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CLINICAL INVESTIGATION

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Multifocal ERG in multiple evanescent white dot syndrome

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Abstract *Purpose:* To investigate the electrophysiological findings of a multifocal ERG in multiple evanescent white dot syndrome (MEWDS). *Methods:* Multifocal electroretinograms (mf-ERG) were recorded from four patients with MEWDS. The stimulus array consisted of 61 hexagons and was presented according to a binary m-sequence. We analyzed the N1- and P1-wave amplitudes as well as P1 latencies of the first-order kernels. Local responses and concentric ring averaged responses were compared to 20 age-matched normal subjects. All patients underwent fluorescein angiography and indocyanine green angiography. *Results:* In two patients, first-order kernel of N1- and P1-wave amplitudes showed supernormal results at the very beginning (day 1 to day 7) of the disease. By 2 weeks later, N1- and P1-wave amplitudes had decreased to either normal or subnormal values. The two patients who presented 2 weeks after the onset of clinical signs showed subnormal or decreased amplitudes. The P1 implicit times were within normal limits in all patients. *Conclusion:* Our mf-ERG findings show different results during the course of the disease. First-order kernel amplitudes seem to reflect early disturbances of the photoreceptors in MEWDS and are therefore useful in detecting early stages and following up the disease.

Introduction

The multiple evanescent white dot syndrome (MEWDS) is an inflammatory disease found in young, predominantly female patients and was first described by Jampol et al. in 1984 [20]. The etiology remains uncertain and there is no definite evidence of systemic involvement, although an infection is suggested as MEWDS is preceded by a flu-like disease and elevated IgM and IgG levels in some patients [3]. MEWDS is characterized by multiple discrete white dots located at the level of the outer retina or the retinal pigment epithelium (RPE). Patients often experience an acute onset of unilateral visual disturbances with multiple paracentral scotomas, floaters, and photopsae. In the early stages of the disease clinical retinal findings can be subtle and may be overlooked. In more advanced stages ophthalmoscopic changes become more evident and show typical small gray-white patches scattered over the posterior retina, tending to concentrate around the optic disc and along the vascular arcades. Other findings include tiny white or light-orange dots in the center of the macula, often described as granularity of the fovea, vitreous cells, retinal vascular sheathing, and optic disc edema. On fluorescein angiography (FA) early punctate hyperfluorescence of the dots, which often show a cluster or wreath-shaped pattern, can be seen. In the late phase of FA, staining of these lesions and in some cases staining of the optic disc is evident. Indocyanine angiography (ICGA) shows numerous choroidal hypofluorescent lesions that largely outnumber the visible lesions and do not necessarily correspond to either funduscopy or FA [5]. MEWDS was originally described as being monolateral and monophasic but cases of recurrence and bilaterality have also been reported [1, 41]. Spontaneous recovery of vision and normalization of ophthalmoscopic, CGA, and fluorescein findings will occur within 7–10 weeks.

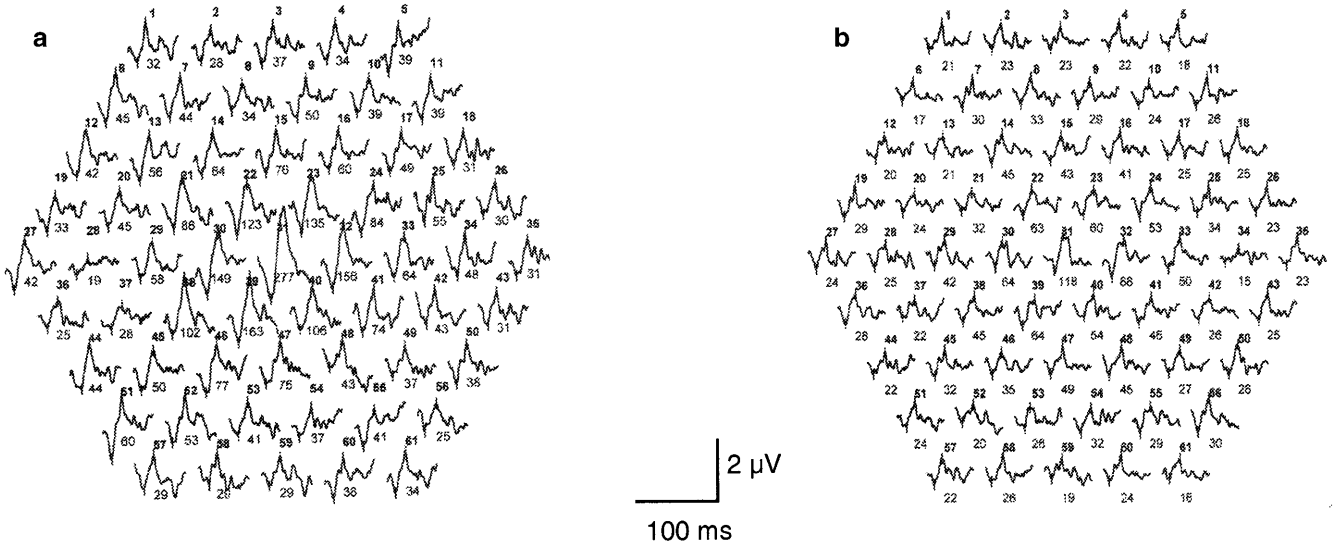


Fig. 1 Multifocal electroretinographic arrays of patient 1 with supernormal responses of her left eye (**a**) in contrast with the normal results of her right eye (**b**)

During the acute stage the a- and b-wave of the Ganzfeld ERG and the early receptor potential amplitudes are profoundly decreased [37].

The multifocal ERG (mf-ERG) developed by Sutter et al. [40] is a method of recording the spatial resolution of focal ERGs within the posterior pole in a short time period using multi-input stimulation. It has proven to be a powerful tool in various congenital and acquired retinal diseases as it reflects retinal function under photopic conditions [2, 12, 17, 23, 25, 26, 27, 29, 30, 31, 32, 35, 36]. The exact origin of each component is still under investigation, but Hood et al. [16] demonstrated in their studies that there is a strong correlation between the components of the multifocal and Ganzfeld ERG. They concluded that the biphasic responses (a negative component N1 and a positive component P1) of the mf-ERG appear to be generated by the same cells generating the a-wave and the positive peaks of the Ganzfeld cone ERG.

Findings with mf-ERG and MEWDS have been published in a case report [18]. The authors describe markedly reduced amplitudes in the areas corresponding to the visual field scotomas, which were still present even 4 months later and indicated a very protracted recovery from retinal dysfunction in MEWDS.

The purpose of our study was to show the early findings in a multifocal ERG in MEWDS.

Patients and methods

Patients

We examined 4 patients with MEWDS. Diagnosis was based on the clinical course and on ophthalmological and angiographic findings. The patients presented at different times after the onset of the disease. Patient 1 had suffered from visual disturbances and photophobia for 1 day, patient 2 had had ocular complaints for 1 week, and patients 3 and 4, for 2 weeks. The patients' characteristics are outlined in Table 1. All patients had an acute onset of blurred vision in one eye and denied previous ocular problems and systemic medical history. Laboratory values (HSV, HZV, CMV, EBV, borreliosis, C-reactive protein, rheumatoid factor, antinuclear antibody) were negative. Fundus examination showed multiple small white lesions located within the deep retina or the RPE extending from the parafoveal area throughout the posterior fundus.

Table 1 Clinical characteristics of patients with MEWDS

Patient	Age (years)/sex	Eye	Duration of ocular complaints	Initial visual acuity
1	25/F	OS	One day	20/40
2	23/F	OS	One week	20/25
3	33/F	OD	Two weeks	20/25
4	25/F	OS	Two weeks	20/25

The macula exhibited granularity and irregularity of the internal limiting membrane reflex. In one patient foveal granularity was also seen in the unaffected, asymptomatic eye, indicating a previous episode of MEWDS. FA revealed a cluster of tiny early hyperfluorescent dots with late staining of these lesions as well as of the optic disc. In two patients (nos. 3, 4) discrete vascular sheathing was evident. ICGA showed numerous early hypofluorescent choroidal lesions throughout all phases.

Methods

Multifocal ERGs (Retiscan Version 3.1, Roland Consult, Wiesbaden, Germany) were recorded binocularly at the patients' first visit and repeated after 2 weeks. Twenty normal, age-matched subjects (age 20–30 years, mean 25 years) were chosen. Informed consent was obtained from all subjects after the experiments were explained. The stimulus array was presented on a monitor (frame rate 60 Hz, mean luminance 180 cd/m^2) and consisted of 61 hexagons which were scaled in size within the periphery and covered an area up to a 30-deg visual field. Each hexagon alternated between black and white (contrast 99%) according to a binary m-sequence. Every active m-sequence lasted 16.6 ms and was followed

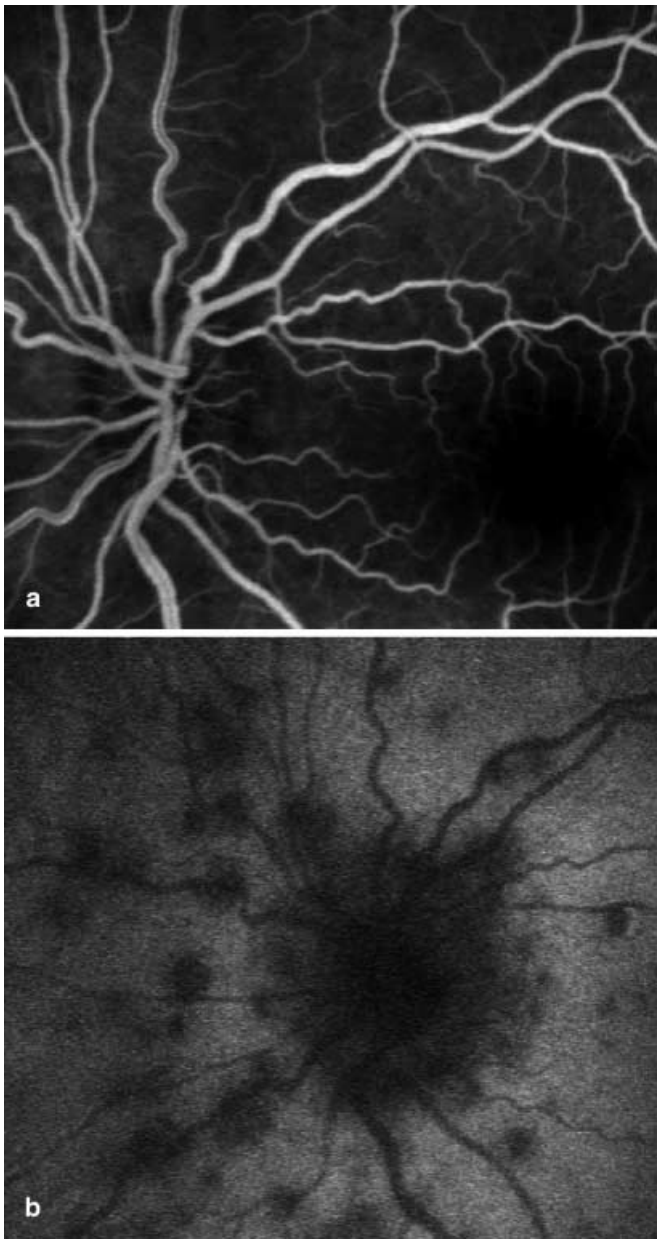


Fig. 2 **a** FA in patient 1 shows normal early phase. **b** The late phase of the ICGA shows peripapillary hypofluorescent flecks

by a rest interval of 66.4 ms before the next active m-sequence was started. Artifacts were rejected by online monitoring. Patients were seated at a viewing distance of 33 cm and had to fixate a central cross. Subjects' pupils were fully dilated (0.5% tropicamide and 1% phenylephrine hydrochloride), and DTL electrodes were used for the ERG recording. Signals were amplified (50,000×) and bandpass filtered (1–300 Hz). The recording session was divided into eight segments (each 47 s) with short breaks in between, and N1 and P1 amplitudes as well as latencies of first-order kernels were analyzed by concentric ring averaging.

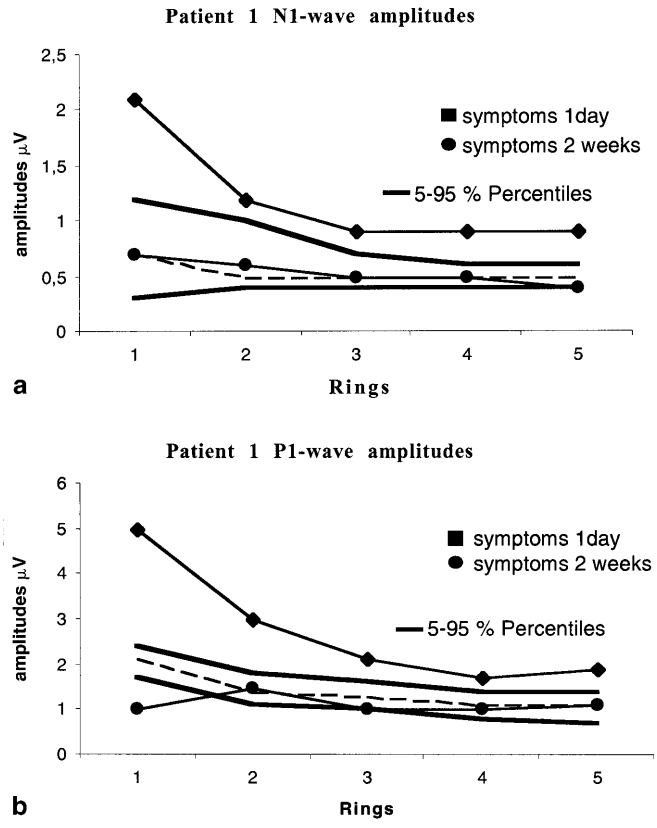


Fig. 3 **a** N1-wave and **b** P1-wave amplitudes of the first-order kernel analyzed by concentric ring averaging in patient 1. The *squares* represent the data 1 day after onset of symptoms and show supernormal results for both waves. The *circles* show decreased results after 2 weeks for N1 as well for P1-wave. The *lines* and *dashed line* enclose the range of normal data (5%, median, 95% percentiles)

Results

Supernormal mf-ERG amplitudes were found in the early course of MEWDS (between 1 day and 1 week), and normal or decreased amplitudes were evident when symptoms had been present for 2 weeks.

Figure 1 shows the first-order local responses of mf-ERG of the left eye in one patient (patient 1) who noted multiple scotomas and photophobia of 1 day's duration in comparison with her asymptomatic right eye. Supernormal amplitudes (N1 and P1 waves) and normal P1 latencies were evident. FA and ICGA showed different results: early FA was normal, while early ICGA revealed peripapillary and posterior pole hypofluorescence, which became more evident in the late phase (Fig. 2). Patchy hyperfluorescence and optic disc staining were seen only in the late phase of FA.

By 2 weeks after the onset of symptoms the mf-ERG amplitudes in patient 1 had decreased to normal and subnormal values (Fig. 3). Angiographically, typical early

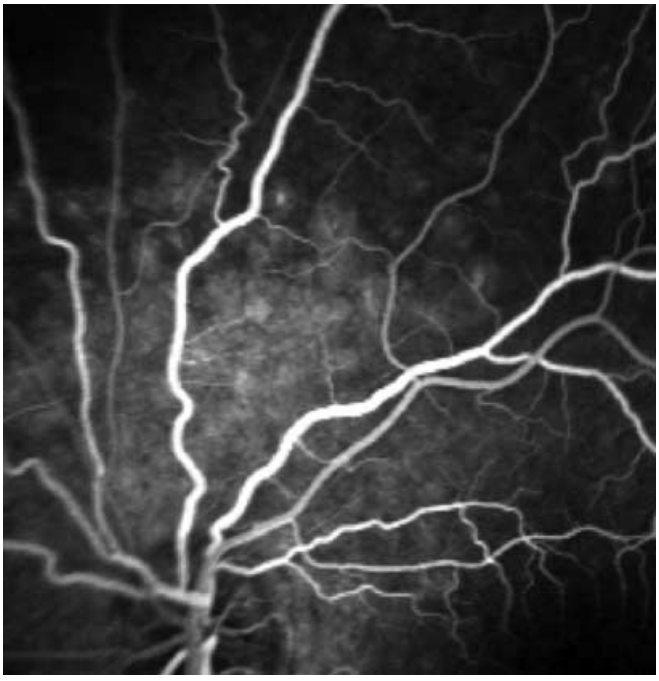


Fig. 4 Two weeks after the onset of symptoms FA shows typical hyperfluorescent spots around the disc in patient 1

hyperfluorescent lesions were noted in FA whereas ICGA hypofluorescent flecks became smaller (Fig. 4). Her visual acuity did not decrease any further.

Patient 2 was referred to our clinic after visual complaints lasting for 1 week. The local responses shown in

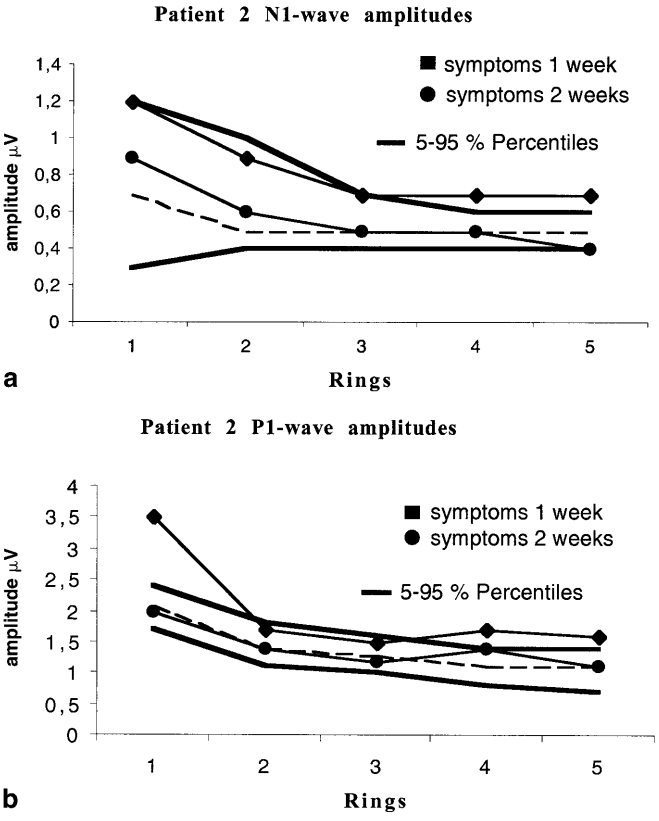
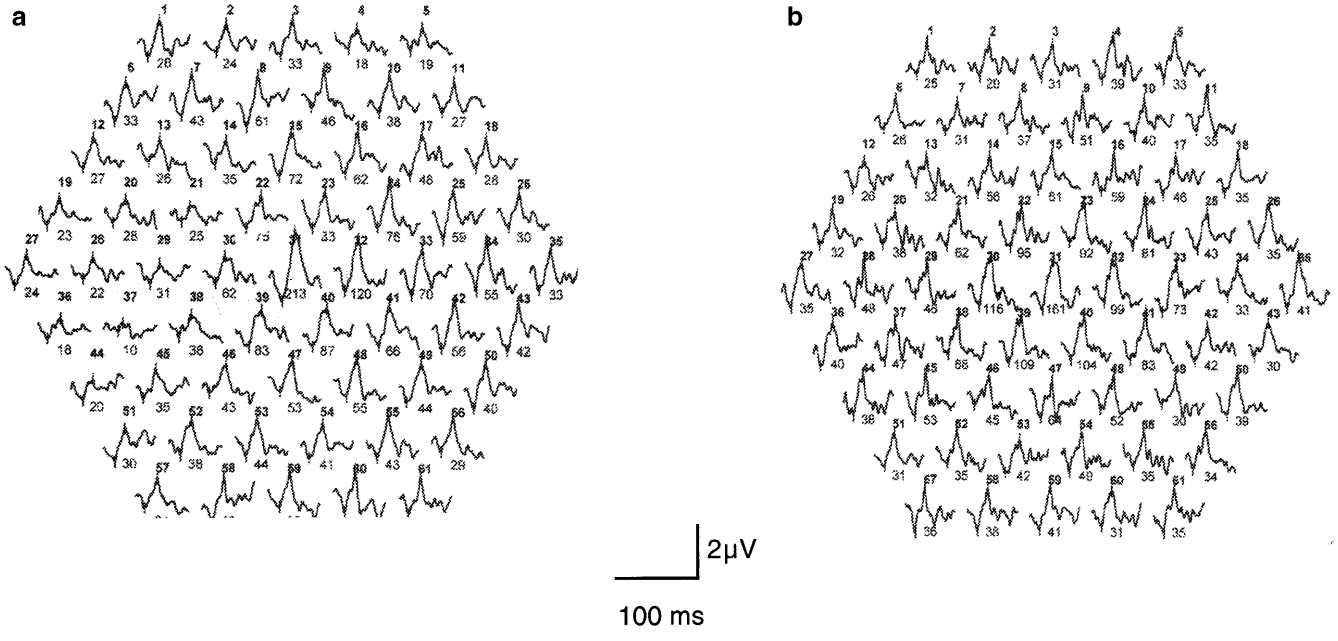


Fig. 6 Mf-ERG N1-wave (**a**) and P1-wave (**b**) amplitudes relative to the eccentricity from the fovea after 1 week and 2 weeks' duration in patient 2. Increased amplitudes can be found for both waves concerning rings 4 and 5 and for the P1-wave for the central amplitude after 1week (*squares*). After 2 weeks (*circles*) N1- and P1-wave results decrease to within normal values

Fig. 5 Mf-ERG local responses of patient 2 show **a** supernormal results concerning mainly the temporal region of her left eye and **b** normal results for her right eye



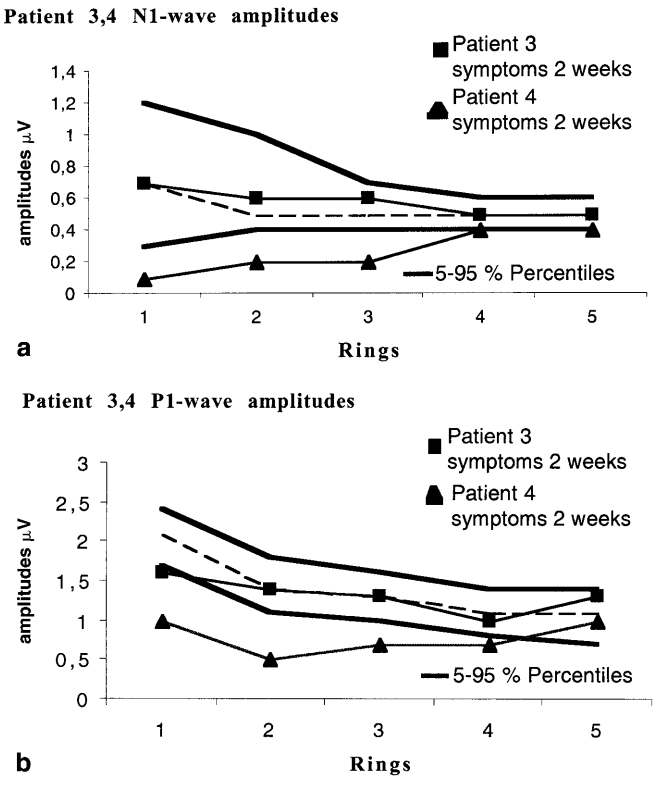


Fig. 7 **a** N1-wave and **b** P1-wave results of patient 3 (*squares*) and patient 4 (*triangles*) show normal to decreased amplitudes of the first-order kernels by concentric ring averaging after a duration of the disease of 2 weeks

Fig. 5 revealed supernormal amplitudes mainly present in the central amplitude and the temporal region. Using concentric ring analyses (Fig. 6), we found supernormal mf-ERG only in the P1-wave amplitude of the central ring and slightly increased values for rings 4 and 5 as well as for the N1-wave amplitude. After 1 week's follow up, N1- and P1-wave amplitudes decreased to normal and subnormal ranges and visual acuity slightly decreased from 20/25 to 20/32.

Patients 3 and 4 were examined more than 2 weeks after the onset of symptoms. Mf-ERG results are demonstrated in Fig. 7. Patient 3 shows subnormal P1-wave (ring 1) and normal N1-wave amplitudes. Clearly decreased amplitudes were evident in patient 4.

In all of our patients P1 latencies were within the normal range.

Typical angiographic findings with early hyperfluorescent dots in FA and hypofluorescence in ICGA in all phases were found in patients 2, 3, and 4.

Patients 3 and 4 experienced total recovery within 6–8 weeks. Patients 1 and 2 still suffered from visual impairment but showed improved angiographic findings and stable, slightly decreased and subnormal electroretinographic changes after 6 weeks' follow up.

Discussion

Our results demonstrate that in early MEWDS (patients 1 and 2) there are supernormal N1- and P1-wave amplitudes of the first-order kernel in mf-ERG which decrease approximately to normal or subnormal values by 2 weeks after the onset of disease. In those seen after more than 2 weeks (patients 3 and 4), we found N1- and P1-wave amplitudes within the normal range or decreased amplitudes. The P1 latencies were normal in all of our patients. In patient 1 supernormal amplitudes were associated with extreme photophobia and almost normal early FA. The typical hyperfluorescent spots became evident only in the late phase of angiography.

Decreased amplitudes in the Ganzfeld ERG and the mf-ERG have been described before in several inflammatory diseases affecting the deeper retina. As the mf-ERG is a relatively new technique, data are sparse. Helbig et al. [14] reported a case of acute zonal occult outer retinopathy and discussed overlapping features with other "white dot syndromes". They suggested that mf-ERG might be a valuable diagnostic tool for localized retinal disturbances when Ganzfeld ERG is still normal, but did not present any data on the mf-ERG. Their patient showed decreased rod and cone amplitudes in Ganzfeld ERG. Fishman et al. [7] and Deutman et al. [6] showed reduced Ganzfeld ERG and electrooculography (EOG) results in patients with acute posterior multifocal placoid pigment epitheliopathy in early studies when mf-ERG was not yet available. Sieving et al. [37] demonstrated in 11 patients with MEWDS that Ganzfeld ERG measurements showed profound diffuse retinal involvement during the acute stage, with rod responses somewhat more impaired. In other white dot syndromes such as multifocal choroiditis and panuveitis, punctate inner choroidopathy, and diffuse subretinal fibrosis syndrome, Ganzfeld ERG has been used [33]. In all of these instances reduced (or subnormal) results were demonstrated. However, it has to be considered that although our results seem to contrast with these prior reports, mf-ERG reflects only the cone activity of the central retina, while Ganzfeld ERG does not represent macular function well. Another reason for different results might be the time when the ERGs were derived. Sieving et al. [37] showed decreased Ganzfeld ERG results 6 days after onset of visual symptoms. Huang et al. [18] showed in one case report reduced amplitudes in mf-ERG after blurred vision for 1 week. Supernormality of ERG is an unusual phenomenon because most retinal abnormalities reduce rather than increase the amplitudes of the ERG. It could reflect an early transient condition of the photoreceptors which may sometimes be hard to verify.

Other conditions that may feature supernormal Ganzfeld ERG are albinism [28], vascular disorders [10, 15, 21], cone dystrophy [9, 22, 34], and siderosis [24] but the pathogenesis remains obscure. Gouras et al. [11] suggested an elevated level of cyclic guanosine monophosphate (cGMP), an internal messenger that is mostly lo-

cated in the deeper cells (both rods and cones) and plays an important role in visual transduction [4, 13].

Although supernormality in the Ganzfeld ERG has not yet been demonstrated in MEWDS, some not directly comparable Ganzfeld data in inflammatory diseases show supernormal responses. Stanford and Robbins [39] demonstrated in their studies in experimental uveitis that there were supernormal amplitudes in ERG before onset of the disease. They induced inflammatory eye disease in rats by inoculating retinal S-antigen. The ERGs were supernormal about 2–3 weeks after inoculation and then deteriorated to subnormal and pathologic as retinal pathology became evident. Ikeda et al. [19] showed that at the onset of an ocular disease, besides a slight rise in the EOG, there are also slightly supernormal a- and b-waves in the Ganzfeld ERG. They considered the EOG to be more sensitive and showed a progressive decline in electroretinographic amplitudes during the course of the disease. They hypothesized that the supernormality is due to an excess of extracellular glutamate, which has been shown to be a major cause of ischemic cell damage [38]. In these studies, supernormality and the presence of vitreous cells were the only signs of inflammation.

Another causative factor of supernormality in ERG in inflammatory diseases may be the breakdown of the blood–retinal barrier. Fishman et al. [8] demonstrated supernormal b-wave amplitudes with fluorophotometry in three patients with cone dystrophy when the blood–retinal barrier showed only moderate breakdown, as can be found at the onset of an inflammatory disease. Our patient 1, who showed the highest supernormality, was examined the day after onset. Her complaints included extreme photophobia, which could be a clinical expression of supernormality in the mf-ERG amplitudes. Funduscopic as well as early angiographic findings were discrete, and mf-ERG could have reflected early alterations in the transduction process of the photoreceptors. As funduscopic and angiographic findings became more evident (patients 2–4), mf-ERG amplitudes also decreased.

The cause of supernormal results in ERG remains uncertain, but they seem to reflect alterations in the photoreceptors which could be inflammatory, toxic, ischemic or genetic in origin. Photophobia apparently plays a role as a clinical expression of supernormality as the latter can be found in albinism and cone dystrophy, where photophobia is evident to some extent.

We are well aware of the fact that very few patients were included in our study. However, the number of patients that present with very early stages of the disease, where we could find supernormal responses in mf-ERG, is low.

Our results suggest that the mf-ERG reflects inflammatory dynamics in MEWDS. It could be useful as an additional, sensitive indicator to detect the first signs of the disease and as a valuable tool in follow-up.

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