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A long term follow up of ocular siderosis: Quantitative assessment of the electroretinogram

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Abstract. Siderosis oculi is a severe sequel of retained, iron made, intraocular foreign body. Iron atoms or ions, dissolved from the foreign body, may diffuse to the retina and produce irreversible cellular damage. Therefore, early extraction of an iron foreign body is recommended. When the risks of surgical intervention outweigh the danger of siderosis, the patient is periodically examined in order to detect the initial signs of siderosis. The most commonly used test for quantitative and objective assessment of retinal function is the electroretinogram (ERG). We report here a long term ERG follow-up (about 8 years) of a patient suffering from a unilateral iron intraocular foreign body. The development of siderosis was detected by any of the ERG responses; cone-dominated, rod-dominated or mixed cone-rod responses. However, the degree of the assessed damage varied and strongly depended upon the flash intensity used to elicit the ERG response and upon the ERG wave chosen to assess retinal function. The relationship between the ERG b- and a-waves showed a profound deterioration reflecting a reduction in signal transmission from the photoreceptors to the inner nuclear layer. These findings suggested that iron toxicity produced more damage to the inner retina than to the outer retina.

Introduction

Siderosis bulbi is a chronic degenerative process induced by chemical reactions between iron particles and ocular tissues. When experimental siderosis was induced in squirrel monkeys by introducing various forms of iron into the vitreous, it was concluded that ferric ions were considerably less damaging than either ferrous ions or nonionized iron [1]. However, in a subsequent study in rabbits [2], it was argued that the process of oxidation from either the nonionized (Fe^0) or the ferrous (Fe^{+2}) forms to the ferric (Fe^{+3}) one played the detrimental role in siderosis. Since ferric ions could not be further oxidized, they did not produce siderosis. Because of the deleterious effects of iron toxicity on retinal function, it is highly recommended to extract iron foreign bodies as soon as possible. However, when the risks of surgical intervention outweigh the chances of development of siderosis, periodic determination of retinal function must be introduced to detect the early signs of retinal malfunction. In such cases, the means for objective assessment of retinal function are important. The electroretinogram (ERG), which is the most commonly used objective indicator of retinal function [3, 4], becomes essential especially when the ocular media are opaque and the use of subjective visual tests is prevented.

The ERG changes in siderosis bulbi have been well documented qualitatively [5]. In the early stages of the process, the a-wave is of normal or even supernormal amplitude while the b-wave is reduced in size (Neg+ and Neg− phases). As siderosis progresses, the ERG is gradually reduced in amplitude (Neg I, II and III stages) and eventually becomes nonrecordable. Similar ERG changes have been demonstrated in experimental siderosis induced by implanting iron foreign bodies into eyes of rabbits [6]. The differential effect of iron toxicity on the ERG a- and b-waves, indicated that the degeneration process affected the inner retinal elements, where the b-wave was generated, before reaching the photoreceptor layer. This conclusion was supported by early receptor potential (ERP) measurements [7] and by histopathologic observations [8].

In the present study, we report a long-term (about 8 years) follow-up of a patient with an iron IOFB. Several ERG measurements were performed on different occasions, prior to and after surgical removal of the foreign body. The degree of retinal damage was assessed from several ERG parameters which were derived from responses elicited by light stimuli of different intensities delivered under light- and dark-adapted conditions.

Case report

A 49 years old male was admitted to the Department of Ophthalmology at the Rambam Medical Center, on January 1982 because of a perforating injury in his right eye. The injury occurred while hitting steel with an iron hammer. Visual acuity at admittance was 6/8.5 and 6/7.5 in the right and left eyes respectively with minimal correction. Intraocular pressures (IOPs) were normal in both eyes. Physical examination of the left eye revealed no abnormalities.

In the right eye, there was a temporal subconjunctival hemorrhage and a small perforating wound of the sclera at 10 o'clock position, 2 mm from the limbus. Anterior chamber depth was normal with a microscopic hyphaema.

The pupil was round and reactive and the crystalline lens appeared clear. A tract of blood was seen in the vitreous, leading from the entrance wound to a retinal hemorrhage located temporally to the macula. Orbital X-ray clearly revealed a small foreign body at the posterior pole of the right eye. A trial to remove the foreign body, using an external magnet failed. Therefore, the scleral wound was closed and a few days later the retina around the FB was treated with argon laser. Since the visual acuity was not compromised by the foreign body, it was decided to postpone surgical intervention and to follow the patient by periodic testing of retinal function using clinical examination and ERG recordings.

Over the next years, signs of ocular siderosis gradually developed. On March, 1986, the patient was again admitted to the Department of Ophthalmology, Rambam Medical Center for surgical extraction of the foreign body. Visual acuity in the right injured eye was 6/10. Anterior subcapsular radial bands of 'rust' could be seen in the lens. The intraocular foreign body was visible at 9 o'clock, partially surrounded by laser burns. Diffuse pigment mottling was seen all over the retina. The patient underwent Pars plana vitrectomy and removal of the foreign body. The foreign body had a spherical shape with diameter of about 0.8 mm and weight of 1.95 mg. Post-operative recovery was normal.

Material and methods

The procedure for ERG recordings has been previously described in detail [9, 10]. The ERG responses were differentially recorded between a corneal electrode (Medical Workshop, The Netherland) and a reference electrode attached to the forehead. An earclip was used as ground. Maximum mydriasis was achieved with 2–3 drops of 1% cyclopentolate HCl and 2.5% phenylephrine HCl. The ERG signal was amplified (Grass P5, USA) by a factor of 10 000 and filtered through a bandpath 0.1–1000 Hz. The amplified signals were digitized at a rate of 1 KHz and stored on a hard disk of a small computer (PC XT compatible). After the ERG recording session, the responses were plotted on a printer for off-line analysis. Light stimuli were delivered from an electronic camera flash attenuated by a set of 'neutral' density and wide-band color filters.

The ERG responses were first recorded under background illumination of 11 foot-lambert to examine the cone system. After 20–25 min of dark-adaptation, the ERG responses were measured with light stimuli of different intensity and color. The response elicited by dim blue light was used to evaluate the rod system. A bright red flash (scotopically matched to the dim blue one) was applied to isolate cone function. Then, a series of white light stimuli were applied to examine the entire dynamic range of the retina.

ERG analysis consisted of amplitude and latency measurements. The a-wave amplitude was measured from the baseline to the trough of the wave. B-wave amplitude was measured from the trough of the a-wave to the peak of the b-wave. B-wave latency was defined by the time interval from stimulus onset to the peak of the b-wave. Signal transmission from the photoreceptors layer to the inner retina was assessed from the relationship between the b- and a-waves amplitudes [9, 10].

Results

Representative ERG responses, measured at various times prior to and after surgical removal (March 1986) of the iron intraocular foreign body, are shown in Fig. 1. The spectral content (Blue or White) of the light stimuli and their intensity (density of the 'neutral' filter interposed in the light path) are denoted to the left of each row of responses. In each pair of traces, the upper one was recorded from the injured right eye and the lower one from the uninjured left eye. The ERG responses, shown in Fig. 1, were recorded with different amplification factors. Therefore, each trace starts with a vertical bar which marks the time of the light stimulus and has a height of 100 μV. Nine months after injury (first column), the ERG responses from the injured right eye were very similar to those obtained from the fellow eye and no signs of retinal malfunction could be detected. At longer time intervals, the ERG from the injured eye gradually decreased in amplitude and acquired an abnormal pattern: the b-wave decreased more than the a-wave. These characteristic ERG changes are similar to those previously described [5].

To evaluate retinal function in the injured eye, we utilized four different ERG parameters:

(1) The amplitude of the cone response which was elicited by a flash of -2.0 log relative intensity in the light-adapted state. (2) The amplitude of the rod response determined from the ERG evoked by a dim blue light stimulus (log relative intensity of -4.0) in the dark-adapted state. The amplitudes of the (3) a-wave and of the (4) b-wave, measured from the mixed cone-rod response elicited in the dark-adapted state by a bright white light stimulus of -1.0 log relative intensity.

In order to account for the random variability in the ERG amplitudes between different recording sessions, we normalized each ERG parameter measured from the injured eye by the corresponding value obtained from the uninjured eye. The resultant ratios are plotted in Fig. 2 as a function of time.

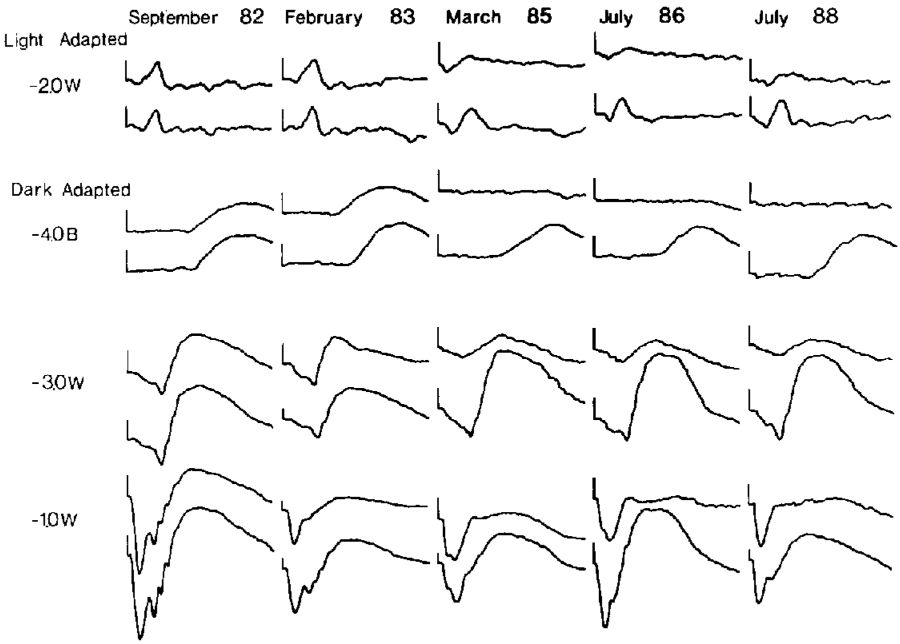

Fig. 1. Representative ERG responses recorded at different times prior to (first 3 columns) and after surgical removal (March 1986) of the foreign body (columns 4 and 5). The responses were recorded under background illumination (first row) or in the dark-adapted state. The intensity of the test stimulus, given in density of the 'neutral' filter interposed in the light path, and its colour content (White or Blue) are denoted to the left of each row of responses. In each pair of traces, the upper one was recorded from the injured right eye and the lower one from the uninjured left eye. The vertical bar at the beginning of each trace has a height of 100 μV and represents stimulus onset. The duration of the responses shown is 150 msec.

The vertical arrow indicates the time of surgical removal of the foreign body. Some data points are missing because in some cases technical difficulties did not allow accurate measurement of all the different ERG parameters. The estimated degree of retinal damage strongly depended upon the ERG responses used to evaluate retinal function. The most severe damage was indicated by the rod-dominated response (solid circles). The rate of deterioration of the rod response was very fast and within three years after injury it was reduced to a nonrecordable level. The least degree of retinal malfunction was inferred from the cone response (open squares). The amplitude of the light-adapted ERG b-wave stabilized within 2 years after injury at a level reflecting about 50% damage and remained relatively constant thereafter. The degree of retinal damage, estimated from the mixed cone-rod ERG depended upon the wave chosen to assess retinal function. The a-wave data (solid triangles) indicated about 50% reduction in retinal

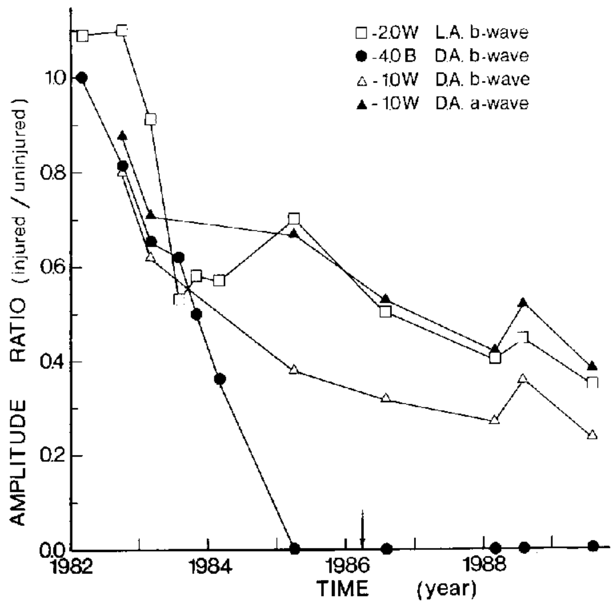

Fig. 2. The progress of retinal siderosis in the injured eye with time. Retinal function in the injured eye was evaluated relative to the uninjured eye from different ERG responses recorded under different adaptation conditions. Cone function was assessed from the response to white light of moderate intensity delivered under background illumination (□). Rod function was estimated from responses elicited by dim blue light stimuli applied in the dark-adapted state (●). Retinal damage was also assessed from the a-wave (▲) and b-wave (△) of the mixed cone-rod ERG response elicited by bright white stimulus in the dark-adapted state. The arrow indicates the time of surgery performed to remove the foreign body.

function in agreement with the assessment based upon the cone response. The b-wave amplitude (open triangles) suggested about 60–70% damage which was larger than the value estimated from the a-wave or from the cone-dominated response, but smaller than the damage calculated from the rod-dominated ERG. Despite a slight post-surgery improvement in 3 of the 4 ERG parameters, seen in one recording session, the main trend in the ERG after surgery was a slow decline.

The differential effects of siderosis on the ERG a- and b-waves can be better appreciated by plotting the relationship between the b-wave and the a-wave amplitudes for a series of ERG responses elicited by white light stimuli of different intensities. These data are shown in Fig. 3 for the injured (solid symbols) and uninjured (open symbols) eyes. Different ERG sessions are represented by different symbols. The two continuous lines mark the normal range (mean $\pm$ 2 s.d.) obtained from 20 volunteers with normal vision [9]. All the ERG data from the uninjured left eye fell within the

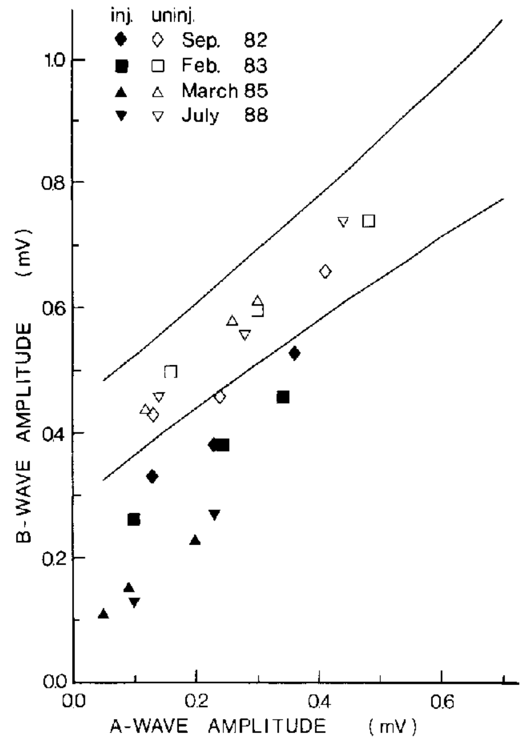

Fig. 3. B-wave to a-wave relationships of the ERG responses recorded from the injured (*filled* symbols) and uninjured (*open* symbols) eyes. Each data point represents a single ERG response recorded during a specific testing session. The data shown were recorded at different times. The two solid lines represent the normal range (mean $\pm$ 2 s.d.).

normal range indicating normal functioning of the retina. This observation support previous claim that the b- to a-wave ratio of an individual is relatively constant despite the large variability seen in the ERG amplitudes measured in different recording sessions [9]. The functional integrity of the retina in the injured right eye was close to the normal range soon after injury (solid diamonds) but slowly deteriorated with time as indicated by the reduction in the b-wave to a-wave ratio. Thus, as siderosis progressed the ERG amplitude declined and its pattern changed; the b-wave amplitude decreased to a greater extent than that of the a-wave.

A more quantitative index of the ERG b- to a-waves relationship is the b-wave ratio. This parameter was derived as follows [9]: For a given ERG response, the a-wave amplitude was used as the independent variable in order to derive the expected b-wave amplitude from the normal b- to a-waves relationship. The ratio between the measured and expected b-wave

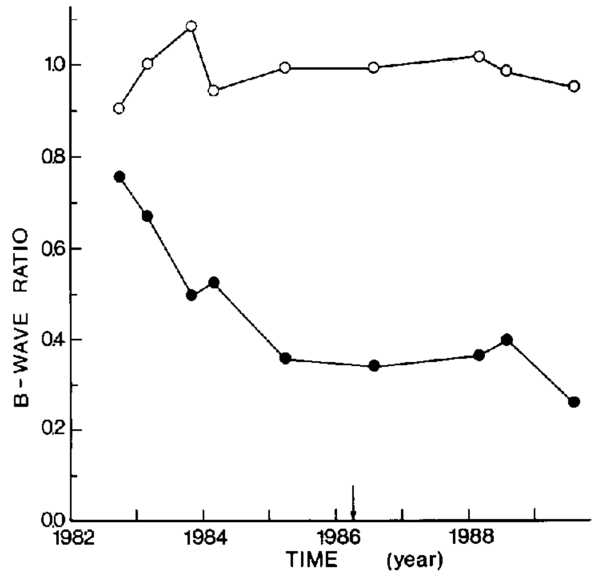

Fig. 4. The effect of retinal siderosis on the b-wave ratio of the ERG. This parameter was calculated as follows: For a given ERG response, the a-wave was used to calculate the expected b-wave amplitude from the normal b-wave to a-wave relationship. The ratio between the measured b-wave and the expected one was defined as the b-wave ratio. For each recording session 3–4 ratios were derived from the ERG responses containing measurable a- and b-waves. These were averaged to give a single parameter which defined the ERG pattern of the eye. Data are shown for the injured (●) and uninjured (○) eyes. The arrow denotes the time of surgical removal of the foreign body.

amplitudes was calculated for all the dark-adapted ERG responses composed of measurable a- and b-waves which were recorded during a single ERG session. These values were averaged to obtain a single parameter which described retinal function. For a normal retina, the mean b-wave ratio, is 1.00 ± 0.18 (2 s.d.). The b-wave ratio for the uninjured (open circles) and injured (solid circles) eyes of our patient are shown in Fig. 4 as a function of time. The vertical arrow signifies the time of surgical removal of the IOFB. The b-wave ratio of the uninjured eye was normal in all 9 ERG sessions conducted within a time range of about 7 years. In the injured eye, the b-wave ratio was slightly subnormal in the first ERG testing which was conducted 9 months after injury. Thereafter, the b-wave ratio decreased monotonically with time indicating a gradual deterioration in retinal function until a value of less than 0.4 was reached. At that time, the IOFB was surgically removed. The b-wave ratio remained relatively stable for the next 3 years but showed a clear decrease at the last ERG recording session (July 1989).

Discussion

The data presented here describe a long term follow-up of a patient with intraocular iron foreign body. The ERG responses clearly reflect the time course of the development of siderosis. Our findings agree with previous qualitative descriptions of the ERG changes inflicted by siderosis in humans [5, 7] and in rabbits [6].

The degree of retinal damage estimated from the ERG responses varied considerably depending upon the retinal system (cones or rods) which was preferably activated by the photostimulation conditions. The least degree of damage was seen in the cone-dominated response while the largest damage could be concluded from the rod-dominated one (Fig. 2). The differential effect of siderosis on the cone- and rod-ERG responses may be attributed to a greater susceptibility to iron toxicity of the rod system compared to the cone system. This conclusion supports previous reports on the greater susceptibility of the rod system compared to the cone system to retinopathic factors such as vitamin A deficiency [11, 12] and light-induced degeneration [13]. The latency of the cone-dominated ERG did not exhibit any significant changes during the development of siderosis. Thus, retinal degeneration induced by iron differs from the pathological processes occurring in retinitis pigmentosa, where latency lengthening of the light-adapted ERG is one of the major ERG characteristics [4, 11].

Iron toxicity exerted a differential effect upon the ERG a- and b-waves and therefore, different degrees of retinal damage could be concluded depending upon the ERG wave used to evaluate retinal function. The dependency of the a-wave amplitude upon the progression of siderosis was very similar to that exhibited by the cone-dominated response (Fig. 2). Retinal function, derived from the b-wave amplitude, decreased with time to an intermediate level between that assessed from the cone response and the value derived from the rod ERG. This observation supports the notion that the a-wave of the ERG mainly reflects the electrical activity in the cone system while the b-wave represents a mixture of equal contributions by the cone- and the rod-systems.

The differential effect of siderosis on the ERG a- and b-waves has been noted before and was used for a qualitative determination of the stage of siderosis [5, 7]. A more quantitative measure of this observation is offered by the b-wave ratio [9]. The advantages of this parameter for electroretinographic evaluation of retinal function can be appreciated from its stability in the uninjured eye over a period of about 7 years despite fluctuations in the amplitudes of the ERG waves. In the eye with the IOFB, the b-wave ratio decreased monotonically with time after injury. No specific point in time could be identified in which the b-wave ratio changed significantly to allow an objective decision of the need for surgical intervention.

Knave suggested to surgically remove an iron IOFB before the ERG amplitude dropped by 50% [5]. We have shown here that the effect of siderosis upon the ERG depends on the state of adaptation and on the parameters of the light stimuli (Fig. 2). Therefore, the time for surgical intervention will depend upon the ERG parameter chosen to monitor retinal function. In the case discussed here, surgical removal of the foreign body was probably applied after the siderosis had reached an irreversible stage since both the ERG amplitudes and b-wave ratio continued to decline after surgery. Experiments on animal models are needed to determine the relationship between the different ERG parameters and morphological changes in order to develop a more accurate index for assessing the rate of progression of siderosis. Such an index may provide the information needed to identify the point in time when the pathological process is approaching the irreversible stage and surgical intervention becomes obligatory.

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