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Fundus autofluorescence in children and teenagers with hereditary retinal diseases

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Abstract *Introduction:* In adults, evaluation of fundus autofluorescence (AF) plays an important role in the differential diagnosis of retinal diseases. The aim of this study was to evaluate the feasibility of recording AF in children and teenagers and to define typical AF findings of various hereditary retinal diseases during childhood. *Methods:* Fifty patients aged 2 to 16 years with hereditary retinal diseases were analysed using the HRA (Heidelberg Retina Angiograph). To enhance the AF signal, a mean of up to 16 single images was calculated. Twenty healthy children (aged 4–16 years) served as controls. *Results:* In many children as young as 5 years of age and even in one 2-year-old child good AF images could be obtained. To achieve high quality images, larger image series (about 50 single images) were taken and appropriate single images were chosen manually to calculate the mean. Characteristically, Stargardt disease shows a central oval area of reduced AF, often surrounded by

more irregular AF. In patients with Best disease, a central round structure with regular or irregular intense AF is visualised. Some patients with X-linked retinoschisis show central radial structures. In many patients with rod-cone dystrophies, a central oval ring-shaped area of increased AF is present. In early-onset severe retinal dystrophy (EOSRD) with *RPE65* mutations AF is completely absent, whereas in other forms of Leber congenital amaurosis, AF is normal. *Discussion:* Fundus autofluorescence may visualise disease-specific distributions of lipofuscin in the retinal pigment epithelium, often not (yet) visible on ophthalmoscopy. AF images can be used in children to differentiate hereditary retinal diseases and to facilitate follow-up controls. In many cases, four single images are sufficient to analyse the AF pattern.

Keywords Fundus autofluorescence · Children · Hereditary retinal disease

Introduction

Fundus autofluorescence (AF) is due to the accumulation of lipofuscin in the retinal pigment epithelium (RPE). An important fluorescent component of lipofuscin is A2E, which is derived from N-retinylidene-phosphatidyl-ethanolamine chemically modified upon digestion of phagocytosed photoreceptor outer segments [14–17, 23]. In healthy individuals it accumulates with age within the lysosomal

compartment [16, 36]. Alterations in AF reflect changes in the lipofuscin contents of the RPE that may not be visible on ophthalmoscopy.

In adults, evaluation of fundus autofluorescence (AF) plays an important role in the differential diagnosis and follow-up of retinal diseases, especially in age-related macular degeneration and hereditary diseases [3–5, 9–11]. Little is known about the feasibility of recording AF in younger children with hereditary retinal dystrophies, where testing

may be hampered by lack of compliance, nystagmus and photophobia.

The aim of this study was to systematically evaluate AF in children and teenagers with hereditary retinal dystrophies and to characterise typical AF findings of various diseases.

Materials and methods

Subjects

All individuals included in this study were informed about the objectives of the examination and volunteered to participate. Informed consent was taken from the parents or legal guardians according to the tenets of the Declaration of Helsinki. The study was approved by the Ethical Committee of the University of Regensburg.

Fifty children and teenagers aged 2–16 years with hereditary retinal diseases attending our department in the years 1999–2004 were included in the study (28 boys and 22 girls). Clinical examination included best-corrected visual acuity, refraction, slit-lamp biomicroscopy and funduscopy, and evaluation of nystagmus. Diagnosis was mainly based on clinical findings and electrophysiology (according to the International Society for Clinical Electrophysiology of Vision [ISCEV] standard); molecular genetic results were available in 22 of the patients. For comparison, we also examined 20 children aged 4–16 years with no sign or symptom of any retinal disease attending our department for other causes like refractive errors, squint or anterior segment pathologies.

Fundus autofluorescence

Autofluorescence was recorded using a standard confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph, HRA; Heidelberg Engineering, Heidelberg, Germany). Alignment of the head and eye position and gain adjustment were performed with the infrared mode; subsequently the camera was switched to the AF laser. The detector sensitivity of the laser scanning camera was adjusted to the amount of AF present. Series of about 50

single pictures per eye were taken with a velocity of 6 images/s. Total exposure times were kept as short as possible, and the field of view was always $30 \times 30^\circ$. To increase the signal-to-noise ratio of the AF signal, we aligned up to 16 images (a minimum of 4 images) using the software integrated into the instrument and calculated a mean image from these [22]. These single images were chosen manually on the basis of good quality and identical fundus area.

Results

The distribution of age and retinal diseases of the 50 patients is shown in Fig. 1. AF images were obtained in 48 out of 50 children with hereditary retinal diseases and in 19 out of 20 children with no retinal disease. Only 3 children (one aged 3 years with Leber congenital amaurosis, one aged 4 years with X-linked retinoschisis, and one aged 4 y with strabismus) could not cooperate sufficiently to obtain at least four images showing the same image area without artefacts. Photophobia and nystagmus made testing difficult, especially in patients with Leber congenital amaurosis (4 patients), but these problems were overcome by showing a fixation light behind the examiner, using larger image series and choosing manually the single images for calculating means.

Age-matched controls

Children in this group had no signs or symptoms of hereditary retinal disease, but 8 had strabismus. In all 19 children in whom we could obtain images, AF was easily detectable outside the fovea, optic nerve head, and large vessels. The fovea was darker than the surrounding retina, and AF was absent in the area of the optic nerve head and the large vessels (Fig. 2).

Stargardt macular dystrophy/cone-rod-dystrophy

We examined 14 children aged 6–16 years with either Stargardt macular dystrophy (STGD; 12 children with normal electroretinogram [ERG], with or without fundus

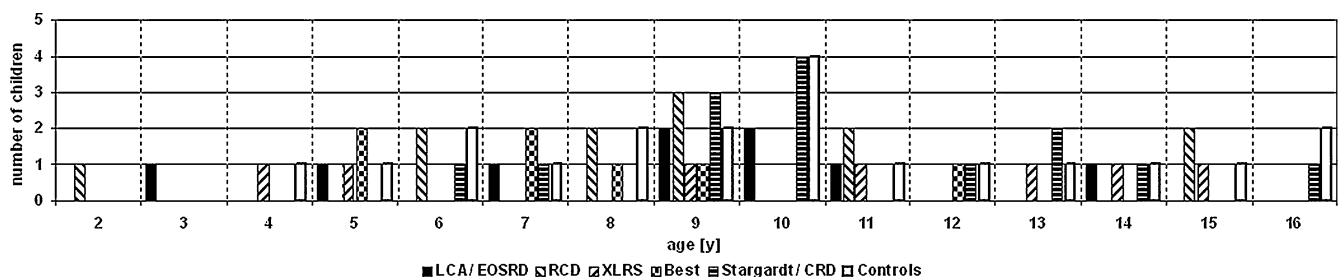
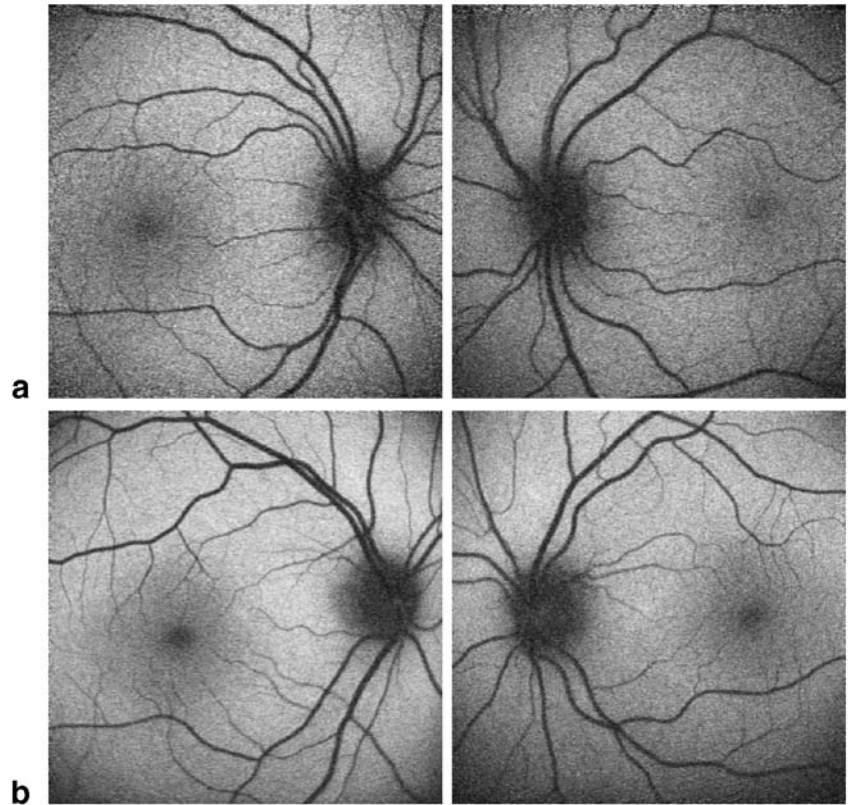


Fig. 1 Age distribution of 50 patients with hereditary retinal diseases and 20 age-matched controls

Fig. 2 Examples of AF in children with no retinal disease. **a** A 5-year-old girl, visual acuity (VA) 0.6/0.6, strabismus. **b** An 11-year-old boy, VA 1.0/1.0, healthy



flavimaculatus, 5 with molecular genetically determined *ABCA4* mutations) or with cone-rod dystrophies (CRD; 2 children with reduced amplitudes in photopic more than scotopic Ganzfeld ERG). In all patients we were able to obtain AF images. These showed a central oval area of reduced AF in all patients. In patients with fundus flavimaculatus, this area was surrounded by small disseminated spots of reduced and increased AF (Fig. 3b,c). The AF aspect of CRD was similar (Fig. 3d).

Best vitelliform macular dystrophy

Seven children aged 5–12 years with molecular genetically determined Best vitelliform macular dystrophy were examined [34]. AF images were of obtained in all of them.

Deposits of lipofuscin-like material were visualised in all patients. A typical vitelliform lesion shows as a central round area of increased AF (Fig. 4a). In the pseudohypopyon stage, increased AF is more pronounced in the lower part of the lesion (Fig. 4b). Later stages present with more irregular AF within the lesion and with disseminated spots of increased AF (Fig. 4c).

X-linked juvenile retinoschisis

Seven boys aged 4–15 years with X-linked juvenile retinoschisis (XLRS) were examined. One 4-year-old boy did not have sufficient cooperation for AF. Examples of AF images are shown in Fig. 5. Central AF was abnormal in all patients. Some patients showed central radial structures (Fig. 5a–c), others a more irregular AF pattern (Fig. 5d).

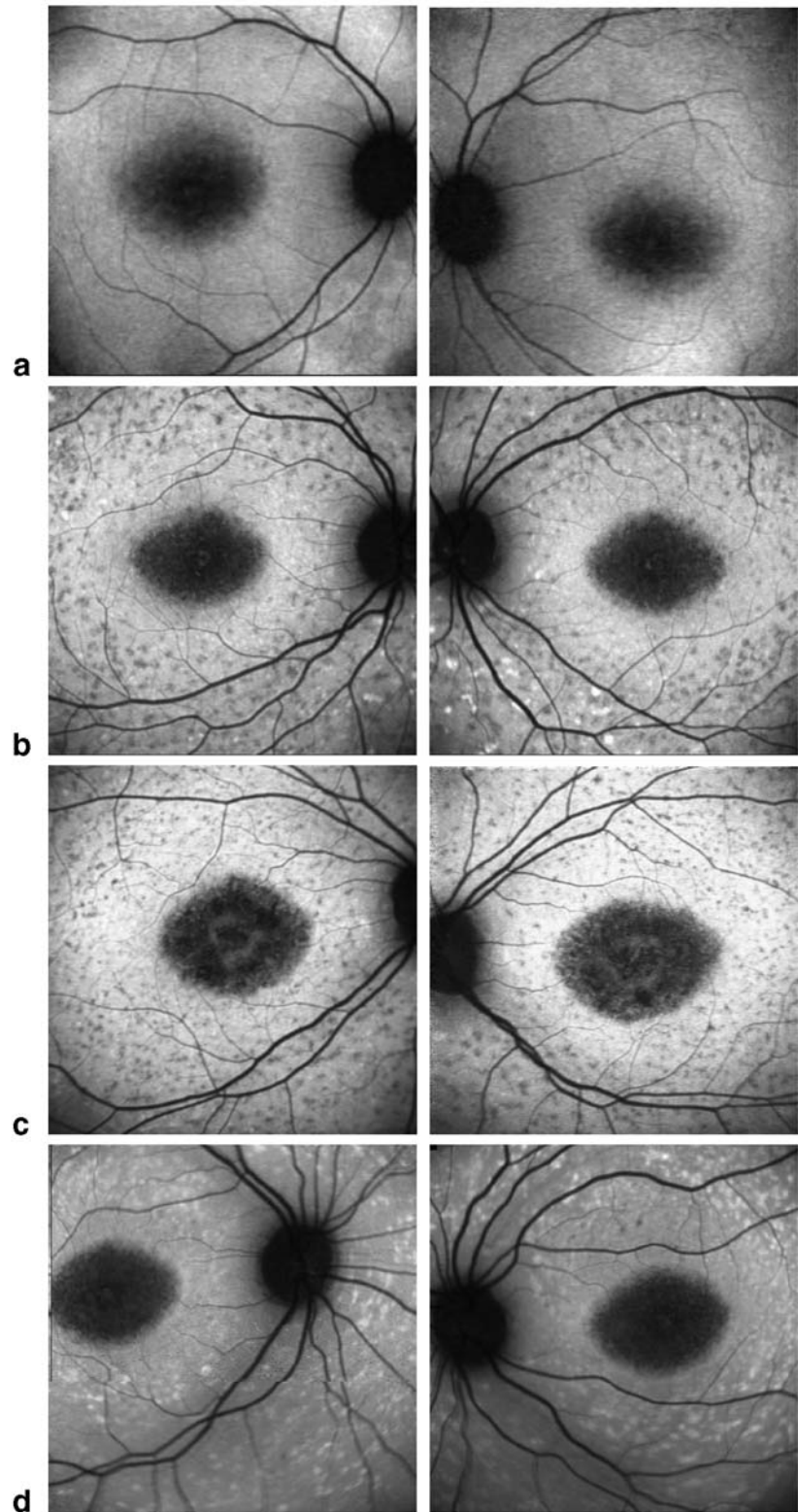
Rod-cone dystrophy

We examined 12 children aged 2–15 years. These included 11 patients with rod-cone dystrophy (RCD) and one with Bardet-Biedl syndrome. A characteristic feature was a parafoveal ring of increased AF. This ring showed a high degree of interocular symmetry, the size of the ring was not correlated with visual acuity (Fig. 6).

Leber congenital amaurosis/early onset severe retinal dystrophy

Ten children aged 3–14 years were examined, 4 with typical Leber congenital amaurosis (LCA) and 6 with early

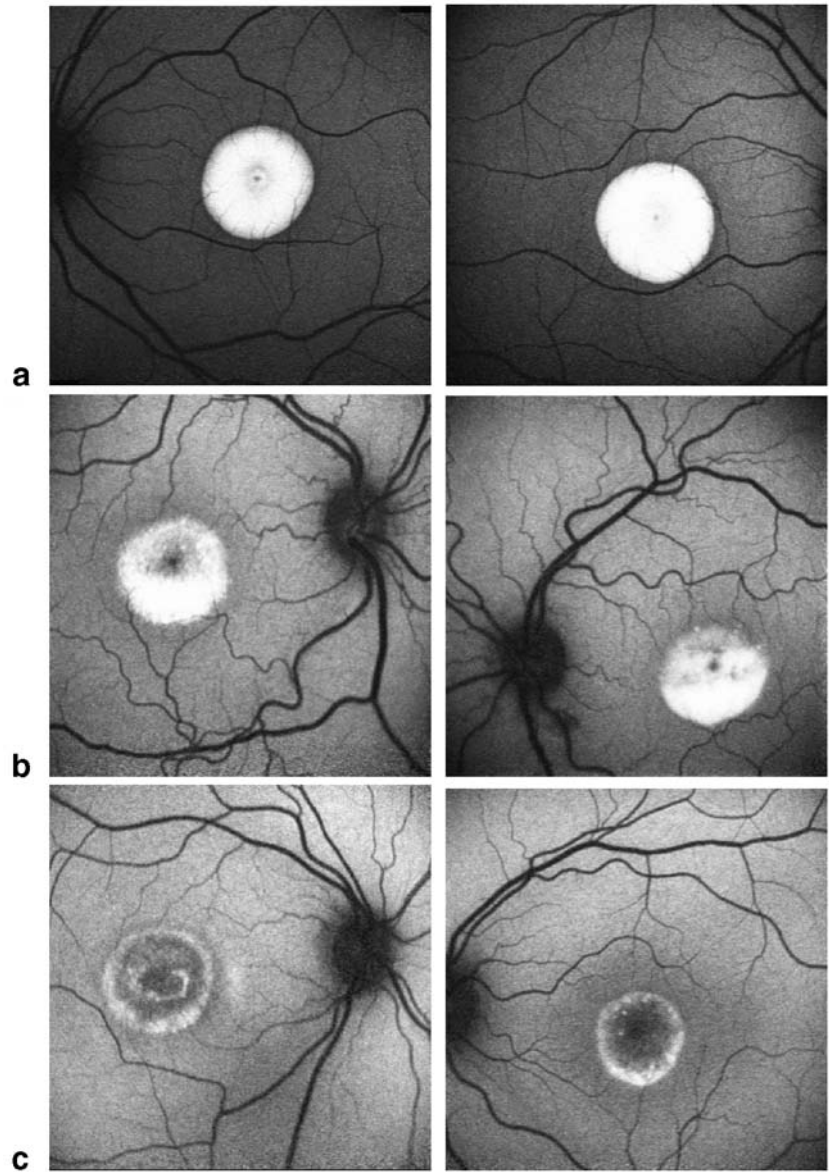
Fig. 3 Autofluorescence in patients with Stargardt disease/cone-rod dystrophy. **a** Stargardt disease (in a 10-year-old girl, VA 0.1/0.1): central oval area of reduced AF surrounded by small disseminated spots of reduced and increased AF. **b** Stargardt disease with fundus flavimaculatus (in a 9-year-old girl, VA 0.1/0.1): central oval area of reduced AF surrounded by small disseminated spots of reduced and increased AF. **c** Stargardt disease with fundus flavimaculatus (in a 10-year-old girl, VA 0.1/0.1, mutation in *ABCA4*): central oval area of reduced AF with some irregularities inside, surrounded by small disseminated spots of reduced and increased AF. **d** Cone-rod dystrophy (in a 10 year-old girl, VA 0.1/0.1, no molecular genetics performed): central oval area of reduced AF surrounded by small disseminated spots of increased AF



onset severe retinal dystrophy (EOSRD) associated with *RPE65* mutations [22, 25]. Testing was difficult due to photophobia and nystagmus. One 3-year-old boy with LCA

did not show sufficient cooperation. In the other 3 children with LCA AF was clearly present (Fig. 7a). In the children with EOSRD associated with *RPE65* mutations,

Fig. 4 Autofluorescence in patients with Best vitelliform macular dystrophy. **a** A 5-year-old boy, with *hBest1* mutation, VA 1.0/1.0, vitelliform stage: central round areas of increased AF. **b** An 11-year-old boy, with *hBest1* mutation, VA 0.8/0.8, pseudohypopyon stage: increased AF (more pronounced in the lower part of the lesions). **c** A 14-year-old boy, with *hBest1* mutation, VA 0.3/0.9, OD vitelliruptive stage with some scarring, OS vitelliform stage: irregular AF within the lesion with disseminated spots of increased AF, OD centrally: no AF corresponding to the scar.



no AF at all was visible (Fig. 7b): The image brightness over the optic disc, i.e. an area with physiological absence of AF was comparable to that of the posterior pole.

Discussion

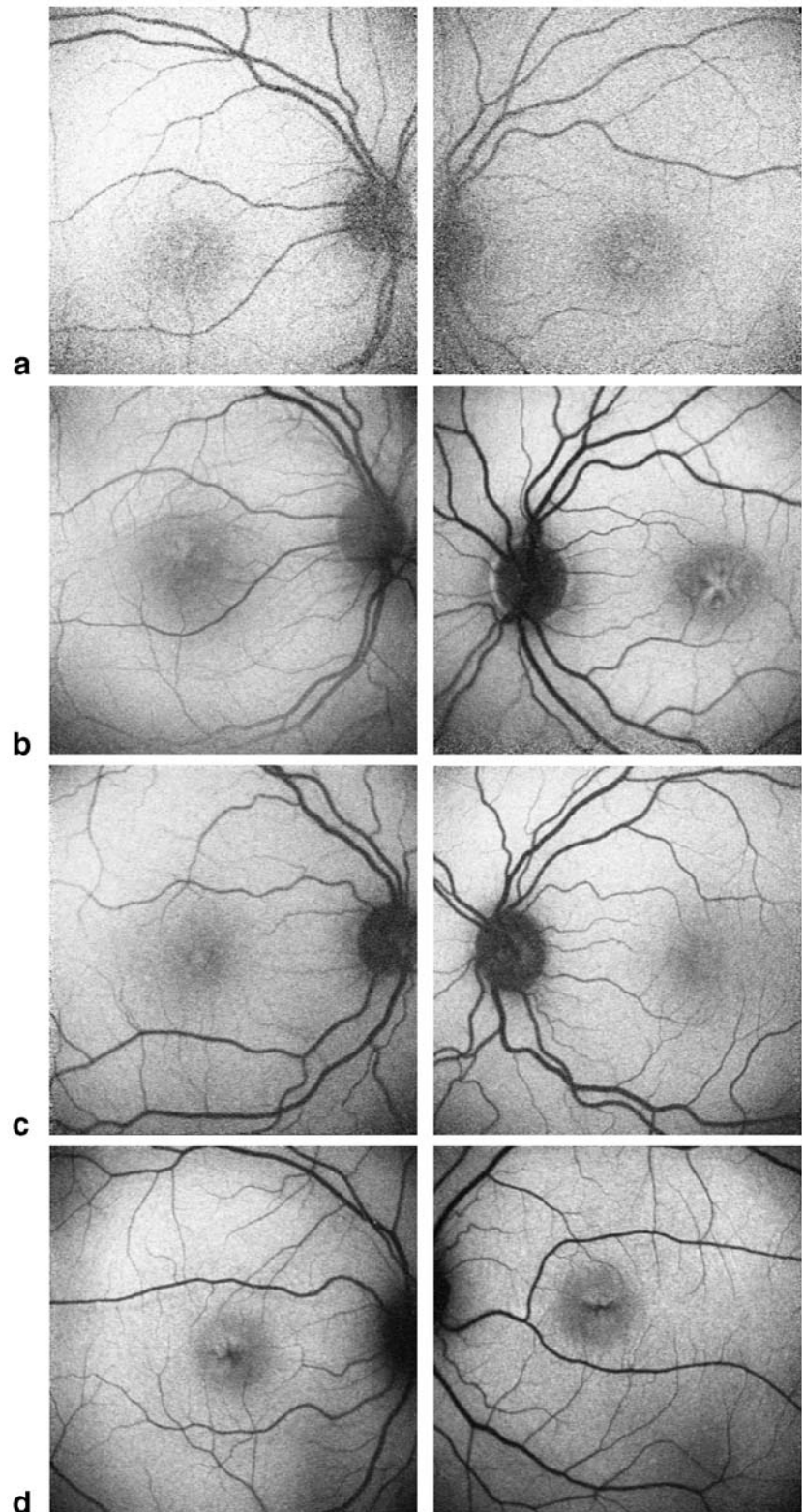
This is the first systematic evaluation of fundus autofluorescence in children with hereditary retinal diseases, and age-matched children. Up to now the earliest age at which AF recordings are technically possible and whether there is any AF already present in younger children have not been clear. No more than one report of a 6-year-old child with Best disease and one age-matched control has been published [31]. In our study, evaluation of fundus AF could be

obtained in most children starting from 5 years of age, and even in one 2-year-old girl. We could not see any correlation of the images with age. AF findings in healthy children were similar to those in adults [6, 10, 18, 22, 27].

To achieve high quality images, it is mandatory to record image series of about 50 single images and to choose appropriate single images manually. Light safety in young children with retinal degeneration and with normal retinal status is crucial. Special care was given to shorten exposure time. The American National Standards Institute (ANSI) norm (with no differentiation between children and adults) allows exposure times of 108 min for 30°. Actual exposure times of about 1 min are therefore about a 100-fold lower than the allowed HRA thresholds.

We identified typical AF patterns in children with five hereditary retinal diseases.

Fig. 5 Autofluorescence in patients with X-linked juvenile retinoschisis. **a** A 5-year-old boy, VA 0.4/0.4: central radial structures of increased AF. **b** Same patient as **a** at the age of 7 years (VA stable): clearer AF image due to better cooperation: central radial structures of increased AF. **c** A 14-year-old boy, VA 0.4/0.4: centrally irregular AF. **d** A 15-year-old boy, VA 0.6/0.4: radiating AF structure corresponding to the cystic maculopathy



In Stargardt macular dystrophy (STGD, OMIM 248200) central oval areas of reduced AF were present in all patients. In fundus flavimaculatus these were surrounded by

small disseminated spots of increased and reduced AF. These are assumed to be active flecks (increased AF) or resolved flecks (reduced AF) [20]. Our findings were sim-

Fig. 6 Autofluorescence in patients with rod-cone dystrophies: parafoveal ring of increased AF in all patients. **a** A 2-year-old girl, VA 0.3/0.3, rod-cone dystrophy (OD: left: central area of increased AF, right: lower part of the retina with confluent spots of increased AF). **b** A 6-year-old boy, VA 0.16/0.16, rod-cone dystrophy. **c** An 11-year-old girl, VA 0.05/0.05, rod-cone dystrophy (the patients in Fig. 6b and c are siblings). **d** A 15-year-old girl, VA 0.1/0.2, Bardet-Biedl-syndrome

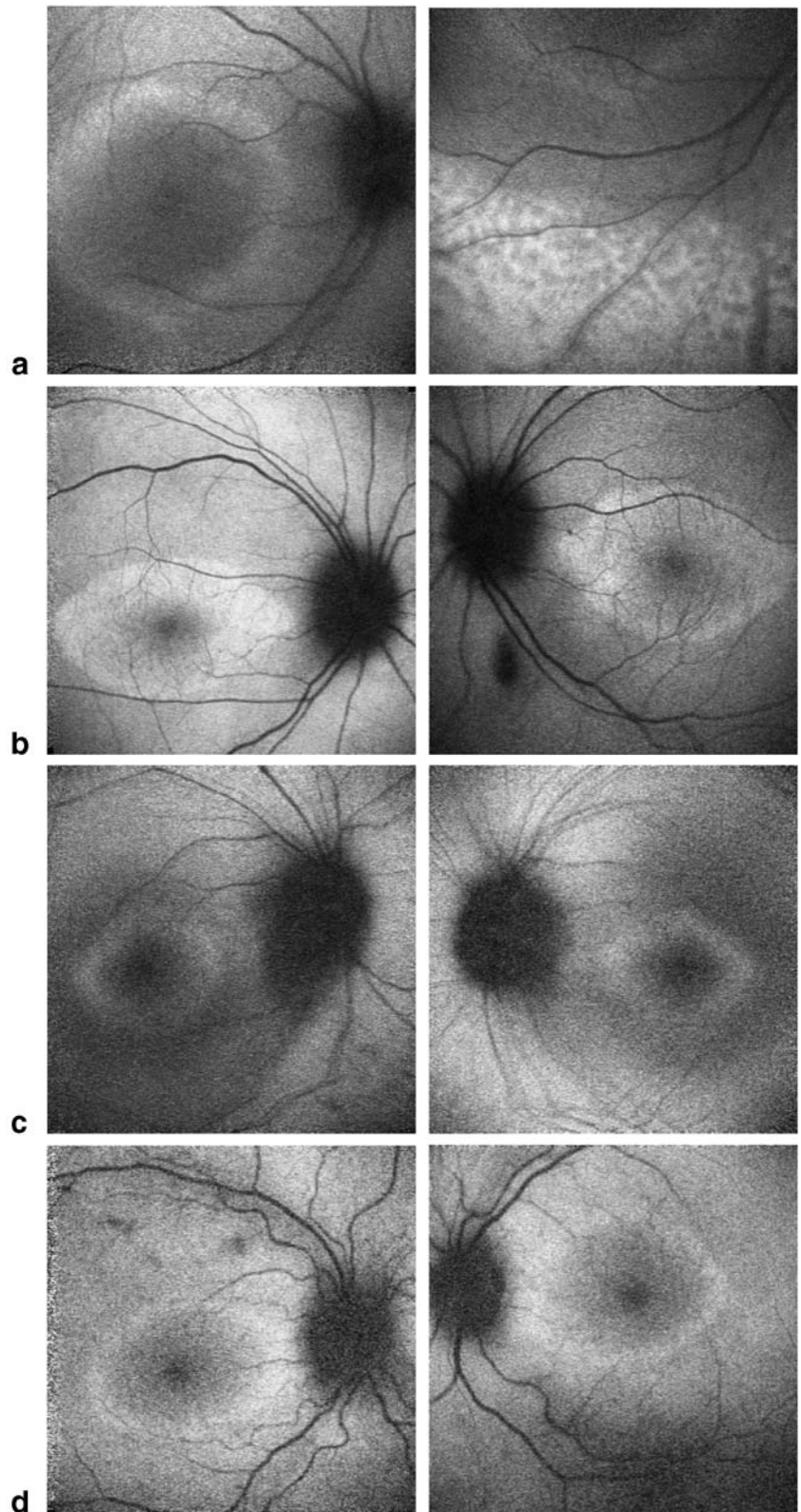
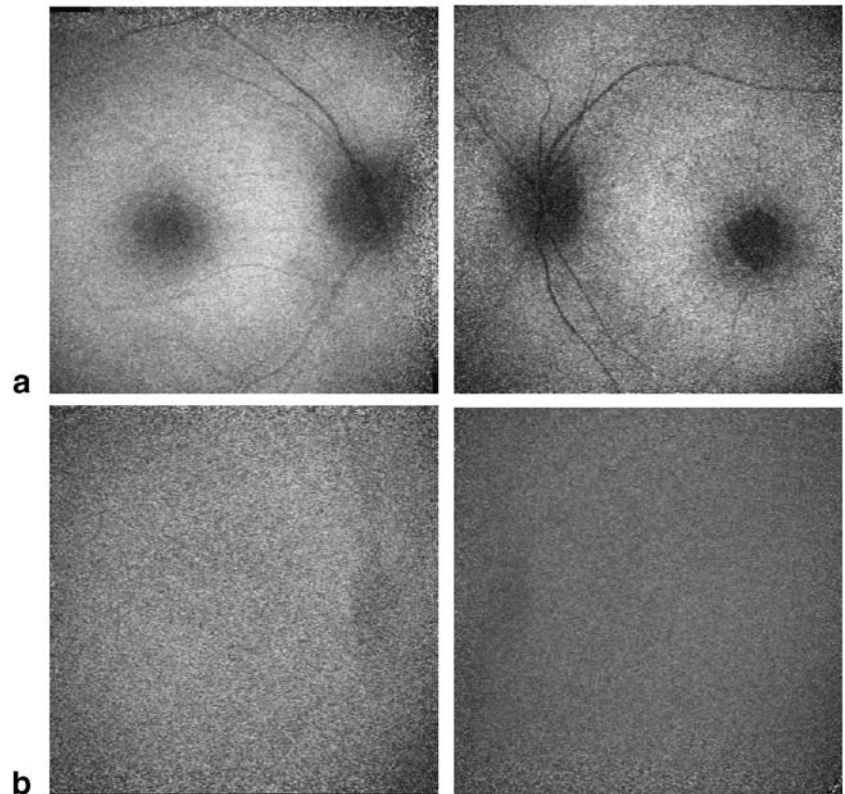


Fig. 7 Autofluorescence in patients with Leber congenital amaurosis (LCA) and early onset severe retinal dystrophy (EOSRD). **a** A 7-year-old girl, VA 0.1/0.1, LCA (unknown genotype, no mutations in *RPE65* detected): AF clearly present. **b** A 12-year-old girl, VA 0.1/0.2, EOSRD with *RPE65* mutations: no AF. (As there was no AF detected, the sensitivity of the detector was upregulated. The normal optic disc does not have any AF. As image brightness over the optic disc is comparable to that of the posterior pole in this image, the brightness is due to the upregulated detector sensitivity and not due to “real” AF. For details see [22])



ilar to those in adults [9, 10, 19–21]. There was no systematic difference in AF between STGD and CRD in our patients. Lois et al. [21] postulated that patients with low levels of AF at the centre and low or normal levels temporally and nasally may have more peripheral cone and rod dysfunction than patients with higher peripheral AF levels. Cideciyan et al. [2] suggested a disease sequence for *ABCA4* mutations to start with normal AF intensity, which increases and then decreases again in advanced disease stages.

In Best vitelliform macular dystrophy (OMIM 153700) deposits of lipofuscin-like material in the subretinal space can easily be visualised and are often more striking than on ophthalmoscopy. This is in accordance with descriptions in the literature [1, 10, 12, 31, 34]. Lesion size did not correlate with visual acuity, but lower visual acuity was associated with a more irregular AF pattern due to scarring or haemorrhage.

In X-linked retinoschisis (XLRS; OMIM 312700) AF imaging is not a standard diagnostic tool. Our AF findings reflect the typical radiating cystic maculopathy. AF intensity in the bright radial structures was similar to AF intensity outside the macula, AF intensity in the darker structures was comparable to a reduction in AF normally present due to shadowing effects of macular pigment. To date no AF findings have been published in patients with XLRS. This aspect in some of our patients was similar to

those with isolated foveal retinoschisis [13]. Although alterations in the RPE may occur later in the disease process [8, 30], the typical finding in XLRS implies a superficial splitting within the nerve fibre layer, which can be visualised by optical coherence tomography (OCT) [7, 24, 30]. The AF alterations presented here could therefore reflect effects of differences in retinal thickness and/or shadowing effects or effects of different macular pigment content without actually representing changes in the lipofuscin content of the RPE.

Young patients with rod-cone dystrophies presented with a parafoveal ring of high-density AF. This is similar to findings in adults [26, 28, 35] and may represent a boundary of demarcation between normal and severely abnormal retinal function, as shown by correlations with pattern ERGs and fine matrix mapping [26, 28]. No areas of decreased AF were present in our patients, in contrast to older patients with decreased AF at the site of atrophic areas [32, 33].

In typical Leber congenital amaurosis AF was clearly present [22, 29]. In contrast, patients with early onset severe retinal dystrophy associated with *RPE65* mutations did not show AF. Due to a defect in the retinol cycle, formation of rhodopsin is absent or largely decreased and therefore no lipofuscin is formed in the RPE [22]. Lack of AF despite an essentially normal looking fundus is a clinical marker of this genotype.

Conclusion

Evaluation of fundus autofluorescence is possible in many children as young as 5 years of age and even in some younger children. Fundus AF may visualise a disease-specific distribution of lipofuscin in the retinal pigment epithelium, often not (yet) visible on ophthalmoscopy. AF images can be used in children to differentiate hereditary retinal diseases and to facilitate follow-up controls. To achieve high quality images, it is mandatory to record

larger image series and choose appropriate single images manually. In many cases, four single images are sufficient to analyse the AF pattern.

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