate a different disease stage and does not necessarily mean that the abnormality is limited to the areas of focal deposits.

In macular dystrophies characterized by pale deposits at the level of the RPE the shape, size and number of deposits changed over a period of at least 6 months. These changes with time were less dramatic than those in age-related macular disease, confirming the impression from clinical observations that the progression of the disease is slow.

It has been a matter of dispute whether or not high quantities of lipofuscin have any effects ofn RPE cell function [4]. The levels of background autofluorescence measured in eyes with macular dystrophies were much higher than those measured in age-matched normal controls. This suggests that high quantities of residual bodies do not cause detectable functional alteration of the RPE for several years, although in the long term this may be an important cause of dysfunction.

As expected, autofluorescence over age-related drusen was within normal limits. This is consistent with results derived from previous in vivo autofluorescence studies [3, 15]. Spectral analysis demonstrated that the autofluorescence over age-related drusen canot be differentiated from the background [2]. In some eyes there were focal hyperfluorescent areas that did not correspond with drusen. During the follow-up, such focal hyperfluorescent areas occurred in eyes with previously normal fundus autofluorescence. Those areas of increased autofluorescence not visible on ophthalmoscopy correspond to a group of RPE cells containing higher quantities of lipofuscin that their neighbors [15] and may represent areas at high risk for cell loss. It has been shown histologically that the number of photoreceptor cells is reduced in the presence of increased quantities of lipofuscin in the RPE, leading to the proposal that autofluorescent material may accumulate prior to cell death [6]. This is supported by our observation that in eyes with geographic atrophy new areas of atrophy developed at sites of previously increased fundus autofluorescence. In more advanced stages of macular degeneration, absent autofluorescence corresponded well with areas of geographic atrophy.

Over time, the size of reduced fundus autofluorescence seen over areas of geographic atrophy increased and the shape changed in 62% of patients.

Fundus autofluorescence in eyes with choroidal neovascularization due to age-related macular disease changed over time, and focal areas of increased autofluorescence became hypofluorescent. The changes of fundus autofluorescence seen in eyes with geographic atrophy and choroidal neovascularization are not surprising given that accumulation of lipofuscin in the RPE reflects the level of metabolic activity which is largely determined by the quantity of photoreceptor outer segment renewal. There is constant degradation of residual bodies in the RPE [7, 13], so progressive loss of lipofuscin would occur if metabolic demand were reduced due to photoreceptor cell death.

Changes over time in the intensity and spatial distribution of fundus autofluorescence may have relevance for the outcome of disease and allows many more observations to be made than is the case if data are available from histological studies alone. The relevance to clinical practice and research in retinal diseases of recording the intensity, spatial distribution and changes in autofluorescence over time to may be clarified by incorporating the technique into longitudinal studies. It is evident that measurement of autofluorescence may give an indirect indication of progression of disease and may provide information important to the understanding of the mechanism of disease.

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