Yellowish flecks in Leber's congenital amaurosis

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SUMMARY The fundus abnormalities of Leber's congenital amaurosis are extremely variable, from normal to salt-and-pepper changes to typical retinitis pigmentosa. A less commonly seen appearance is that of multiple, irregular shaped, yellowish white flecks deep in the midperipheral retina in a periarteriolar distribution. The nasal fundus as well as the posterior pole are spared. Such a case is presented along with a four-year follow-up together with the fluorescein angiographic findings. The flecks appear to be specific for this entity.

In 1896 Leber originally described a syndrome of congenital blindness with nystagmus, poor pupillary response, and fundus findings of tapetoretinal degeneration.¹ In 1954 Franceschetti and Dieterle² emphasised the importance of a markedly abnormal or extinct electroretinogram (ERG) in the diagnosis of the syndrome complex now known as Leber's congenital amaurosis. Other findings of this autosomal recessive inherited disease include photophobia, digito-ocular sign, and subsequent sunken eyeballs. There may be associated ocular and systemic abnormalities such as keratoconus, keratoglobus, cataract, strabismus, mental retardation, deafness, renal dysgenesis, and neurological deficits. The modern nomenclature of Leber's congenital amaurosis has been challenged by some investigators as to its representation of the views of the original author.³

The fundus changes in this syndrome are extremely variable⁴ from normal⁵ to salt-and-pepper changes to typical retinitis pigmentosa,⁶ and occasionally the changes may resemble choroideraemia.⁷ Commonly the ophthalmoscopic picture may be quite polymorphic.⁷ Rarely the fundus abnormalities may include macular colobomas⁸ and optic disc oedema.^{4,9} A less commonly known fundus presentation of Leber's congenital amaurosis is the appearance of multiple, irregular shaped, yellowish white flecks deep in the peripheral retina. The purpose of this paper is to emphasise this variant of the fundus appearance in this entity. Fluorescein angiography findings, which have not previously

been described, are presented. The diagnostic ERG and the awareness of the polymorphism of the fundus appearances are emphasised.

Case report

The patient, a boy born in 1970 and enrolled in an institute for the partially sighted, was referred to the University of Nijmegen Ophthalmology Department because of unusual fundus lesions noted by his school ophthalmologist in 1978. He was a product of a full-term pregnancy complicated by measles during the seventh month of gestation. The perinatal history was uneventful. He was noted to have nystagmus and an inability to follow objects at 3 months of age. ERG and EOG performed at another institute at age of 6 months were reported as unrecordable and flat, respectively. He displayed the digito-ocular sign. His milestone development was delayed with sitting up at 12 months and walking at 19 months. No neurological deficits were present. He is at present reported to have slight learning disability. His parents, who are third cousins, had normal eyes on examination. His only sib was also normal.

On examination in 1978 his visual acuity was poor light perception bilaterally. Searching nystagmus was present. He displayed enophthalmos, while slit-lamp examination revealed entirely normal anterior segment. The pupils were 5 mm in diameter with a very slight, sluggish reaction to light. Ophthalmoscopy revealed optic discs of normal size and colour, with no evidence of disc oedema. Foveal reflexes were normal and the arterioles were attenuated. Yellowish white flecks, with well

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Fig. 1 Yellowish flecks in the mid periphery in a periarteriolar distribution seen on initial examination in 1978.

defined borders but becoming more confluent peripherally were found in a periarteriolar distribution in the midperiphery (Fig. 1). The nasal fundus as well as the posterior pole and the far periphery fundus adjacent to the ora serrata were spared. In this spared peripheral zone salt and pepper changes were seen. These lesions were remarkably symmetrical bilaterally.

In October 1982 a follow-up examination revealed essentially unchanged ocular status. These lesions, however, appeared more greyish in the peripheral aspects and the far peripheral pigmentation was more evident. The lesions appeared to have diminished in size in the peripheral margin (Figs. 2B, 3B) as compared with comparable areas seen in 1978 (Figs. 2A; 3A). A fluorescein angiogram showed hypofluorescence corresponding to the yellowish white flecks (Fig. 4). No staining or leakage of fluorescein resulted from these lesions, while hypofluorescence and window defects corresponded with hyper/hypopigmentation of the salt and

pepper retinal changes. There was also leakage from the peripheral vessels over the areas of the flecks (Fig. 5).

Discussion

In addition to these unusual yellowish white flecks in the midperiphery of the fundus our patient presented with nystagmus, digito-oculo sign, congenital blindness, and an unrecordable ERG, confirming the diagnosis of Leber's congenital amaurosis. This striking fundus appearance is a rare picture seen in the syndrome complex of Leber's congenital amaurosis. It was first described by Franceschetti and Forni¹⁰ as 'marbilized fundus' with its unusual mosaic pattern and periarteriolar distribution of well-demarcated yellowish lesions located deep to the retinal vessels. Other authors reported on this unusual fundus variant of Leber's congenital amaurosis.¹¹⁻¹⁶

The age of onset of these fundus lesions was

Fig. 2A

Fig. 3A

Fig. 2B

Fig. 3B

Figs. 2A and 3A The extensive distribution of these flecks are reduced in size and colour after four years of follow-up (Figs. 2B and 3B).

unknown in our patient. Two patients described in the literature^{12 14} were initially reported to have a normal appearing fundus and later found to have these lesions at the age of 21 months and 4 years when follow-up examinations were performed. It is unclear what these lesions, which appear to be deep to the retina, represent histologically. Mizuno *et al.*¹⁴ reported on two patients, one whose fundus photo-

graphs were not shown but had a clinical description which resembled the lesions found in our patient; the other patient had a different fundus affection of multiple white spots scattered throughout the entire fundus except for the macular area. Pathological study of the latter case revealed changes of the entire photoreceptor layer, with the outer segments of the cones either shortened and disorganised or

Fig. 4 Blockage of fluorescence by the yellowish white flecks.

Fig. 5 Leakage of fluorescein from the peripheral vessels over the areas of the flecks.

completely absent. Lack of cellular differentiation was observed from the outer nuclear layer to the pigment epithelial layer. The most striking pathological feature was the presence of large deposits between the retina and the retinal pigment epithelial layer. They corresponded to the white spots and consisted of fragments of inner segments, apical processes of pigment epithelial cells, and macrophages. It is difficult to conclude that the same pathological lesions occurred in our patient, as Mizuno *et al.*¹⁴ described a different clinical picture in the fundus.

Previous reports of Leber's congenital amaurosis showed the pathology to be as variable as the clinical appearance of the fundus. Complete disorganisation of all retinal layers has been reported,¹⁷ as have normal inner retinal layers, with disorganisation of the photoreceptor cell layer and external granular layer.^{18,19} Mizuno *et al.*¹⁴ postulated that the pathological lesion represents a primary dystrophic disorder, as lack of cellular differentiation was prominent. A secondary degenerative process resulted in cellular debris and macrophages in the subretinal layer. This may be the case, as the degenerative process is seen as spots or flecks developing after birth.

Fluorescein angiography of these yellowish white lesions showed hypofluorescence without leakage or staining. Mizuno *et al.*¹⁴ described a patient with a similar clinical appearance in the fundus, but fluorescein angiography showed fluorescence during the choroidal phase without leakage or staining.

Leakage of fluorescein from the peripheral vessels in Leber's congenital amaurosis has not been described before. It is not a surprising finding, as an association between retinal dystrophies and retinal vascular disease had been noted previously.^{20,21} An appearance like Coats's disease has been associated with retinitis pigmentosa.²⁰ Witschel²² has suggested that a toxic substance may be released by this degenerative process of the retina in retinitis pigmentosa, thus causing vascular leakage and a Coats's-disease-like picture.

The clinical presentation of such flecks may confuse the clinician.¹² They appear to be more or less specific for this disease and may be diagnostic of a special subgroup of Leber's congenital amaurosis. Other flecked retina patterns such as fundus flavimaculatus, retinitis punctata albescens, fundus albipunctatus, drusen,²³ crystalline retinopathy,²⁴ vitamin A deficiency,²⁵ and Kandori's flecked retina²³ are generally easily distinguished from Leber's congenital amaurosis. A flecked pattern in a palisade distribution appears quite similar; however, the location is confined to the posterior pole.²⁶ The larger, yellowish, fleck-like patterns such as are found in multiple vitelliform disease are clearly different.²⁷

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