Electrophysiological assessment of aphakic cystoid macular oedema

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SUMMARY Focal electroretinograms (FERG), pattern electroretinograms (PERG), and visual evoked potentials (VEP) were studied in a group of 30 aphakic patients with cystoid macular oedema (ACME). When compared with a control group of age-matched aphakics, 35% of patients were found to have abnormal FERG responses and 53%—over half of whom had normal FERG responses—showed abnormal PERG amplitudes. Although most of the patients had associated optic disc leakage, VEP latencies were normal in 26 out of 30. These results may explain the more severe visual loss seen in some ACME patients where the ophthalmologically visible retinal changes do not seem sufficient to explain such reduction in vision.

Aphakic cystoid macular oedema (ACME), originally described by Irvine¹ and Gass and Norton,² remains a poorly understood condition which affects from 5% to 50% of the aphakic population depending on the time at which the patient is tested.³ Some patients improve spontaneously, whereas others develop irreversible visual loss in spite of attempted therapy.⁴ Alterations in capillary permeability in the posterior segment result in leakage of fluid from the perifoveal capillaries and from the optic nerve head.² However, the visual loss is often not explained by the observed macular oedema, and visual acuity may vary considerably in patients with resolved macular oedema. Since most patients with ACME have a variable degree of optic disc leakage on fluorescein angiography, and often no other evidence of papillopathy (normal clinical appearance of the discs, normal fields, and pupillary responses), we attempted to determine whether subtle underlying ganglion cell or optic nerve head dysfunction might be contributing to the unexplained visual loss.

We utilised electrophysiological measures to differentiate the site and nature of the visual dysfunction in ACME patients. The localised nature of this disease necessitated the use of tests of foveo-macular function: photoreceptor and bipolar dysfunction

(outer retinal layers) were assessed by means of a focal electroretinogram (FERG); inner layer neuronal (ganglion cell) disturbances were measured by a pattern electroretinogram (PERG). The visual evoked potential (VEP) was used as an indicator of the integrity of the entire visual pathway with emphasis on macular function.

Subjects and methods

Case selection and methodology. Thirty aphakic patients with postoperative development of decreased visual acuity due to ACME were studied. Disc leakage was graded as mild, moderate, or massive, the grade being based on fluorescein angiography (FA). ACME was graded from 0 to 4, the grade also being based on FA: 0=observable oedema with no macular leakage; 1=less than perifoveal oedema; 2=minimal perifoveal oedema; 3=perifoveal oedema of approximately 1 disc diameter; 4=severe perifoveal oedema.⁴ An age matched group of aphakic patients with good visual results and no disc or macular oedema were selected as controls.

All subjects were refracted to their best corrected visual acuity (VA), and appropriate lenses were used during electrophysiological testing. Goldmann visual fields and pupillary responses were tested. Dilated fundus examinations including slit-lamp biomicroscopy with the Goldmann contact lens and disc were performed on all patients. Those patients with

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evidence of preoperative optic nerve disease, previous retinal detachment, macular degeneration, glaucoma, other retinal disease, corneal pathology, or a history of preoperative inflammatory eye disorder (for example, vitritis) were excluded.

FOCAL ELECTRORETINOGRAM (FERG)

Stimulus. The stimulus consisted of a tightly clustered array of red (630 nm) LEDs mounted in the rear of a ganzfeld bowl. A ground glass placed in front of the LEDs diffused the light so that it was a uniform circle of red light subtending 10° at the eye. The stimulus was sinusoidally modulated (Interstate F44) around a mean luminance of 50 cd/m^2 and at a maximum depth of 100% (i.e., 0 to 100 cd/m^2), at temporal frequencies ranging from 10 to 40 Hz. The bowl luminance was maintained at 25 cd/m^2 . This level was shown in preliminary testing to eliminate activation of the peripheral retina by scattered light from the stimulus. In control experiments the amplitude of the recorded FERG response was eliminated when the stimulus was imaged on the optic nerve head, and the response amplitude grew dramatically under both central and optic nerve fixation when the background light was turned off. After the pupil was dilated with 1% tropicamide (Mydracil) the patient placed his head in a ganzfeld bowl and fixated the centre of the LED array.

Recordings. FERG responses were recorded by means of a gold foil electrode⁵ hooked over the lower lid and referenced to the ipsilateral ear. The contralateral ear served as earth. The fellow eye was patched in all tests.⁶ The electrical signal was amplified by a Grass P511J preamplifier (gain = 10 000) with bandpass filter settings appropriate to the frequency of stimulation. The amplified signal was summed ($n=128$) on a Nicolet 1170B signal averager. Any sweeps containing large amplitude potentials due to blinks or eye movement were eliminated from the averaged response by setting the artefact rejection control of the Nicolet to an appropriate level. The averaged responses were then recorded on an X-Y plotter for later analysis.

PATTERN ELECTRORETINOGRAM (PERG)

Stimulus. A black-and-white checkerboard, reversing position 11 times/s, was generated on a Conrac video monitor (model QQA 14-N) by an Institute of London (T221) pattern generator. Each check subtended 1° of visual arc/side, and the entire pattern on the television screen measured $16 \times 23^\circ$. Average mean luminance of the display was set at 50 cd/m^2 and the pattern contrast was 50%. These parameters have been shown by previous work to produce the largest PERG response in normal persons.⁷

Recordings. The PERG responses were mono-

cularly recorded with a gold foil electrode. Signals from the eye were amplified and averaged in the same manner as the FERG responses.

VISUAL EVOKED POTENTIALS (VEP)

Stimulus. The same stimulus apparatus used for PERG stimulation was used to generate VEP responses. Check size was reduced to $1/2^\circ$, reversal rate slowed to 1.5 rev/s for transient potentials, and the screen was moved away from the subject and subtended $8 \times 11.5^\circ$. For recording the steady state VER the reversal rate was increased to 11 rev/s and the contrast lowered to 6.0%.

Recordings. A gold cup electrode was positioned 2.5 cm above theinion and referenced to the right ear lobe. The left ear lobe served as earth. The amplification and averaging remained the same as in the PERG and FERG. The latency of the transient response was measured as the time from stimulus onset to the peak of the first prominent positive wave (P100). Steady state response amplitude was measured from the most negative portion of the wave to the top of the following positive peak.

Results

Control subjects. Seventeen aphakic subjects (26 eyes), ranging in age from 40 to 85 years (mean 66.9), were studied. Best corrected visual acuities in this group ranged from 20/20 to 20/30 with a mean of 20/25. Twelve eyes had intracapsular cataract extractions (ICCE), seven of which had intraocular lenses (IOL) (one iris clip and six anterior chamber lenses (AC)). Ten eyes had extracapsular cataract extractions (ECCE), eight of which had posterior chamber (PC) IOLs. The 11 controls without IOLs required high plus lenses (i.e. $> +10$ dioptres for correction).

ACME patients. Thirty ACME patients (33 eyes), ranging in age from 57 to 86 years (mean 72.4) and with visual acuities ranging from 20/20 to 20/200, with a calculated mean of 20/94, were tested. The distribution and duration of macular oedema and optic disc leakage in these patients is shown in Table 1. Twenty-seven of the 33 eyes had optic disc leakage associated with macular oedema. Five eyes had optic disc leakage with grade 0 macular oedema, and two eyes had macular oedema with no disc leakage.

Four eyes with prior leakage on fluorescein angiography had no leakage or macular oedema at the time of electrophysiological testing: patient 30 (Table 1) had prior ACME grade 3 and massive disc leakage of eight months' duration; patient 31 had prior ACME grade 1 and mild disc leakage of 12 months' duration; patient 32 had prior ACME grade 2 and moderate disc leakage of 4.5 months' duration; and patient 33

Table 1 Clinical profiles of ACME patients and comparisons among electrophysiological tests (●=abnormal response)

Age	Sex	Eye	VA	Pro- cedure	IOL	Vitrect- omy	CME grade	Optic disc leakage	Duration (months)	VEP latency	VEP ampli- tude	PERG	FERG		
													10	30	40
1	58	M	OS	60	ECCE	PC	No	2	Massive	5	●	●			
2	64	F	OD	200	ICCE	No	No	1	Massive	16	●	●			
3	86	F	OD	100	ICCE	IC	No	4	Moderate	11	●	●			
4	59	F	OD	30	ICCE	No	No	3	Moderate	11		●			
5	67	F	OD	30	ECCE	PC	No	3	Moderate	1		●			
6	83	F	OS	60	ICCE	AC	No	2	Moderate	1					
7	72	M	OD	200	ICCE	No	No	2	Moderate	5	●				●
8	66	F	OD	70	PHACO	PC*	No	1	Moderate	10		●			
9	57	M	OD	25	ICCE	No	No	0†	Moderate	4					
10	57	M	OS	50	ICCE	No	No	1	Moderate	4					
11	76	M	OS	200	ECCE	AC*	No	4	Mild	2.5	●	●	●		
12	55	F	OD	100	ECCE	No	Yes	4	Mild	5					●
13	57	F	OD	200	ECCE	No	No	3	Mild	2		●			●
14	76	M	OD	80	ICCE	No	No	2	Mild	6	●	●	●	●	●
15	76	M	OS	80	ICCE	No	Yes	3	Mild	6	●	●	●	●	●
16	60	F	OS	200	ICCE	No	No	1	Mild	12	●		●	●	●
17	73	F	OD	200	ICCE	IC*	Yes	1	Mild	2		●			●
18	70	F	OD	70	ICCE	AC	No	1	Mild	5					
19	73	F	OD	25	ICCE	No	No	0†	Mild	36		●			
20	75	M	OS	100	ICCE	AC	No	3	Mild	3		●			●
21	67	M	OD	200	ECCE	AC	No	2	Mild	5.5					
22	81	M	OD	100	ECCE	PC	No	2	Mild	1		●		●	●
23	82	F	OS	200	ECCE	AC	No	1	Mild	4		●		●	●
24	84	F	OD	100	ICCE	IC	No	0†	Mild	12		●			
25	84	F	OS	100	ICCE	IC	No	0†	Mild	12		●	●		
26	76	F	OD	100	ICCE	AC	No	0†	Mild	9					
27	53	M	OS	30	ICCE	No	No	1	Mild	6		●	●		
28	74	F	OS	25	ICCE	No	No	2	None	11					
29	61	F	OD	40	ICCE	AC	No	2†	None	1.5					
30	61	F	OD	40	ICCE	AC	No	0†	None	8					
31	77	F	OD	25	ICCE	No	No	0†	None	12					
32	71	F	OD	25	ECCE	PC	No	0†	None	4.5					
33	73	F	OD	50	ICCE	IC	No	0†	None	8		●			●

IC=Iris clip. *Lens Removed. †Grade 0 ACME at the time of testing (see text for prior extent).

had prior ACME grade 2 and mild disc leakage of eight months' duration.

Twenty-three of the eyes had intracapsular extractions, 12 with IOLs (five iris clip), one of which required removal, and seven AC lenses). Nine eyes had extracapsular extractions—four with PC IOLs and three with AC IOLs, one of which required removal. One eye had a phacoemulsification (PHACO) with a PC lens which required removal. Three of the 33 eyes had vitrectomies (two ICCE and one ECCE). Seventeen patients' eyes required high plus lenses for correction. The appearance of the optic nerve head by Goldmann contact lens examination, Goldmann visual fields, and pupillary responses were normal in 31 of 33 eyes. One patient (Table 1, No. 2) had severe postoperative ischaemic papillopathy (4+ hyperaemic disc and massive optic nerve head leakage), with an afferent pupillary defect and a residual 3° visual field; another patient (No. 11) also sustained a postoperative ischaemic papillopathy with disc pallor, an altitudinal visual field loss, and an afferent pupil defect.

There was low correlation between the grade of macular leakage and visual acuity, the grade of disc leakage and visual acuity, and the duration of leakage and visual acuity (Table 2).

ELECTROPHYSIOLOGICAL RESULTS

Controls. The electrophysiological data of the controls tested with high plus lenses were not significantly different from those having IOLs. Likewise the data for ICCE versus ECCE controls were not found to be significantly different. Therefore the data from all controls were grouped for further analysis. Focal ERG amplitudes for 10 Hz averaged 7.8 ± 3.6 μ V, for 30 Hz 5.4 ± 2.5 μ V and for 40 Hz 5.6 ± 1.6 μ V. Control FERG amplitudes ranged from 3.2 to 14.8 μ V at 10 Hz, 2.2 to 10.9 μ V at 30 Hz, and 3.2 to 9.2 μ V at 40 Hz. Pattern ERG amplitudes at 50% contrast for this series averaged 8.7 ± 3.3 μ V. The range of PERG amplitudes in this group was from 4.5 to 17 μ V, and the interocular difference in amplitude averaged 1.2 ± 0.6 μ V. The mean VEP latency for the controls was 104.5 ± 10.1 ,

Table 2 Correlation coefficients between clinical and electrophysiological measures in patients with ACME

	Duration	VA	CME grade	Optic disc leakage	VEP latency	VEP amplitude	PERG	FERG		
								10	30	40
Duration	1.0	-0.19	-0.30	-0.17	-0.12	0.24	-0.09	0.16	0.26	-0.02
VA		1.0	0.25	0.30	0.17	-0.34	-0.41	-0.19	0.38	0.04
CME grade			1.0	0.37	-0.02	-0.24	-0.01	-0.36	-0.27	0.03
Disc leakage				1.0	0.21	-0.57	-0.33	-0.27	-0.18	0.18
VEP latency					1.0	-0.36	-0.30	-0.23	-0.06	-0.30
VEP amplitude						1.0	0.24	0.33	0.20	0.13
PERG							1.0	0.11	0.21	0.03
FERG 10 Hz								1.0	0.54	0.16
FERG 30 Hz									1.0	0.16

with a range of 90 to 131 ms. The mean steady state VEP amplitude at 6.0% contrast was $8.6 \pm 2.9 \mu\text{V}$. Steady state VEP amplitude ranged from 3.8 to $20.2 \mu\text{V}$ in this control group. None of the electrophysiological measures differed from those of a second control group of nine age matched aphakic normal persons.

ACME patients. The electrophysiological results of the aphakic patients with ECCE and ICCE, and those with or without IOLs, did not differ significantly and were combined for further analysis. 3% (1/31) of the FERG amplitudes at 10 Hz, 16% (5/31) at 30 Hz, and 36% (11/31) at 40 Hz were found to be below the range established by the control group.

Seventeen of 32 eyes (53%) had PERG amplitudes below the control range. Of these, eight had unilaterally absent PERG responses and the remaining nine had a mean interocular difference in amplitude of $4.6 \pm 1.7 \mu\text{V}$. Eight of 17 had both abnormal FERG and PERG responses, and nine of 17 had only abnormal PERG responses. Those patients with only abnormal PERG amplitudes had a calculated mean visual acuity of 20/98, whereas those with both tests abnormal had a calculated mean visual acuity of 20/123. This difference was not statistically significant. The difference in the PERG response, therefore, was not related to reduction in visual acuity in this group. It is also interesting to note that the patient group with only abnormal PERG responses had a significantly longer mean duration (11.8 months) than the other ACME patients.

Only four patients (five eyes) had prolonged latencies (>131 ms). Two of these patients (Table 1, patients 2 and 11) sustained postoperative ischaemic papillopathy with visual field defects, afferent pupillary defects, and optic nerve head changes. The third patient had slightly prolonged latencies (133 ms) in both eyes with normal pupillary responses, normal visual fields, and normal optic discs. The fourth patient, likewise, had slightly prolonged latency (136 ms) with normal pupillary responses, visual fields, and optic discs.

Ten of 31 (32%) of the ACME eyes had steady state VER amplitudes below the control range.

A correlation matrix showed little relationship between the grade of macular oedema and a single electrophysiological result, between the grade of disc leakage and the electrophysiological results, or between duration of oedema and the electrophysiological results (Table 2). However, of the four patients with no leakage (disc or macula) at the time of testing three had normal electrophysiological findings. The remaining patient had persistent visual loss (20/50) and abnormal electrophysiological results.

Discussion

The major findings of this study were: (1) focal electroretinogram amplitudes were abnormal in 35% of the patients tested who had aphakic cystoid macular oedema; and (2) pattern electroretinogram amplitudes were abnormal in 53% of ACME patients, with over one-half of these patients having no associated FERG abnormalities.

The focal electroretinogram is a specific test of the temporal responsiveness of the central 10° of retina, and, like the flash electroretinogram b wave, the presence of a FERG response requires integrity of the outer retinal layers and particularly Mueller cell function.⁸ Certain macular diseases have been shown to be associated with reduced FERG amplitudes. The deficits are initially observed at the higher temporal frequencies and involve the lower frequencies as visual acuity decreases.⁹ Thus, for example, in Stargardt's disease with visual acuity between 20/60 and 20/100 the FERG response is absent at all temporal frequencies.⁹

Histological studies of human CME eyes have shown pathological changes occurring predominantly in the outer retinal layers, namely, accumulation of fluid in Henle's outer plexiform layer and in the bipolar neural layer,^{2 10-12} photoreceptor cell dropout, and Mueller cell swelling and necrosis in the

outer retinal layers.¹⁰ Our findings of FERG reduction in ACME patients supports these prior histopathological findings.

Recently the PERG has been shown to reflect inner retinal layer function. Maffei and Fiorentini¹³ showed a marked reduction of PERG amplitude and preserved diffuse flash ERG amplitude some weeks after section of the cat optic nerve and after ischaemia caused by temporary blockage of the retinal artery. The clinical importance of the PERG lies in the fact that it has been shown to be abnormal in diseases in which the optic nerve is primarily or secondarily affected and where the flash ERG is normal. In patients with severe visual loss and poor acuity caused by optic neuritis, ischaemia, or compression of the nerve no PERG response has been found in spite of normal flash ERG responses.¹⁴⁻¹⁶ These findings support the hypothesis of an inner retinal layer origin for the PERG.

Seventeen of 31 (53%) of the ACME eyes in our study had abnormal PERG amplitude. These patients fell into two groups: nine of the 17 eyes had normal FERG responses and abnormal PERG responses, and eight of the 17 showed abnormalities in both responses. FERG reduction itself may cause a reduced PERG, since the functioning of the inner layers must reflect the quality of the input from the outer retinal layers. However, a large number of these patients had normal outer retinas as reflected in their normal FERG responses. In the presence of a normal FERG, PERG abnormalities must solely reflect inner retinal layer dysfunction. Although most of the visible pathological changes have been described as occurring in the outer retina, it appears that perifoveal capillary leakage and optic disc leakage may additionally cause significant changes in inner retinal layer physiology. A recent histological analysis of a human CME (not aphakic) eye reporting swollen mitochondria in optic nerve ganglion cells and swelling of the associated glial cells¹⁷ provides supportive evidence for a lesion of the inner retinal layer in ACME.

Since most patients with ACME have associated disc leakage in addition to macular oedema on fluorescein angiography, we used the VEP to test latency in these individuals. VEP latencies have been shown to be prolonged in cases of optic neuritis of demyelinating origin, ischaemic or compressive optic nerve disease, or optic atrophy.^{18,19} Although 27 of 33 eyes examined in this study showed some degree of optic disc leakage, only four patients had delayed VEP latencies. Two of these patients had severe postoperative ischaemic papillopathy, with associated visual field loss, afferent pupillary defects, one with optic disc pallor, and the other with 4+ disc hyperaemia. Thus there is rarely significant change in

the conduction pathway of the optic nerve associated with optic disc leakage in ACME.

The steady state VEP has been previously used as a sensitive assay of the processing of spatial contrast information.²⁰ VEP contrast deficits with normal Snellen acuities have previously been demonstrated with the VEP.^{21,22} 32% of the patients in this study showed abnormal VEPs at low contrast when compared with matched controls. These findings, however, can be used only as indicators of non-specific visual loss, since patients with both macular disease²³ and optic neuropathy²¹ have been shown to have abnormal steady state VEP responses.

We found poor correlation between the electrophysiological results and the grade of macular leakage, or the duration of leakage, or the visual acuity. Similarly we found little correlation between visual acuity and disc leakage, or between visual acuity and ACME grade. These low correlations probably represent the limitations of the measurements. ACME grade and disc leakage may fluctuate, and the grade assigned at any particular time may not reflect the past extent of the leakage. Likewise duration alone does not reflect the severity of the pathology. For example, patients 30-33 had no leakage (disc or macula) at the time of testing, whereas all had prior clinical ACME of varying severity. Higher correlation may be found if the entire time course of the disease (including these fluctuations in degree) in a particular patient are included.

CONCLUSIONS

In addition to the obvious outer retinal layer pathology described by histological study and confirmed in the present study by abnormal FERG findings we found PERG abnormalities in a large number of ACME patients. These results suggest additional unobserved pathology involving the inner retinal layers in aphakic cystoid macular oedema, a disorder which has previously been thought of as predominantly an outer retinal dysfunction. This may explain the more severe visual loss seen in some patients where the ophthalmologically visible retinal changes do not seem sufficient to explain such reduction of vision.

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