The electroretinogram and electro-oculogram: Clinical applications

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Routine examinations with an electroretinogram (ERG) were performed on a large number of patients. The results are discussed in those areas where the ERG aided in diagnosis, contributed to the understanding of a disease, or assisted in following the course of a disease. The electro-oculogram (EOG) as an adjunct to the ERG is also discussed. Mention is made of the few diseases which may be detected only by the EOG. The use of both the ERG and EOG may provide more insight into the nature and extent of a disease process and at times may aid in providing a specific diagnosis.

Key words: electroretinogram, electro-oculogram, a-wave and b-wave amplitude, retinopathy, color blindness, night blindness.

Most workers in clinical electroretinography use a statistical approach in the evaluation of patients. A standard routine is followed and the results are compared with those obtained under similar conditions from a group of normal subjects.

The electroretinogram

Many diseases cause considerable alteration of some portion or all of the electroretinogram (ERG); therefore, only a few responses under selected conditions are necessary to detect such obvious qualitative abnormalities. On the other hand, a few diseases cause more subtle abnormalities detected only by quantitative comparisons of series of values obtained under the same conditions. Such differences may readily be dismissed as "normal variability," if only one or two responses are obtained. Therefore, in routine testing sufficient responses should be obtained so that quantitative comparisons with normal data can be made.

The value of comparisons of a large number of responses under the same conditions is illustrated for albinism (Figs. 1 to 7). The test was done so that quantitative evaluation of the following parameters was possible: (1) the growth of the b-wave amplitude or the b-wave peak (implicit) time during dark adaptation (Figs. 1 and 2), (2) variation of the a-wave or b-wave amplitude with light intensity (Figs. 3 and 4), (3) relationship of the a- or b-wave peak time to light intensity (Figs. 5 and 6), and (4) the relationship of the b-wave amplitude to flicker frequency (Fig. 7). Note the many differences which exist, some of them subtle, between the albinos and the control
Fig. 1. Growth of b-wave amplitude obtained with one intensity with time in the dark. Means of all b-wave amplitudes from a control group of 8 normal subjects, from 5 universal albinos, from 3 ocular albinos, and from 6 carriers of ocular albinism are shown. The normal mean plus or minus twice its standard error is also shown. The means of the 2 albino groups are similar or slightly larger than the control group mean during the first 10 minutes, but significantly larger after 10 minutes. (From Krill, A. E., and Lee, G. B.: Arch. Ophthal. 69: 32, 1963.)

Fig. 2. B-wave implicit time plotted in relation to time in the dark. Same groups are in Fig. 1. Note the consistently shorter implicit time in the universal albino. (From Krill, A. E., and Lee, G. B.: Arch. Ophthal. 69: 32, 1963.)
is necessary, which in turn may affect the ERG. In our experience anesthesia may cause up to a 50 per cent reduction in the scotopic b-wave amplitude. However, the photopic responses, the scotopic a-wave, and the peak times of all responses are either only minimally affected or not altered at all. Most diseases which are important as causes of blindness in infants cause marked alteration of some or all of these usually unaffected components, as will be noted later. Some workers claim far less effect of anesthesia on the scotopic ERG, but unfortunately this has not been our experience.

Usually the infant or child to be tested is brought in at 8:00 A.M. without any food since the previous midnight and without water after 4:00 A.M. The child has been previously evaluated by a pediatrician, and a hemoglobin of normal value has been recently obtained. Light anesthesia without intubation is used, and the infant usually goes home by 2 hours after waking up. We are at present evaluating the effects of other anesthetics, such as rectal barbiturates, on the scotopic b-wave.

In general, with most techniques of evaluation used at present, the ERG is a mass response dependent on the intactness of most of the outer retina, namely the receptors and the bipolar cell layer. Rather than tabulate findings in all of the many diseases that have been studied, only those areas will be discussed where the ERG has aided in diagnosis, contributed to the understanding of a disease, or assisted in following the course of a disease.

Infants and young children with unexplained visual loss. Included in this category are infants and young children with poor vision who do not have sufficient ocular findings to explain their visual status. No or only minimal eye ground changes of questionable significance are noted. Subjective testing may be impossible or the results may be unreliable, so that objective testing is often the only method of obtaining any sort of retinal evaluation. Such children have often been seen by many
ophthalmologists, since the parents may want a definite explanation of their child's poor vision. Some in this group, thought to have cerebral blindness because of the absence of retinal changes, have even had an extensive neurologic work-up (including pneumoencephalogram at times). One of the most difficult concepts to get across to the neurologist or pediatrician (sometimes even to the ophthalmologist) is that one may have severe retinal disease without ophthalmoscopic changes.

Often a definite diagnosis can be made after an ERG. It may then be possible to provide insight into the probable future course of the disease process, the type of schooling which will probably be needed, and the genetics of the condition. Obviously an exact diagnosis is of epidemiologic significance.

Four conditions which may cause a significant degree of blindness in the infant on a retinal basis without producing obvious eyeground changes are (1) congenital retinal dystrophy (amaurosis congenita of Leber), (2) total color blindness, (3) congenital stationary night blindness, and (4) albinism (the ocular and incomplete universal types).

Congenital retinal dystrophy, first described as retinitis pigmentosa with congenital amaurosis by Leber in 1869, was described by later workers under several headings including (1) hereditary retinal aplasia, (2) dysgenesis neuroepithelialis, and (3) heredoretinopathy congenitalis.
monohybridia recessiva autosomalis. Fundus changes may be absent or minimal. Eyeground changes, when present, most commonly consist of diffuse pigmentary stippling and/or pale optic nerves. Associated ocular findings may include nystagmus, esotropia, cataracts, and high myopia. The ERG is diagnostic. The record is extinguished or only minimal responses are obtained under any condition.

In general this is a progressive disease with ultimate severe deterioration of acuity, fields, and night vision. The eyegrounds between the ages of 8 to 14 may resemble those seen in retinitis pigmentosa. The inheritance is autosomal recessive.

In the complete form of total color blindness, photophobia, nystagmus, and visual acuity of about 20/200 are usual findings. This is a stationary condition in which fields and night vision remains un-
affected. The inheritance is autosomal recessive. Histologic studies have shown both a marked deficiency of cones and the presence of abnormal ones in the macula.

The two most frequent abnormalities reported on the ERG are a minimal or absent single-flash photopic response (Fig. 8) and a very low flicker fusion frequency (Fig. 9). The fusion frequency becomes lower as the stimulus intensity increases; with very bright flickering lights, sometimes no responses are noted. These abnormalities in the presence of a normal or only mildly abnormal scotopic record are diagnostic for total color blindness. A less frequently reported, but also diagnostic finding in this condition, is the loss or marked decrease of the entire first portion of the response to orange-red light seen in the fully dark-adapted eye (Fig. 10).

Fig. 7. The b-wave amplitude from a universal albino are compared with normal data. Note the supernormal b-waves of the albino at the slower flicker frequencies (up to 10 cycles per second).

Fig. 8. Shown are single-flash photopic responses from a normal subject, Patient 1 with a cone degeneration and Patient 2 with total congenital color blindness. Note that photopic responses are absent in Patient 2 and minimal in Patient 1. (From Krill, A. E.: Trans. Amer. Acad. Ophthal. Otolaryng. 70: 1063, 1966.)
Fig. 9. A comparison of flicker b-wave amplitudes from a patient with total congenital color blindness and a normal control group of 25 subjects (mean plus or minus two standard deviations). The patient has a fusion frequency of 4 cycles per second and the normal control group about 70 cycles per second. (From Krill, A. E.: Trans. Amer. Acad. Ophthal. Otolaryng. 70: 1063, 1966.)

Fig. 10. Scotopic orange-red response from a normal subject, patient with total congenital color blindness and a patient with a cone degeneration. Note that the first portion of the response is absent from the patient with the cone degeneration and only minimal from the subject with total color blindness. (From Krill, A. E.: Trans. Amer. Acad. Ophthal. Otolaryng. 70: 1063, 1966.)
The findings in the incomplete form of total color blindness are the same as in the complete form, but lesser in degree. Photophobia and nystagmus may be absent and visual acuity less impaired. Sloan and Newhall even reported one patient with acuity of 20/40. The chromatic defect is usually incomplete for certain colors and may vary with the size of the field and the level of luminance. The ERG shows the same changes as in the complete form, but frequently to a lesser extent.

A unique group of patients are those in whom blue cones are minimally or not involved. If these cones are only a small portion of all retinal cones, the ERG in such patients should be similar to that recorded from patients with complete achromatopsia and indeed this is true. The carrier female of this condition may show minimal abnormalities with the ERG, such as a lower than normal flicker fusion frequency.

Congenital stationary night blindness may be inherited as an autosomal dominant, autosomal recessive, or X-linked recessive disorder. All males with the X-linked type have abnormal acuity, varying from 20/40 to 20/200, and myopia, usually of at least 4 diopters. Nystagmus may be noted with more severe reduction of acuity. Some patients with the autosomal recessive type have abnormal acuity. Of our 4 patients with this type of congenital night blindness and abnormal acuity, 2 were myopes. All patients with congenital night blindness have normal daylight fields.

The unique finding on the ERG from all forms of congenital night blindness is the almost identical peak times of dark- and light-adapted responses (Fig. 11). Normally the peak time of the dark-adapted b-wave is at least twice as long as that of the light-adapted b-wave. Other less specific abnormalities may be noted. A marked reduction of the scotopic b-wave is characteristic (Fig. 11). In some patients the scotopic a-wave may also be subnormal. Other patients show both subnormal light- and dark-adapted responses.

There is no problem in recognizing the universal albino. However, incomplete universal albinism may be difficult to recognize, particularly in dark Caucasians or in Negroes. However, these patients have lighter skin and hair than unaffected members of their families. This type of albinism is usually inherited as an autosomal dominant, but occasionally as an autosomal recessive trait.

Ocular albinism affects only the eyes and may be difficult to recognize. Both the iris and retina or only the retina may be deficient in melanin. This form of albinism is inherited as a sex-linked recessive trait and therefore affects males only. The female carrier may show typical defects.

The typical eyeground and iris changes in albinism are well known, but at times the eyegrounds of the incomplete universal or ocular albino are difficult to distinguish from those of a light-colored person. This becomes particularly difficult in the infant, since the eyegrounds are almost “albinotic” during the first 6 months of life, particularly in the blonde infant.

The scotopic ERG is supernormal in all forms of albinism, particularly during the first two decades of life. For some reason, normal or smaller than normal responses are seen in the older albino. This may reflect retinal damage secondary to chronic excessive exposure to light.

Interpretation of specific eyeground changes in the infant or young child.

Pigmentary retinopathy. A pigmentary retinopathy in an infant or young child may have a number of different causes. Rubella, and possibly other viruses, and irradiation may all cause changes during the first trimester of pregnancy and result in a prominent diffuse pigmentary retinopathy in the neonate. This type of retinopathy is of no visual consequence and the ERG is normal.

As indicated previously, the eyegrounds of amaurosis congenita of Leber may show diffuse pigmentary stippling, and here the ERG is severely abnormal.
Syphilis is another possible cause of a diffuse pigmentary retinopathy in the infant. The ERG is usually normal but may be subnormal. There is no reason to expect a different pattern in any other diffuse inflammatory process, such as with the diffuse chorioretinitis which may be caused by inclusion virus disease.

Pigmentary retinopathies may begin later in childhood. A postinfectious retinopathy or an early retinal degeneration are the two considerations. Usually a virus has been cited as an infectious cause and, of the viruses, morbilli is by far the most common. Other viruses cited include variola, vaccinia, epidemic parotitis, encephalitis, and Bechet's disease (of questionable virus etiology). Rubella contracted in childhood may produce a retinitis similar to that found in cases of congenital rubella. Rarely, typhoid fever, diphtheria, scarlatina, and typhus produce a pigmentary retinopathy.

With an infectious retinopathy, the child is normal at birth and there is usually an abrupt loss of vision in the course of convalescence from some childhood disease. The fundus picture at this stage may resemble that of a central retinal arterial occlusion or spasm. Although this fundus appearance is only transient, there is usually permanent impairment of retinal function. Acuity, visual fields, and dark adaptation are usually abnormal and an ERG may show extinguished or minimal response. Eventually these children develop a pigmentary retinopathy.

Night blindness is the usual first complaint in early retinal degenerations. Gradual progression is characteristic. The ERG is markedly abnormal in most early retinal degenerations and may even be absent. However, in some children with either early autosomal dominant retinitis pigmentosa or early choroideremia, fairly large subnormal responses may be noted. Family studies in such patients are usually quite informative.

**Optic atrophy and other changes.** Congenital or early onset blindness with optic atrophy as the only finding may have many causes, but in our experience amaurosis congenita of Leber is the most common. Of the other causes only syphilis may show some moderate alteration of the ERG. With any of the other causes the ERG is normal. These include ganglion cell infiltration disease, such as infantile amaurotic idiocy and Niemann-Pick's disease, discrete hereditary optic atrophy without central nervous system involvement (either of autosomal recessive or dominant inheritance), or optic atrophy with central nervous system involvement (for example Behr's optic atrophy) or secondary to central nervous system involvement.

Attenuated retinal arterioles may be the sole finding in an infant with either congenital syphilis or amaurosis congenita of Leber.

**Early or atypical retinal degenerations at any age.** An early or sometimes even long-standing retinitis pigmentosa may show no or questionable ophthalmoscopic changes. A 13-year-old girl complained of poor vision and night blindness but had normal eyegrounds. Several members of her family were known to have retinitis pigmentosa, and an autosomal dominant type of inheritance was obvious. A definitive diagnosis was made in this child after the finding of an extinguished ERG. A 32-year-old man with a long history of progressive night blindness had questionable ophthalmoscopic changes. Only one of 3 ophthalmologists who examined the patient thought that the eyegrounds were abnormal. A diagnosis of retinitis pigmentosa was made after the finding of an extinguished ERG.

One of the 5 characteristic findings in the Laurence-Moon-Biedl-Bardet syndrome is supposedly retinitis pigmentosa. However, only about 15 per cent of patients with this diagnosis have the typical ophthalmoscopic appearance of retinitis pigmentosa. Almost all of the patients, however, do develop night blindness, which indicates the presence of a diffuse disturbance of retinal function in this disease.
Fig. 11. Electroretinogram showing normal photopic and scotopic responses and responses elicited under same conditions from two patients with congenital nightblindness. In the normal subject the peak (implicit) time of the scotopic a- and b-waves is considerably slower than that of the photopic a and b-waves. Note how these times are almost identical in the two subjects with congenital nightblindness. In both patients there is a marked reduction of the scotopic b-wave amplitude. However, in one patient there is reduction of the scotopic a-wave amplitude as well (bottom row).

16 patients we have studied 15 had extinguished or almost extinguished records. Eight of these patients had either no eyeground changes or minimal peripheral changes. Obviously the demonstration of a diffuse disturbance of retinal function is a more meaningful criterion in this disease than the presence of retinitis pigmentosa.

An old inactive chorioretinitis may resemble a retinal degeneration, but the finding of a markedly abnormal or extinguished ERG points to the latter diagnosis. As indicated previously, a fairly large ERG may be obtained in early retinitis pigmentosa of autosomal dominant inheritance or in choroideremia. The demonstration of a changing ERG on follow-up studies is of course characteristic of a retinal degeneration.

Unexplained abnormal acuity, visual symptoms, or eyeground changes in adults. Toxic amblyopia. Patients with toxic amblyopia, particularly on a nutritional basis, may be difficult to diagnose. Alcoholics may deny a history of drinking and not eating. Initially no eyeground changes may be seen although visual acuity and fields may be abnormal. Or bilateral optic disc pallor may be seen, causing concern about the possibility of a central nervous system lesion and suggesting the need for thorough neurologic evaluation. The ERG is always abnormal in nutritional amblyopia in our experience. In optic nerve disease secondary to central nervous system disease the ERG is normal.

The b-wave amplitudes and visual fields of a 41-year-old man are shown in Figs. 12 and 13, at the time of initial evaluation and after treatment with large doses of vitamins. He had no eyeground changes.

Genest27 studied nutritionally deficient natives in Thailand and Indonesia and showed a clear-cut relationship between vitamin A blood levels and a- and b-wave amplitudes of the ERG.
It appears that drugs which may be toxic to the optic nerve (for example quinine and methyl alcohol) are toxic to the outer retina as well. In spite of the absence of ophthalmoscopic alterations, changes in the ERG will be noted, perhaps even before changes in the optic disc are evident. The ERG may be helpful in following such patients. Of course, if it is uncertain whether optic atrophy is on a toxic or central nervous system basis, it is to be emphasized again that optic nerve atrophy secondary to central nervous system disease does not affect the ERG.

Primary toxic retinopathy. Certain drugs selectively have retinal toxic effects. Optic nerve changes may occur relatively late. In this category are NP-207, thioridazine, LSD-25, and chloroquine. There is considerable world literature on chloroquine, but suffice it to say that changes may be detected with the ERG at times before ophthalmoscopic or even other visual changes are detected. For this
Superior Retinal Arterial Occlusion

Central Retinal Arterial Occlusion

Fig. 14. Electroretinograms from a patient with a left superior retinal arterial occlusion and from another with a left central retinal arterial occlusion. In each patient there is a smaller b-wave from the affected left eye. A much greater decrease is noted in the patient with the central retinal artery occlusion.

reason this test should be used in screening such patients.

Vascular insufficiency. The b-wave of the ERG is sensitive to changes in retinal circulation. These changes may provide evidence of a suspected previous central retinal artery spasm or transient occlusion. A marked loss of the b-wave with a normal a-wave is characteristic (Fig. 14). In contrast to congenital night blindness, which may have the same findings, the peak time of the scotopic b-wave in vascular disease is normal or slower than normal.

Changes in the b-wave on the side of diminished blood flow may aid in the diagnosis of carotid artery disease. In some patients a consistently smaller b-wave, regardless of the test conditions, may be noted on the side of reduced blood flow (Fig. 15). In others a significantly smaller b-wave can be demonstrated only under special conditions such as (1) during the early period of dark adaptation, (2) with the use of dim illumination (Fig. 16), or (3) with flicker studies. The flicker data from a patient with a right carotid insufficiency 2 days before and 8 days after surgery are shown in Fig. 17.

Wulfing uses the ERG in conjunction with ophthaldynamometry and feels that this is a more sensitive technique than either method alone for detecting carotid insufficiency.

Cone degenerations. The onset of this condition is usually in the first 3 decades. There are only 2 families with more than one affected member. In both the inheritance is probably autosomal dominant.

The characteristic findings are reduced
visual acuity, severely defective color vision, and an ERG which shows changes similar to those described for total color blindness (Figs. 8, 9, and 10). In contrast to other types of macular degenerations, severe color blindness is an early complaint. No characteristic macular changes are seen and, in fact, initially the changes in the macula may be quite subtle. Temporal pallor, a frequent finding in this disease, may be the prominent feature early in this condition. Thus, in early disease particularly, the clinician may see nothing to explain visual loss or he may see only temporal pallor and suspect that he is dealing with a central nervous system problem. However, typical alterations of the ERG enable a precise diagnosis.

Evaluation of retinal status after intraocular iron foreign body. Characteristic changes in the ERG may enable prediction of the retinal status after an intraocular iron foreign body. This may be impossible because of a cataract. Early there is an abnormally large (supernormal) ERG. With more advanced retinal involvement the b-wave becomes subnormal and eventually the ERG is extinguished.

A parameter to follow in certain diseases. As indicated, the ERG may be markedly affected in nutritional amblyopia or in certain vascular insufficiencies such as carotid artery disease. In such conditions the ERG can be considered as an additional method of evaluating the effectiveness of therapy.

Marked alteration of the ERG may occur with an acute diffuse choroiditis (Fig. 18). With subsequent recovery from the disease the ERG returns to normal or close to normal values.

In both hyperthyroidism and aldosteronism the ERG is supernormal. This has been shown in both human subjects and animals.

A loss of the wavelets on the ascending limb of the scotopic b-wave may be an initial finding in diabetic retinopathy even before ophthalmoscopic changes are evident. The prognostic value of this finding is uncertain.

Areas of possible future value. Small-area electroretinography is now possible because of the computer. Theoretically the focal ERG could be used as an objective method of evaluating macular function or
Fig. 17A. Preoperative flicker responses from patient with partial right carotid obstruction. All b-waves from the right eye are smaller in amplitude before surgery.

Fig. 17B. Postoperative flicker responses from same patient shown in Fig. 17A. After a right carotid endarterectomy the b-waves are either equal from the two eyes or small randomized differences at a few frequencies are seen.
a more objective method of perimetry. One of the basic problems, though, at present is the large number of responses necessary to summate to obtain consistent differences between retinal areas. A few groups, however, have now had limited success in some patients in showing alterations of the focal ERG in macular disease. One group uses a ratio of macular and optic disc responses as a parameter, eliminating the necessity of "pure" focal responses at either area and thereby decreasing the total number of responses needed at either area. This latter technique may be more suitable for patients but more data must be seen before its ultimate value can be assessed.

There is need for more stress tests designed specifically for individual diseases. The combination of ophthalldynamometry and electroretinography for possible carotid artery disease is one such test. Perhaps the performance of a Master's two-step test before an ERG in patients with suspected carotid artery disease would also be of value.

The eventual knowledge of the significance of all the subcomponents of the ERG and of newly discovered components, such as the early receptor potential, hopefully may broaden the clinical value of the ERG.

**The electro-oculogram (EOG)**

In general the EOG is an adjunct to the ERG. The latter test is definitely more useful if one is limited to one objective type of measurement. However, there are a few diseases where only the EOG is abnormal or where it may show changes earlier than the ERG. Such diseases will be discussed in this section. The use of both tests may provide more insight into the nature and extent of a disease process and at times aid in providing a specific diagnosis.

**Amaurosis congenita of Leber.** All infants with this diagnosis have severely abnormal electroretinograms. However, according to Henkes and Verduin, some infants have a markedly abnormal EOG, whereas others have a markedly abnormal EOG, whereas others have a normal or close to normal EOG. They speculated that the first group has progressive disease (the more common type) and the latter group has stationary disease.

No group has enough long-term data to confirm or reject these speculations.

**Chloroquine retinopathy.** Either the
Electroretinogram and electro-oculogram

Fig. 19. A plot of EOG ratios from 18 patients (25 eyes) with vitelliruptive macular degenerations and two carriers (4 eyes) of this condition. The normal group (the mean plus or minus two standard deviations is shown) is not broken up according to age. The affected individuals and carriers are divided according to age. It can be seen that the ratios are abnormal in all subjects and bear no relationship to age, and therefore duration of the disease.

EOG or ERG or both may be abnormal in early chloroquine retinopathy. Therefore it is necessary to screen patients on this drug with both tests.

Siderosis retinae. According to one group, the EOG may be abnormal before the ERG in this condition.

Diabetic retinopathy. Henkes found the EOG to be abnormal in some patients with early diabetic retinopathy even at times before eye ground changes were seen. The long-term significance of these data is unknown.

Flecked retina syndrome. Familial drusen, fundus flavimaculatus, and fundus albipunctatus are probably all a consequence of pigment epithelium disease. There are certain functional features which these three conditions have in common which include minimal abnormalities by subjective dark-adaptation or by the ERG, but frequent moderate to severe abnormalities by the EOG. The designation "flecked retina syndrome" originated to describe the features which the 3 diseases have in common.

Vitelliruptive (vitelline) macular degeneration. Vitelliruptive macular degeneration deserves special mention because in this condition the ERG is usually normal but the EOG is always abnormal, usually to a marked extent, regardless of the age of the patient or the apparent severity of the disease (Fig. 19). In fact, the EOG is abnormal even in carriers of this condition, who show no ophthalmoscopic changes or visual acuity abnormality (see Fig. 19). Therefore, this test serves as a genetic marker to trace this autosomal dominant disease in families where a "skipped generation" is part of the picture.

REFERENCES:
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