Sensitivity of multifocal electroretinography (mfERG) in detecting siderosis

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ABSTRACT • RÉSUMÉ

Objective: To evaluate use of multifocal electroretinography (mfERG) in diagnosing retinal toxicity from siderosis with normal ERG.
Design: Prospective case series.
Participants: Six patients with retained intraocular foreign body were recruited.
Methods: The affected eye of the patients had no clinical evidence of siderosis, had similar full-field photopic 3.0 ERG compared with the fellow eye, and had subnormal visual acuity. Group averages in each MfERG ring for implicit time and amplitude at P1 wave were compared between affected and fellow eye to look for latent siderosis.
Results: On mfERG, no statistical difference in group averaged amplitude was observed; however, a significant difference ($p < 0.05$) was found in group averaged latency between fellow and affected eye at most tested rings (<2 degree, 2–5 degree, and >15 degree rings). Average latency for overall retinal area mapped also showed significant difference ($p = 0.010$).
Conclusions: Increased mfERG latency may serve as an early predictor of retinal damage from siderosis when full-field ERG is normal.

Contexte : Évaluer l'utilisation de l'électrorétinogramme (ERG) multifocal pour diagnostiquer la toxicité rétinienne causée par une sidérose lorsque le résultat de l'ERG en champ total est normal.
Méthodes : Six patients ayant un corps étranger intraoculaire ont participé à l'étude. À l'examen clinique, l'œil affecté ne présentait pas de signe de sidérose, avait un électrorétinogramme en champ total photopique 3.0 tout comme l'œil sain et il présentait une acuité visuelle inférieure à la normale. Nous avons comparé la moyenne des groupes pour chaque anneau de l'ERG multifocal selon le temps implicite et l'amplitude de l'onde P1 de l'œil affecté et celui de l'œil sain pour détecter toute trace de sidérose latente.
Résultats : L'ERG multifocal n'a révélé aucune différence statistique quant à l'amplitude moyenne de groupe; il a toutefois démontré une différence significative ($p <0,05$) en ce qui concerne la latence moyenne du groupe entre l'œil sain et l'œil atteint à la plupart des anneaux testés ($<2°$, 2-5° et $>15°$ anneaux). La latence moyenne pour l'ensemble de la région rétinienne évaluée présentait aussi une différence significative ($p = 0,010$).
Conclusions : Une augmentation de la latence à l'ERG multifocal peut être un indice précurseur de dommage à la rétine causée par une sidérose lorsque le résultat de l'ERG en champ total est normal.

The present protocol for management of retained intraocular foreign body (RIOFB)–iron (RIOFB-I) is surgical removal in most cases.[1,2] Although the timing of surgery (pars plana vitrectomy) and RIOFB removal have not been correlated with visual outcome,[3,4] there are certain advantages to immediate RIOFB removal at the time of primary laceration repair. These include a potentially decreased risk of endophthalmitis and proliferative vitreoretinopathy and a single surgery under anesthesia. Advantages offered by a second-stage surgery for RIOFB removal include a well-healed globe laceration, minimal anterior segment reaction, corneal edema resolution, resorption of hyphema, higher probability of a posterior vitreous detachment, and resorption of vitreous hemorrhage. In addition, it allows for better preparation of necessary surgical equipment, with availability of competent operating room personnel for complex vitreoretinal surgery.

A multitude of factors affect a surgeon's timing for removal of RIOFB. These include presence of concurrent endophthalmitis, systemic stability of the patient, and the availability of well-trained operating room personnel as well as equipment at emergency hours required for repair of globe lacerations. In cases in which delay in IOFB removal is planned because of clinical contraindications such as systemic instability, presence of foreign body in locations that are difficult to reach, or presence of impacted foreign bodies, all of which have higher risk/benefit ratio, follow-up is needed with investigations of sufficient sensitivity so as to warn the ophthalmologist with the first signs of siderosis, assisting the

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ophthalmologist to make the best decision regarding the next clinical step.

Currently used approaches to ascertain existing damage in patients with RIOFB-I include either detecting siderotic changes clinically or eliciting abnormalities in electroretinogram (ERG).[5] The insult caused by ferrous ions on retinal ganglion cells can be appreciated in a staged manner using ERG. On ERG, initially hypernormal a- and b-waves are seen, which may be followed by a steady decline in their amplitudes, which occurs secondary to Müller cell responses to ionic changes in the outer retina.[6] Multifocal ERG is a more sensitive modality to determine electrophysiological changes at the macular region. However, there is no evidence to show its role in patients with RIOFB-I, according to current literature. To evaluate the possible role of multifocal ERG as a tool of choice for follow-up, this study was conducted in patients of RIOFB-I having normal full-field photopic ERG in the presence of unexplained low vision with no clinical evidence of siderosis.

Methods

Patients

Patients presenting to the Retina Services of our tertiary care centre from September 2012 to October 2013 after sustaining hammer and chisel injury with a confirmed diagnosis of RIOFB-I on imaging were recruited. Inclusion was based on unexplained low best corrected visual acuity with no evidence of clinical siderosis and absence of any abnormality on full-field photopic 3.0 ERG (Vision Monitor, Mon2012H, Metrovision, France); that is, those having similar ERG values between the injured and fellow eye were recruited. Clinical signs of siderosis such as abnormal pupillary reaction, diminished accommodation, corneal deposits, iris heterochromia, ocular hypertension/glaucoma, cataract, pigmentary retinopathy, or optic nerve atrophy were ruled out. Patients with media opacity precluding electrophysiological examination, including corneal opacity, traumatic cataract, vitreous hemorrhage, retinal detachment, endophthalmitis, those with bilateral RIOFB, and those with fellow eye pathologic conditions, were excluded from the study. Macular scan on optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec, Jena, Germany) was performed in all patients. Informed consent was obtained from all patients, and principles enshrined in the Declaration of Helsinki were followed.

For ERG evaluation, skin electrodes were used after cleaning the skin. Reference electrodes were placed at each orbital rim. During photopic recording on ERG, full-field (Ganzfeld bowl) stimulation using white background with even and steady luminance of 30 cd/m^2 was used and stimulus energy of 3 cd-s/m^2 at surface of Ganzfeld bowl was given.

MfERG studies

Multifocal ERG (Vision Monitor, Monpack 3, Metrovision, France) was recorded as per the guidelines of International Society for Clinical Electrophysiology of Vision.[7] Patients were light adapted for at least 15 minutes in room light, with fully dilated pupils. A liquid crystal display screen was used to produce 61 scaled hexagonal stimulus patterns (30-degree horizontal and 24-degree vertical field) with central fixation point. Luminance of bright and dark hexagons was kept at 100 cd/m^2 and <1 cd/m^2, respectively. Fixation was monitored using a camera system. The recording was done monocularly using contact lens electrodes after anaesthetizing the cornea with topical 1% proparacaine drops, with refractive correction prescribed for near vision. The fellow eye was tested first, followed by the affected eye, each with fresh disposable corneal electrodes. The stimulus frequency was set at 17 Hz and total duration of pseudo-random stimulation was 5 minutes.

Best corrected visual acuity was measured using Snellen's chart. Values were converted to the logarithm of the minimum angle of resolution score for statistical analysis. Group average for both amplitude and latency was calculated for both the fellow and the affected eye by calculating the average of all local responses from the hexagons in each particular ring for P1 wave. Mean was calculated by averaging the group averages for overall retinal area mapped for both the affected and the fellow eye. Statistical analysis was performed using SPSS 17 for Windows (SPSS Inc, Chicago, Ill.). Intergroup comparison was done using the Mann–Whitney test. $p \leq 0.05$ was considered statistically significant.

Table 1—Demographic details of the 6 patients included in the study

	Eye Involved	Age (years)	Gender	VA	logMAR	Other Signs	Foreign Body Location	Time Since Injury
1	Right	53	Male	6/9	0.18	Secondary glaucoma	Encapsulated retinal (inferonasal)	13 months
2	Left	28	Male	6/12	0.3	None	Retinal (temporal)	1 year
3	Left	20	Male	6/9	0.18	None	Corneal	10 months
4	Left	55	Male	6/24	0.60	None	Multiple retinal, corneal	4 months
5	Left	19	Male	6/36	0.5	None	Retinal	7 months
6	Left	31	Male	6/36	0.48	None	Retinal (temporal to macula)	2 months

logMAR = logarithm of the minimum angle of resolution; VA = vision of the affected eye in Snellen's equivalent

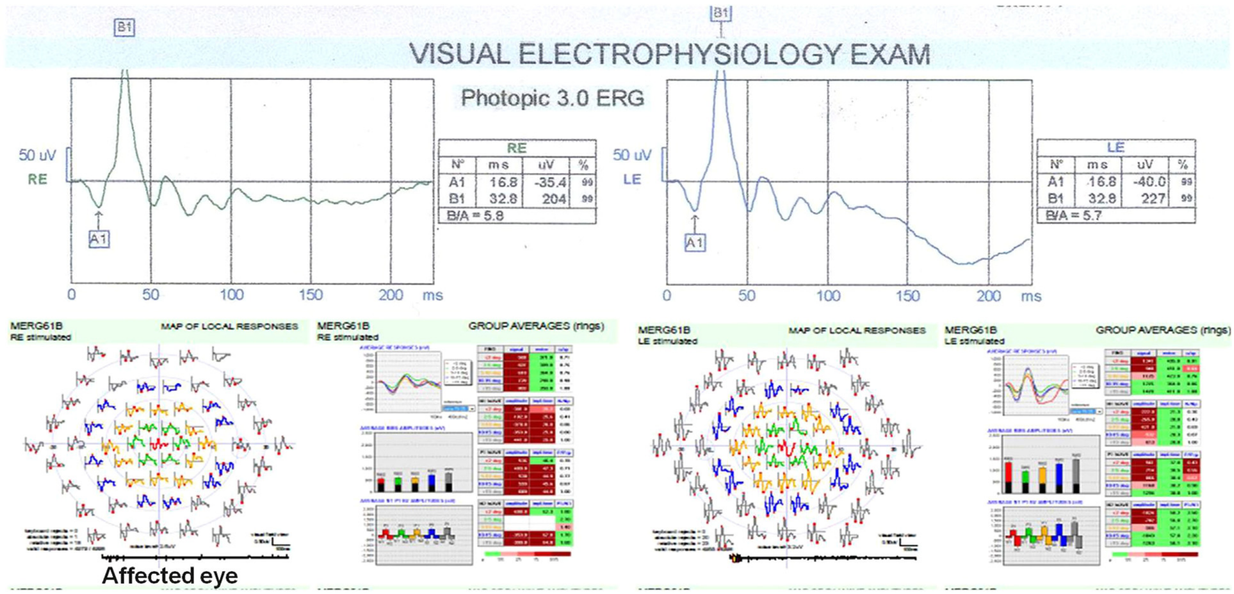

Fig. 1—Representative electroretinography (ERG) of one of the patients shows both the amplitude and the latency to fall in the 99th percentile of the population range and the ratio of B/A to be almost similar between the 2 eyes. Multifocal ERG of the same patient, however, shows the implicit time to fall in the 99.5 percentile range for the affected eye except for <2 degree ring, whereas it lies within the 95th percentile of the normative data range for the fellow eye in group averages. The coloured 3D field view for P1 wave shows a remarkable depressed foveal peak in the affected eye (OD), whereas a normal topographic contour can be appreciated in the left eye.

Results

Six patients were evaluated during the tested period. All were males and had a median age of 24 years (mean: 31.28 ± 15.8 years). The median visual acuity in the affected eye was 6/18 (r = 6/9–6/36, Snellen's equivalent) and that in the fellow eye was 6/6. Median duration after trauma was 8 months (r = 2–13 months). Optical coherence

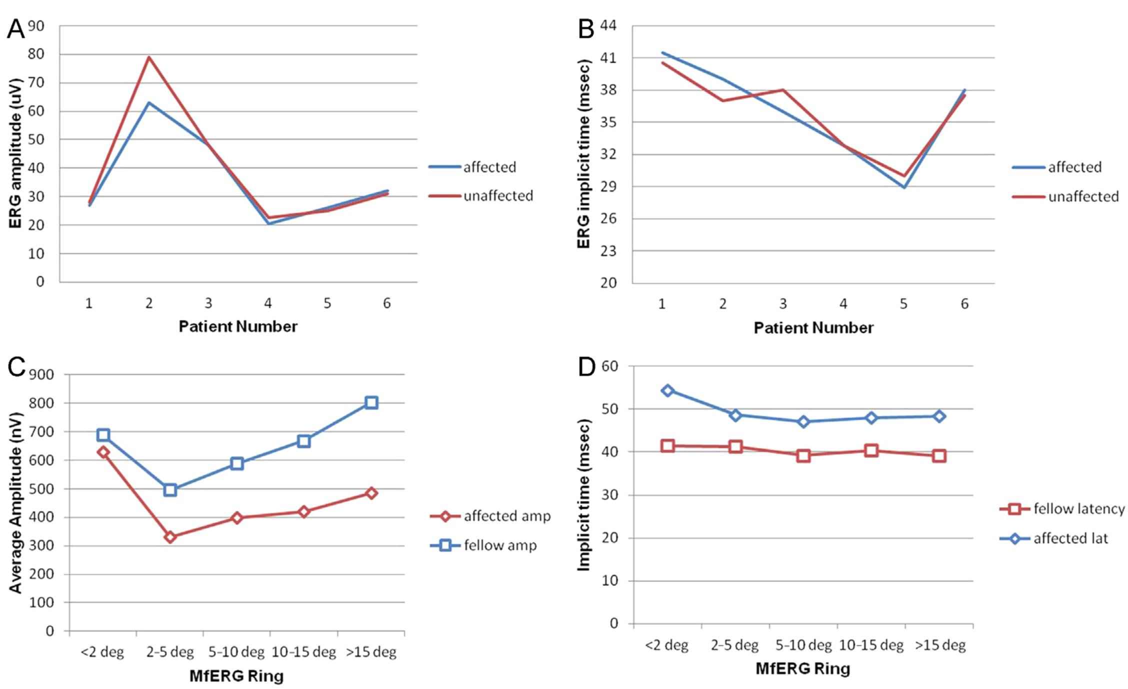

Fig. 2—(A and B) Graphs show a comparison of full-field photopic electroretinography (ERG) amplitude (A) for all 6 patients and implicit time (B) in the affected eye compared with the good eye. Note that full-field photopic ERG recording yielded no significant difference between the affected and the fellow eye in any of the patients with respect to both amplitude ($p = 0.9$) and the implicit time ($p = 0.8$). (C) Average multifocal ERG (mfERG) amplitude at each ring for all 6 patients as depicted in the graph. (D) Graph shows average mfERG implicit times for all the patients. The graphs show that the average values for amplitude are lower for the affected eyes, whereas implicit time shows higher mean values in the affected eyes.

tomography (macular scan) was normal in all patients. The location of the foreign body was retinal/vitreal in 5 cases and intracorneal with projection into the anterior chamber in 1 case (Table 1). Figure 1 depicts the representative ERG of a patient who had RIOFB in his right eye, showing both the amplitude and the latency to fall in the 99th percentile of the population range and the ratio of B/A to be similar between the 2 eyes. MfERG of the same patient, however, shows the implicit time to fall in the 99.5 percentile range for the affected eye except for a <2 degree ring, whereas it lies within 95th percentile of the normative data range for the fellow eye in group averages. The coloured 3D field view for P1 wave shows a remarkable depressed foveal peak in the affected eye (OD), whereas a normal topographic contour can be appreciated in the left eye.

ERG results

The group average for the amplitude of the affected eyes of full-field photopic ERG was 30.07 ± 16.21 uV, whereas that for the unaffected eyes was 38.95 ± 21.58 uV ($p = 0.9$; Mann–Whitney test). Similarly, the group average of the implicit time for full-field photopic ERG was 36.03 ± 4.56 milliseconds and that for the unaffected fellow eyes was 35.97 ± 3.84 milliseconds ($p = 0.8$; Mann–Whitney test). Hence, no significant difference was observed in the average of latency or the amplitude between the affected and the fellow eye on full-field photopic ERG (Fig. 2).

MfERG results

MfERG amplitude as well as implicit time recorded for P1 wave were analysed. The overall averaged amplitude for P1 wave at all tested rings of mfERG in the affected eyes was 442.47 ± 354.2 nV (median 366.6 nV; range, 60.4–1073.2). The overall averaged latency for all rings was 49.34 ± 8.6 milliseconds and median latency was 46.13 milliseconds (range, 40.9–62.1 milliseconds). Similarly, the mean amplitude in fellow unaffected eyes was 648.63 ± 291 nV and median was 508.5 nV (range, 416.2–1098.8 nV). The mean latency in the fellow eyes was 40.29 ± 1.9 milliseconds and median value was 39.83 milliseconds (range, 38.02–42.64 milliseconds). Table 2 shows mean amplitude and latency for all patients at each individual ring. Figure 3 shows average amplitude and implicit time at each ring location for all patients as individual points in a spread graph comparing the affected and the fellow eye.

There was no statistical difference in amplitude between the affected and the fellow eye at any of the tested rings or for the average of at all rings combined (Fig. 4, Table 2). There was a significant difference in latency between the fellow and the affected eye at <2 degree, 2–5 degree, and >15 degree rings (p = 0.004, 0.037, and 0.024, respectively; Mann–Whitney test). This difference reached borderline significance at the remaining 2 ring locations,

Table 2—Mean ± standard deviation (median) amplitudes and implicit time for P1 wave on mfERG for all patients at each of the tested rings at macula (viz. <2 degrees, 2–5 degrees, 5–10 degrees, 10–15 degrees, and >15 degrees)

Patient	Amplitude (nV) Mean ± Standard Deviation (median)				Latency (msec) Mean ± Standard Deviation (median)			
Average at Each Eccentricity (degree)	Affected Eye	Fellow Eye	*p*	Normal Lab Range	Affected Eye	Fellow Eye	*p*	Normal Lab Range
<2	629 ± 386.2 (536) (r = 360–1399)	687.7 ± 347.3 (729.5) (r = 235-1142)	1	700.3–1500.7	54.52 ± 8.27 (52.4) (r = 46.4–62.4)	41.5 ± 4.1 (42.4) (r = 36.2–45.3)	**0.004**	37.0–44.0
2–5	331.3 ± 263 (216) (r = 69.9–790)	496.677 ± 240.9 (424.5) (r = 251–844)	0.1	578.6–1436.8	48.7 ± 7.8 (47) (r = 39.7–58.3)	41.3 ± 3.5 (40.5) (r = 38.5–45.5)	**0.037**	37.0–43.0
5–10	397.56 ± 304.6 (368.5) (r = 69.4–901)	587.8 ± 308.5 (440.5) (r = 324–1074)	0.3	605.5–1256.8	47.17 ± 9.27 (45.1) (r = 34.3–59)	39.2 ± 0.75 (39.6) (r = 38.1–39.9)	0.053	37.2–41.0
10–15	419.3 ± 367.3 (327.5) (r = 36.6–1062)	668.2 ± 432.9 (579) (r = 241–1201)	0.2	597.2–1178.7	48.0 ± 10.8 (45.1) (r = 34.2–65.4)	40.3 ± 2.3 (39.9) (r = 37.8–43.1)	0.054	39.1–43.2
>15	485.1 ± 425.3 (401.5) (r = 65.7–1214)	802.8 ± 418.7 (792) (r = 353–1294)	0.1	534–967.3	48.4 ± 8.9 (44.8) (r = 39.6–61.5)	39.1 ± 1.0 (39.7) (r = 38–40.1)	**0.024**	39.1–44.5
Average of all locations	452.5 ± 341.9 (442.5) (r = 120.3–1073.2)	648.6 ± 291 (508.5) (r = 416.2–1098.8)	0.15		49.3 ± 8.6 (46.1) (r = 40.9–62.1)	40.3 ± 1.9 (39.8) (r = 38.0–42.6)	**0.010**	

There is a significant statistical difference or difference in the mean values is almost reaching statistical significance between the affected and the fellow eye for implicit time at all tested locations (Mann–Whitney test; $p < 0.05$ significant). p values which are significant are represented in bold.

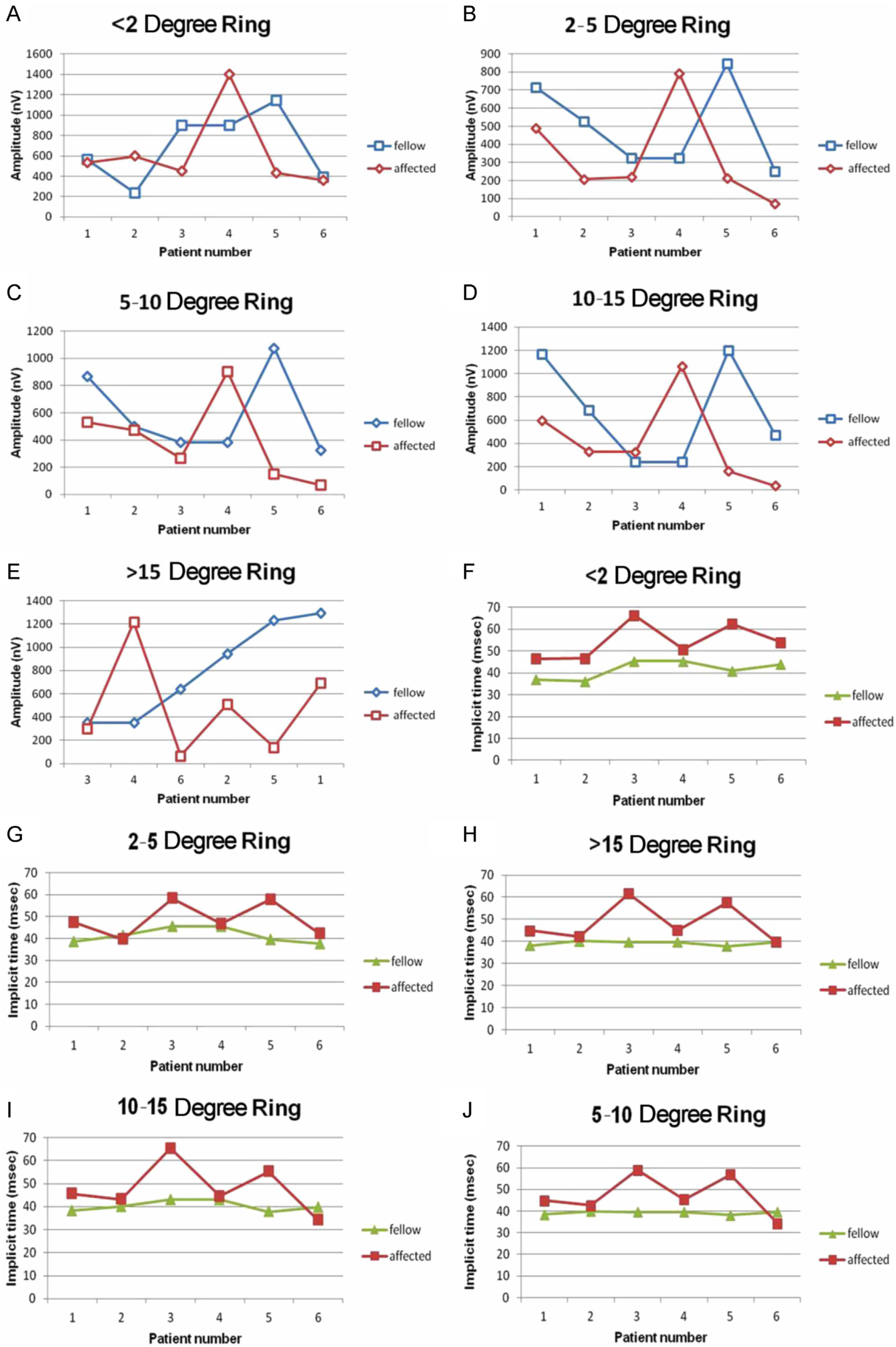

Fig. 3—(A–E) Graphs show individual patient data at each ring location for amplitude in nV. (F–J) Graphs show individual patient data for implicit time in milliseconds between the affected and the fellow eye. Note that patient number 4 had intracorneal foreign body jutting into the anterior chamber.

2–5 degrees and 5–10 degrees (p = 0.053 and 0.054, respectively) (Fig. 5, Table 2). There was also a significant difference in the average latency at all rings between the affected and the fellow eye (p = 0.010; Mann–Whitney test) (Table 2; Fig. 3).

Discussion

ERG is conventionally used to detect abnormalities in photoreceptor and neuronal function in the event of retinal dysfunction. Full-field ERG recording measures overall retinal function; hence, small areas of abnormality within the macula may remain undetected using this test alone.[8] Cones are the predominant photoreceptors in the macular region, which contains fewer rods. Because MfERG selectively tests macular function by measuring local ERG responses from the cone-driven retina under light adapted conditions, it aids in spatial localization of retinal dysfunction.[7]

Multifocal ERG was performed in this study, which included patients with RIOFB-I and normal retinal function on ERG, with no evidence of clinical siderosis that had delayed presentation and diminution of visual acuity. It is not rare in our setting to have late presentation. The reasons for late presentation in our country include poor awareness of the patient and the referring physician, failure to detect an RIOFB at primary health centres, referral to tertiary centres because of nonavailability of operational resources, and dearth of operating room personnel trained in complex vitreoretinal surgeries. The median time for surgery for the removal of RIOFB after patient presentation was 1–2 weeks, which in our institutional setup may incur because of a pre-existing operation room backlog.

Multifocal ERG analysis indicated a significant increase in implicit time among the affected eyes in the presence of normal comparative ERG. This disparity in the outcome of ERG and mfERG may be indicative of differential damage to cone system by the ferrous ions contained within the RIOFB. An increase in implicit time on mfERG may be indicative of subtle macular toxicity caused by subclinical siderosis. The greater susceptibility of cones compared with rods to the oxidative insult caused by ferrous ions has been established in mice models.[9] Evidence for the differential neuronal vulnerability to iron-induced oxidative damage was also found by Sohn et al. in rat culture neurons.[10] Further evidence of iron toxicity leading to foveal dysfunction comes from the potential role of iron in age-related macular degeneration.[11] Similarly, drusenoid changes along with macular atrophy have been observed in aceruloplasminemia-associated retinal iron overload.[12]

According to our results, delay in implicit time was a more sensitive parameter for the detection of photoreceptor damage compared with amplitude testing. The delay in implicit time may be related to iron-induced direct cone dysfunction. It may, however, additionally occur because of an impaired rod-cone interaction, as has been observed by Seeliger et al. in patients of retinitis pigmentosa.[13] They believed that delay in implicit time on mfERG could be attributed to rod degeneration, cone outer segment changes, and slowing of inner nuclear layer responses.

Conclusion

Implicit time testing may be diagnostically superior to amplitude testing in patients with RIOFB-I. Despite a small number of participants enrolled and a low strength analysis, the results of this study may provide additional academic data in early detection of eyes with latent siderosis and also can help in prognosticating the functional outcomes postoperatively. However, any metallic IOFBs should not be left in the eye regardless of time of presentation and the availability of ocular electrodiagnostics if vision is to be salvaged.

Disclosure: The authors have no proprietary or commercial interest in any materials discussed in this article.

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