Doc Ophthalmol (2015) 130:231–240
DOI 10.1007/s10633-015-9484-z

CLINICAL CASE REPORT

Electrophysiological and microperimetry changes in vitamin A deficiency retinopathy

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Received: 6 August 2014 / Accepted: 21 January 2015 / Published online: 28 January 2015

Abstract
Purpose To describe a follow-up case of vitamin A deficiency (VAD)-related retinopathy with macular involvement monitored with electroretinography and microperimetry.
Methods Flash (ERG), pattern (PERG), and multifocal (mfERG) electroretinography were recorded in parallel with microperimetry before and during 7-month follow-up of vitamin A treatment on a 65-year-old man presented with a 1-year history of night blindness. The patient had undergone ileostomy procedure for Crohn's disease 14 years ago. His best corrected visual acuity was 6/6 in each eye. Fundus examination revealed macular and mid-peripheral yellow-white lesions compatible with drusen.
Results Before treatment, PERG was reduced, and mfERG was reduced and delayed, worse in responses from the central rings. These results revealed evidence of bilateral macular and central cone dysfunction. The flash ERG showed reduced dark-adapted 0.01 ERG (rod response); a-wave of dark-adapted 3.0 and 10.0 ERG was normal but b-wave was reduced (negative configuration); light-adapted 3.0 ERG was slightly reduced. The flash ERG revealed evidence of bilateral generalised retinal dysfunction affecting the rod more than cone system. Microperimetry showed deep reduction in retinal sensitivity. Fixation stability was unstable with eccentric locus. During treatment, ERG and microperimetry demonstrated significant improvements. Fixation stability reached normal values after the third treatment week.
Conclusions This case illustrates the importance of electrophysiological investigation in early VAD-related retinopathy detection correlated with microperimetry. Our findings indicate a more delayed central cone function recovery than that of generalised rod and cone function. There was a marked correlation between ERG and microperimetric changes.

Keywords Vitamin A deficiency · Crohn's disease · Microperimetry · ERG

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Introduction

The fat soluble vitamin A can exist as retinol, its ester, and retinoic acid. Retinol and its derivatives play an

essential role in metabolic functioning of the retina, growth and differentiation of epithelial tissue, and immune response. In particular, they are fundamental to corneal and conjunctival epithelial cell RNA and glycoprotein synthesis [1, 2], whilst retinal is the integral chromophore which combines with both rod and cone opsins to form rhodopsin and activated cone opsins, leading to functional photo transduction. The signalling properties of visual pigments modulate many aspects of the function of rods and cones, producing their unique physiological properties [3].

Vitamin A deficiency may be primarily attributed to malnutrition, malabsorption, or impaired metabolism associated with liver disease and affects several organs in the body. The systemic effects and anterior ocular segment changes of vitamin A deficiency are noted usually when the deficiency is more acute, compared to the visual defects noted in the slow chronic cases. It has been previously demonstrated that vitamin A deficiency may occur in patients with active Crohn's disease. There is a marked correlation between serum/tissue vitamin A concentrations and the activity of the disease [4–6]. Malabsorption of vitamin A has also been documented to occur after surgical intervention for Crohn's disease and morbid obesity [5–14]. In these reports, vitamin A deficiency developed within months and up to 36 years after surgical intervention. Night blindness is the most common and earliest symptom of vitamin A deficiency [15]. Loss of visual sensitivity and eventual shrinkage and loss of photoreceptor outer segments in chronic vitamin A deficiency have been previously reported [16–18]. Similarly, visual field and electrophysiological changes including flash electroretinography (ERG) and pattern ERG have been described in patients with vitamin A deficiency [7, 18–20].

Microperimetry technology, also known as fundus-related perimetry, is a psychophysical examination similar to the standard visual field test, with the advantage of superimposing sensitivity and fixation data over the fundus image, resulting in precise anatomical-functional correlation. Microperimetry with eye tracker has been used for more than a decade in the assessment of macular pathologies particularly in patients with loss of central fixation [21, 22]. The functional parameters evaluated with microperimetry are retina sensitivity, fixation stability, and fixation location, also known as the preferred retinal locus (PRL). Conventional microperimetry is commonly a mesopic examination which projects stimuli of withe light across the retina, particularly over the macular area. The white light spectrum excites both rods and cones photoreceptors.

To the best of our knowledge, microperimetry and correlations with mfERG changes in patients with macular dysfunction due to vitamin A deficiency have not been reported previously.

We report in this case, one patient who has Crohn's disease and developed nyctalopia 14 years after the ileostomy procedure. At initial presentation, the electrophysiologic results revealed generalised retinal and macular dysfunction; however, serum vitamin A level was normal. We describe the microperimetric findings (MAIA Centervue, Padova, Italy) in parallel with the electrophysiologic changes including multi-focal ERG (mfERG) in this patient, before and after vitamin A treatment.

Case report

A 65-year-old man presented with a 1-year history of night blindness, which had progressed in the preceding few weeks. Fourteen years previously, he had undergone Crohn's disease-related ileostomy procedure for chronic malabsorption. There was no family history of consanguinity or any other eye disorders.

At presentation, full ophthalmic examination was performed, and best corrected visual acuity was 6/6 in each eye; red-green colour vision deficiency as determined with Ishihara colour plates was normal for each eye. Anterior segment examination was unremarkable. He was pseudophakic (in the bag IOLs) from surgery in both eyes 10 years prior to the first presenting complaint. Posterior segment examination revealed macular and mid-peripheral yellow-white lesions compatible with drusen; otherwise the fundus was normal. Pattern ERG (PERG) and flash ERG conforming to ISCEV standards were performed [23, 24]. The PERG showed reduced P50 and N95 components in both eyes. The flash ERG showed that dark-adapted 0.01 ERG was reduced; a-wave of dark-adapted 3.0 and 10.0 ERG was normal but b-wave was reduced (negative ERG); light-adapted 3.0 ERG was slightly reduced but with normal peak time, whilst 30-Hz flicker responses were normal in both eyes. These results indicate generalised retinal dysfunction, affecting the rod more than the cone system, and subnormal macular function (Fig. 1). In view of his

past medical history and his ERG results, vitamin A deficiency-associated retinopathy was suspected. However, at this time point, his serum vitamin A level was normal (1.9 μmol/L; normal reference range 1.3–2.9), therefore the patient remained under observation.

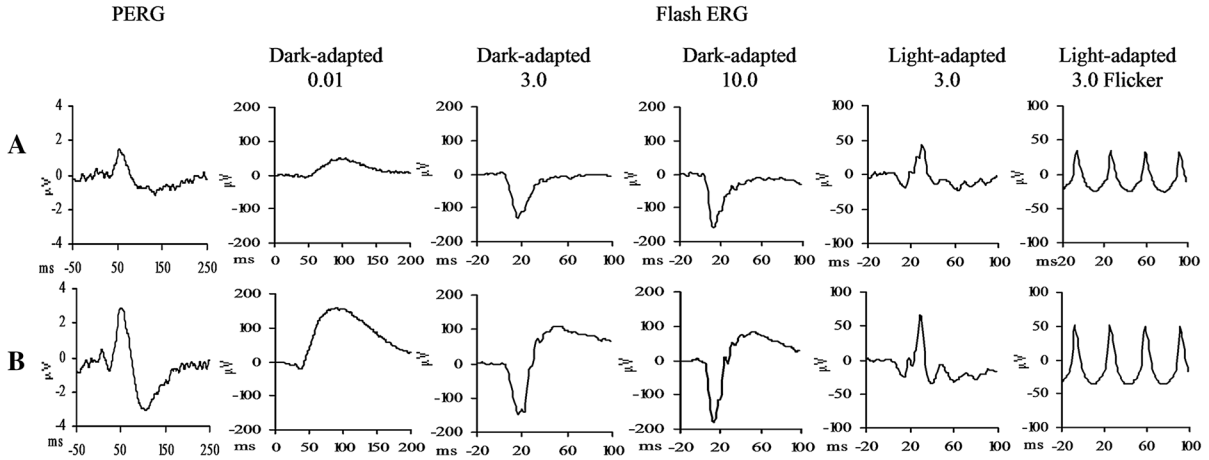

Fig. 1 PERG and flash ERG recorded at initial presentation (**a**) and age-matched normal (**b**). The PERG was reduced in both eyes. The flash ERG showed moderate reduction in scotopic responses with negative configuration and mild reduction in light-adapted 3.0 ERG with normal latency in both eyes

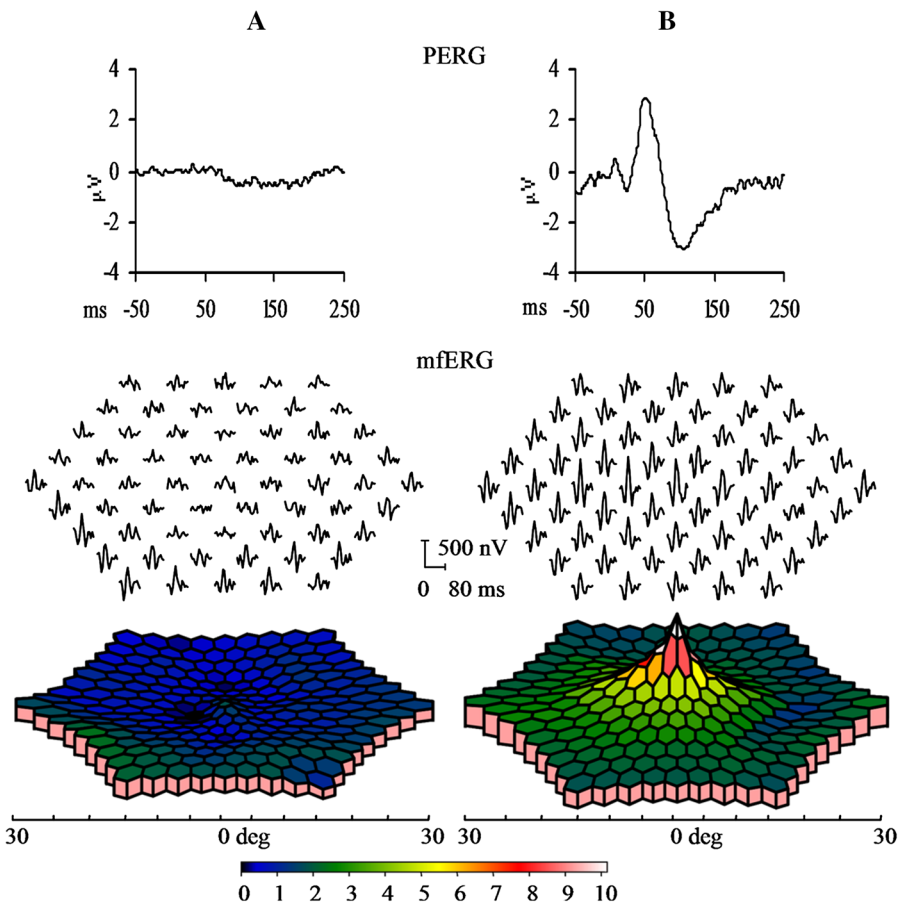

Fig. 2 The PERG and mfERG recorded at pre-treatment (**a**) and age-matched normal (**b**). The PERG was undetectable, whilst the mfERG was reduced and delayed, worse in the central rings than the outer rings in both eyes and showed evidence of significant deterioration of macular function compared to results recorded at initial presentation

Eighteen months later, the patient complained of worsening symptom of nyctalopia. His visual acuity remained 6/6 in each eye. PERG was almost absent in both eyes, and mfERG recorded to ISCEV standard [25] and showed reduced and delayed responses, worse in the central rings (0°–15°) compared to the outer rings (15°–30°) (Fig. 2). His flash ERG recording showed undetectable dark-adapted 0.01 ERG with further reduction in b-wave of dark-adapted 3.0 and 10.0 ERGs. Similarly, a-wave reductions (with photopic cone responses appearance) were observed (Fig. 3). These results showed clear evidence of deterioration of macular and generalised retinal function, more marked in rod system and also macular function compared to earlier examination. His serum vitamin A level became subnormal (0.7 μmol/L). Vitamin E levels measured 12.4 μmol/L (normal 14.0–30.0), and total protein levels were also slightly subnormal whilst vitamin B and vitamin D levels were normal. Spectral domain optical coherence tomography (OCT) cross sections demonstrated focal changes typical of drusen. Microperimetry on baseline examination showed an average macular sensitivity of <6 dB on both eyes, demonstrating significant

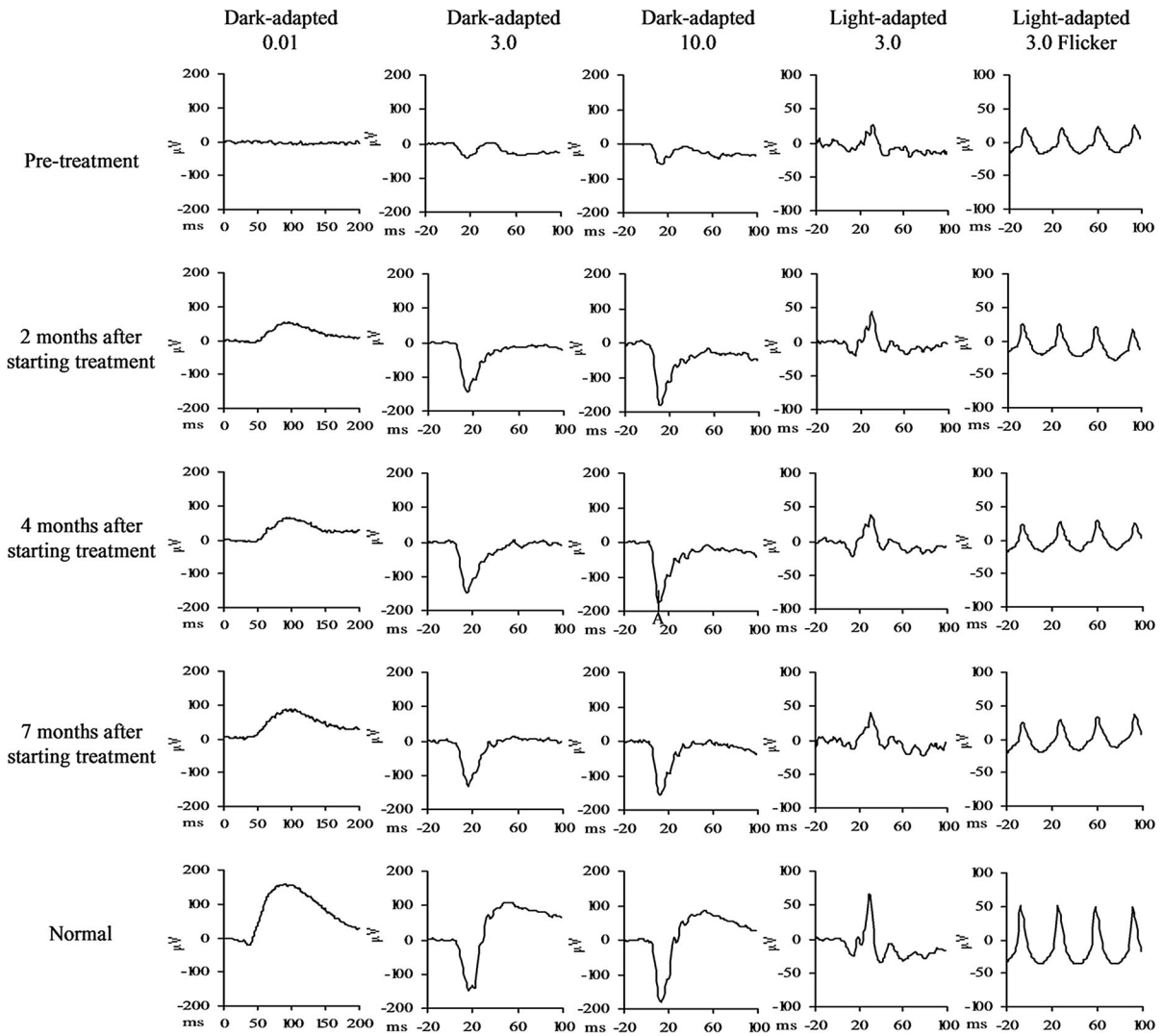

Fig. 3 Flash ERG recorded before and after treatment and age-matched normal. The flash ERG showed significant deterioration in scotopic responses before treatment. Two months after starting treatment, flash ERG showed significant improvement, particularly in rod function. Afterwards, it remained stable, however, still not fully recovered 7 months post-treatment

reduction in sensitivity compared to normals (>29 dB) [25] with large scotomatus area. Both of the eyes had unstable fixation (P1 <75 %) [26], whilst PRL in both eyes were eccentrically located in the supero-nasal area (Fig. 4).

Treatment and follow-up

The patient was given a combination of vitamin A intramuscular injections 100,000 IU/week for 5 weeks and subsequently oral supplements 4,000 units daily as well as vitamin E 140 mg/day.

One week after the first injection, the patient reported improvement of his symptom, with VA maintained at 6/6, whilst microperimetry only showed slight improvement in retinal function parameters. After the second week, microperimetry values of retinal sensitivity showed significant improvement (>20 dB) whilst fixation became highly stable (P1 >95 %) (Fig. 5). Remarkably, a relocation of the PRL, which was originally found eccentrically (Fig. 4), was noted towards the foveal zone (Fig. 6). The fundus remained unchanged. After 1 month of treatment, vitamin A and vitamin E levels returned to normal (3.4, 32.9 μmol/L, respectively). Up to the fourth month of treatment, microperimetry continued to show further increases in retinal sensitivity whilst fixation stability remained maximal. The average macular sensitivity did not reach normal values even at month 7, where it showed a slight decrease on both eyes (Fig. 5).

The flash ERG and mfERG were repeated at 2, 4, and 7 months after initial treatment. At the second month, the flash ERG showed clearly that generalised retinal function, particularly the rod function had improved significantly although values were still subnormal. The mfERG also showed significant improvements in macular function in both eyes. After 4 months, no significant improvement was shown in

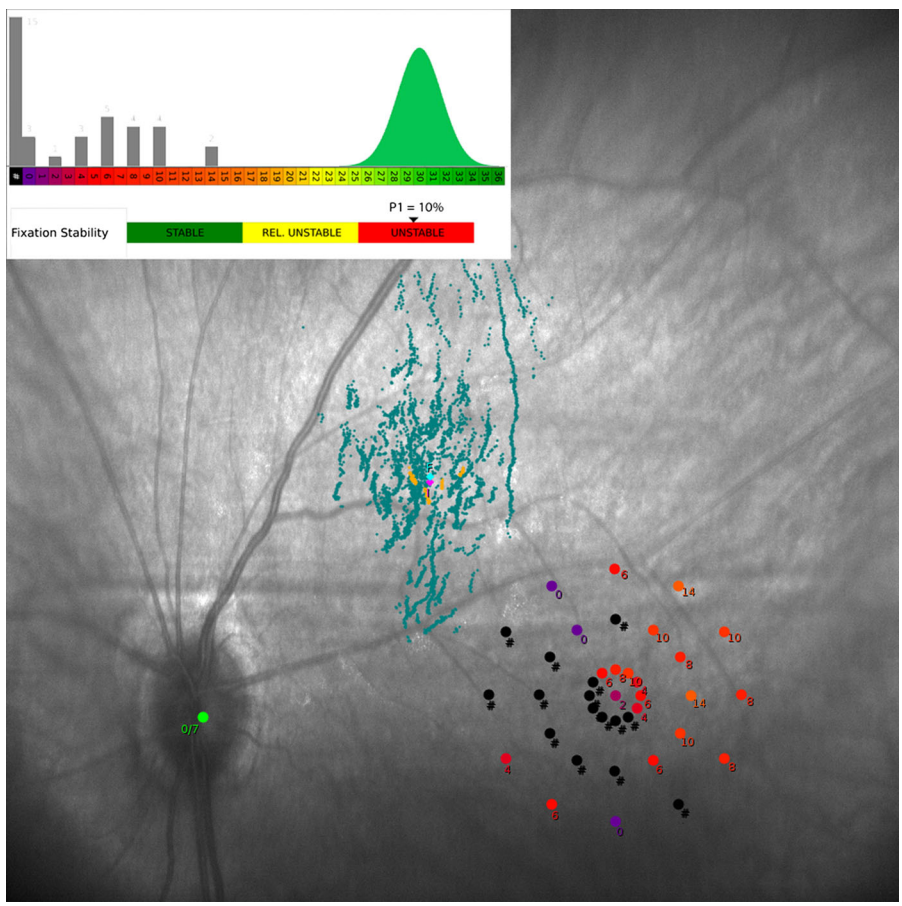

Fig. 4 Baseline microperimetry results. Both eyes showed important reduction in retinal sensitivity (<6 dB) with dense scotoma on the central macula (shown in *black spots* in the MAIA microperimetry outcomes). Fixation stability is clearly unstable and eccentrically located supero-nasal on both eyes

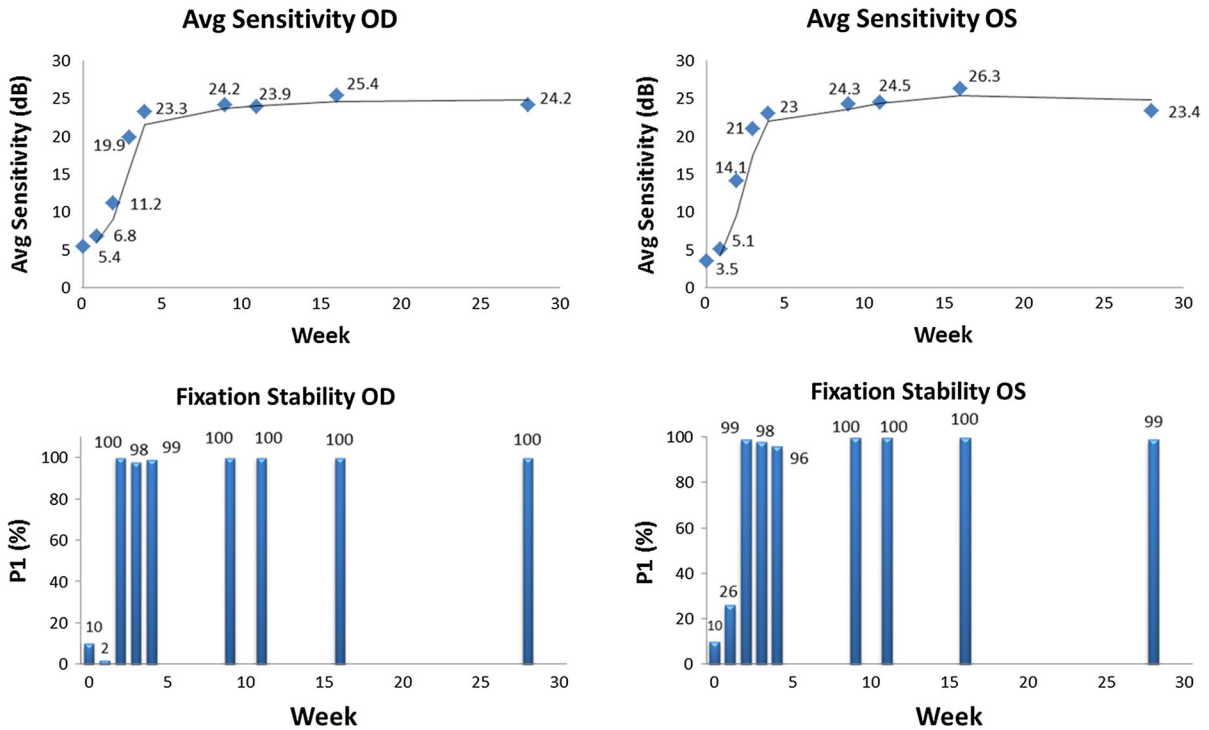

Fig. 5 Microperimetry changes during treatment. After the second treatment week, retinal sensitivity and fixation stability demonstrated significant improvement. Although macular sensitivity of both eyes remained slightly below normative values, fixation stability from the third week remained stable

either the flash ERG or the mfERG despite continuation of treatment. Seven months after treatment, flash ERG remained subnormal and showed no further improvement of generalised retinal function; however, the mfERG revealed significant improvement in the innermost ring (0°–7.5°) and suggested further improvement of macular function although still subnormal (Fig. 7).

Discussion

Electrophysiological changes in vitamin A deficiency and the reversal of such changes following treatment have been previously reported [7, 18–20, 27, 28]. To the best of our knowledge, this is the first report of microperimetry changes in parallel with the electrophysiologic changes, including the mfERG in patients with vitamin A deficiency, and the effects of treatment on these changes.

White-dotted fundus appearance in patients with vitamin A deficiency is a well-recognised feature of this condition [27, 29]. However, the deposits noted in our patient were drusen compatible with the patient's age and not thought to be associated with vitamin A deficiency.

In our case, the flash ERG at initial presentation showed moderate reduction in b-wave in dark-adapted 0.01 ERG; moderate reduction in b-wave but of normal a-wave in dark-adapted 3.0 and 10.0 ERGs (negative waveform) and slight reduction in light-adapted 3.0 ERG. This implies that the retinal function has already been impaired even the vitamin A level was still within the normal limits, and the negative waveform indicating a predominant dysfunction of bipolar cells and the inner layers of the retina [30]. Before the treatment, the flash ERG showed that light-adapted 3.0 ERG, and 30-Hz flicker responses were slightly deteriorated. However, dark-adapted 0.01 ERG was undetectable; a- and b-waves were markedly reduced with similar waveform to that of photopic cone response, and amplitudes were similar between dark-adapted 3.0 and 10.0 ERG. It has been previously suggested [18, 31] that this change may represent a 'photopic hill' phenomenon in a dark-adapted functionally cone-isolated retina. The flash ERG in scotopic responses was more reduced than the photopic

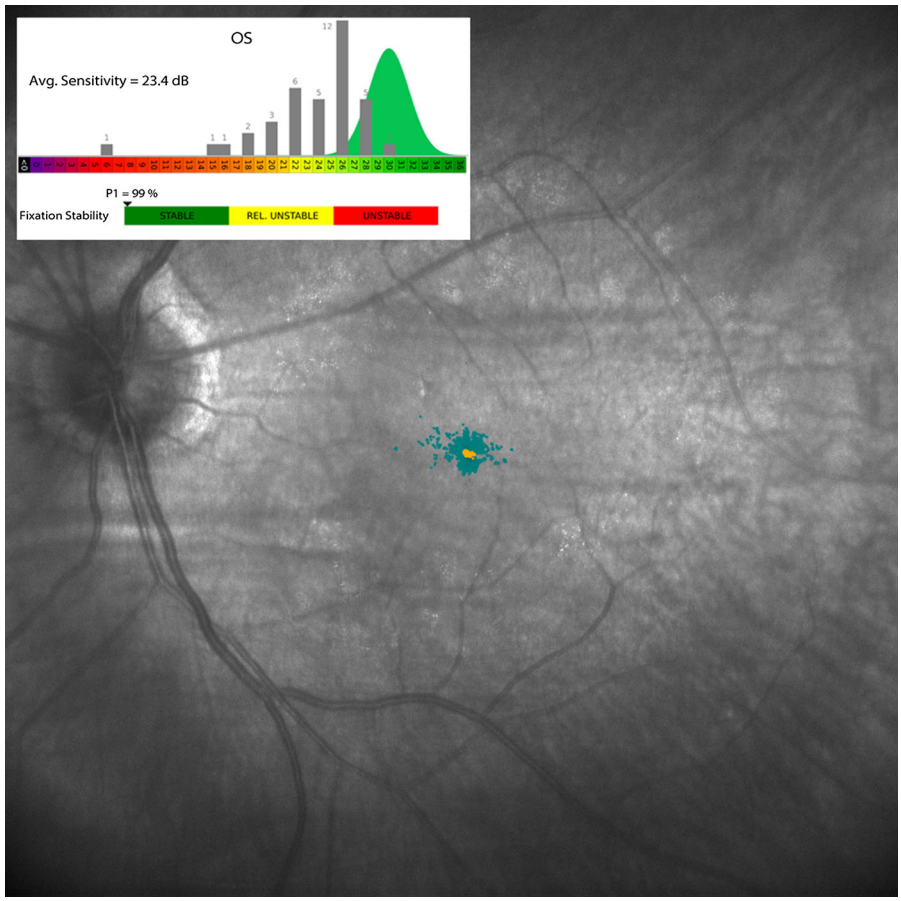

Fig. 6 Microperimetry shows changes in the preferred retinal locus (PRL). PRL shifted from an eccentric (supero-nasal) location towards a central foveal zone after treatment, demonstrating as well a significant improvement in fixation stability

responses, indicating that the damage to the rod system was greater than to the cone system. The reasons for this remain obscure. It has been reported that rod photoreceptor cells depend completely on the output of 11-*cis*-retinal from adjacent retinal pigment epithelial (RPE) cells, whilst cone photoreceptors cells can use 11-*cis*-retinal from the RPE and from a second, cone-specific visual cycle, which appears to involve adjacent Müller (glial) cells [32, 33].

At baseline, microperimetry functional values of unstable fixation, highly eccentric PRL, and poor retina sensitivity demonstrated by large scotomata in the central vision, correlated very well with the PERG and mfERG findings of markedly reduced macular function. Following treatment with vitamin A, microperimetry values improved significantly in both retinal sensitivity and fixation characteristics with important recovery of central vision demonstrated with the PRL located over the foveal area. These improvements paralleled the mfERG changes which showed improvement more in the central rings than the outer rings.

The flash ERG showed significant improvement, more marked in scotopic responses than in photopic responses at 2 months after starting treatment but no further improvement thereafter. The mfERG also showed significant improvement at 2 months but also at 7 months after starting treatment. Our results indicate that the recovery of generalised cone function is slower than that of rod function, and the recovery of macular function is even slower than generalised cone function. This is in keeping with previous report [18]. The interaction of the scotopic and photopic ERG pathways is well described in the literature based on full field ERG findings [18, 19, 34–36]. It has been suggested that restoration of the rod system following vitamin A supplementation in previously deficient patients resulted in reduction in mfERG and photopic response amplitudes [19]. The delayed improvement in retinal sensitivity and fixation stability on

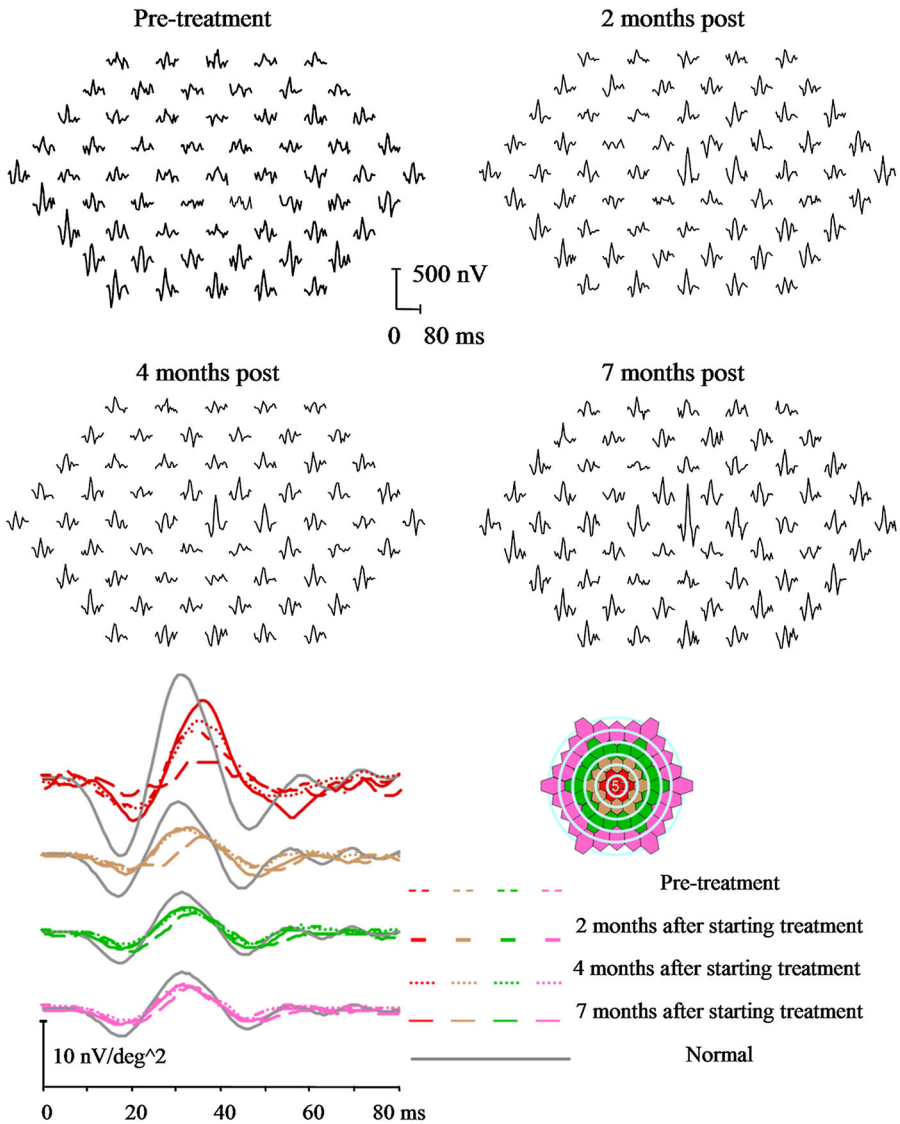

Fig. 7 mfERG before and after treatment. The mfERG showed significant improvements at 2 months and further improvement at 7 months particularly in responses from the innermost ring in both eyes

microperimetry is in keeping with the delayed central cone recovery as seen in the mfERG.

In conclusion, this case illustrates the important role of ERG testing in early detection of vitamin A deficiency-related retinopathy and highlights a marked correlation between microperimetric changes with patient symptomatology and ERG values. Our findings indicate that reduced macular function attributable to vitamin A deficiency could be identified and adequately monitored using microperimetry in addition to electrophysiology.

Conflict of interest Marco Morales: Centervue Consultant. Financial interest. Remaining authors Saker Saker, Harsimar Jhittay, Yaqin Wen, Winfried Amoaku declared that they have no conflict of interest.

Patient consent The patient has signed a consent form and has given permission to the research group of the Nottingham University to collect, store, analyse, and publish his case report in medical scientific journals. The patient has understood that his personal details will be kept confidential.

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