Short report

Pattern electroretinogram in multiple sclerosis

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SUMMARY The pattern electroretinogram obtained in patients affected by multiple sclerosis were compared with those in a normal population. The pattern electroretinogram amplitude in multiple sclerosis optic neuritis frequently appeared normal, but pattern electroretinogram amplitude abnormalities were found in patients suffering from recurrent multiple sclerosis optic neuritis. Pattern electroretinogram examination appears a useful method in the differential diagnosis between axonal and demyelinating optic nerve impairment.

In recent years the pattern reversal electroretinogram technique has been improved by Arden *et al.*^{1,2} and Dawson *et al.*³ This potential can now be studied easily in normal subjects and patients. According to Arden *et al.*,^{4,5} Vaegan *et al.*⁶ the pattern electroretinograms are generated at or near the ganglion cell layer; Maffei and Fiorentini⁷ have observed progressive amplitude reduction in the pattern electroretinogram after cutting the optic nerve in cat, demonstrating the possibility that the pattern electroretinogram potential can be generated by the ganglion cells. In agreement with Armington,⁸ Arden *et al.*,⁵ Sokol and Nadler,⁹ the pattern electroretinogram potential presents a negative a wave and a positive b wave; the latencies of the a and b waves are faster than the flash electroretinogram obtained with the same luminance and adaptation conditions.⁵ The peak to peak pattern electroretinogram amplitude between a and b waves is only about few μV ^{5,6} and it has been shown to be sensitive to pattern contrast and spatial frequency.^{5,8} Best amplitudes are obtained using large spatial frequency stimuli.^{5,8} The pattern electroretinograms are affected in severe amblyopia,^{4,9,10} in optic neuritis as a result of axonal lesion and retrograde ganglion cell degeneration,^{5,6,11,12} and in macular diseases.^{13,14}

Arden *et al.*⁵ have found pattern electroretinogram amplitude abnormalities in patients suffering from

multiple sclerosis optic neuritis, while Kaufman *et al.*¹³ have described normal pattern electroretinogram amplitude in optic neuritis affecting patients with definite multiple sclerosis. Of great interest, therefore, is the question of what value is the use of pattern electroretinogram in the diagnosis of multiple sclerosis optic neuritis, and are there pattern electroretinogram abnormalities which are useful in the differential diagnosis of multiple sclerosis optic neuritis? In this work we have tried to compare the pattern electroretinograms associated with pattern visual evoked potentials (VEPs) in selected patients suffering from multiple sclerosis with a selected normal population in order to establish the clinical significance of the pattern electroretinograms in multiple sclerosis.

Material and method

We selected 20 collaborating patients (mean age 33.9 years, SD 6.39, seven males and 13 females) suffering from definite multiple sclerosis according to the recent classification criteria proposed by Poser *et al.*¹⁵ No patients presented eye abnormalities or diseases other than multiple sclerosis optic neuritis. We excluded also patients who had eye movement dysfunctions at the moment of the electrophysiological evaluation. No patients with gross visual field defects and no patients with visual acuity below 6/12 were included. When necessary some patients were optically corrected for the stimulus distance and mydriatics and cycloplegics were not used. The electrophysiological examination was performed at least 3 months after the last clinical attack of optic neuritis. In patients without signs or symptoms of optic neuritis the electrophysiological evaluation was repeated 3 months later if the VEPs were abnormal. We took these precautions since the pattern electroretinogram amplitude reduction arises in animal or in

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man some weeks after an optic nerve axonal lesion.⁵⁻⁷ The normal subjects (11 males and 14 females) were chosen as controls with age range similar to the patients, in fact the mean age was 32.7 years and the SD was 8.04. These subjects did not present subjective, clinical and electrophysiological signs or symptoms of eye abnormalities or diseases.

The electrophysiological examination in each subject and in each patient was performed as follows:

The flash electroretinogram was recorded by use of contact lens electrodes on eyes adapted to light and dark according to Armington's¹⁶ standard criteria.

The VEPs were obtained by black-white checkerboard pattern reversal stimulus with squares of 55 min of arc. The reference electrode was placed in Fz (international 10-20 system) and the recording electrode 3 cm above theinion. The electrode impedance was maintained below 5000 Ohm. The frequency pass-band was 0.16-160 Hz. The VEP stimulus condition and the stimulating and recording apparatus were the same as those used for the pattern electroretinograms (see below). We studied the VEP N_{75} - P_{100} peak to peak amplitudes and P_{100} peak latencies. The VEP normal values of our laboratory, previously standardised in 60 normal subjects were: mean P_{100} latency 103.33 ms, SD 5.48, 97% confidence upper limit 117 ms; the N_{75} - P_{100} amplitude range was 3-15 μ V; the maximal latency difference between the two eyes was 8 ms, and the maximal amplitude difference between the two eyes was 45%.

The pattern electroretinograms were recorded simultaneously in both eyes. Squares of 55 min of arc in a black-white checkerboard pattern, which keep mean luminance almost constant, were reversed at 1 Hz as stimulus. Ear clip electrodes as reference and platinum active electrodes similar to Arden's were used. The signals were amplified, averaged, and displayed by a Medelec MS6 electromyograph and by a Medelec DAV6 digital averager, incorporating an artifact rejection circuit, which rejected the noise due to blink or eye movements. The analysis time was 200 ms and 128 sweeps were averaged for each trial. The frequency pass-band was 0.8-32 Hz. Each examination was repeated at least three times. The visual stimulator was a Barco TV monitor and the pattern generator was a Medelec VS6; the screen subtended a 19×12 degrees stimulus field at 1.43 m; the black-white contrast was 86%. The fixation, monitored by a TV apparatus, was maintained by a grey check in the middle of the visual stimulus field. We monitored the illuminance conditions by means of an ICE Luxmeter: black 3 lux, white 200 lux, screen illuminance measured near the subject eyes 5 lux. The examinations were performed in a silent, dark room. We considered as pattern electroretinogram parameters the a-b peak to peak amplitudes and b wave peak latencies.

The flash electroretinograms were recorded in both eyes simultaneously, using the pattern electroretinogram electrodes in order to verify the correct contact of the platinum electrodes and their registration symmetry.

Results

In normal subjects the mean pattern electroretinog-

ram amplitude was 3.2 μ V, SD 0.6; the 95% confidence range was 2-4.4 μ V. The 95% statistical confidence difference of the amplitudes between the two eyes was 0.7 μ V. No normal subjects presented pattern electroretinogram amplitudes below 2.1 μ V. The mean b wave latency was 60.9 ms, SD 5. The 95% statistical confidence difference of the b wave latencies between the two eyes was 6 ms. In our work the b wave latencies appeared slightly prolonged compared to Arden *et al*'s results⁵ for the different pass-band frequency range. By using frequency pass-band equal to Arden *et al*'s the latencies appeared similar.

The VEP and pattern electroretinogram data of the patients suffering from multiple sclerosis are shown in the table. Seven of these never had symptoms of optic neuritis (cases 3, 8, 12, 13, 14, 16, 19), but cases 3, 8, 14, 16, 19 had VEP abnormalities; only patients 12 and 13 showed normal VEPs. All patients who presented clinical or subjective signs or symptoms of optic neuritis had VEP abnormalities. Cases 2, 9, 11, 15, 17, 18, 20 had clinical signs or symptoms of bilateral optic neuritis and in these the VEPs revealed bilateral abnormalities, except case 17; in patients 1, 4, 6, 7 the VEPs revealed bilateral abnormalities even if the clinical signs or symptoms had been unilateral. Cases 2, 9, 20 had two or more clinical attacks of optic neuritis in both eyes, cases 15 and 18 in one eye only. Pattern electroretinogram amplitude abnormalities were found in patients 2, 9, and 20 bilaterally and in patients 7, 15, 16, 18 in one eye only. Case 16 had normal pattern electroretinogram amplitudes, but there was a significant difference between the eyes. It is worth noting that all patients, except cases 7 and 16, showed pattern electroretinogram abnormalities in the eyes suffering from recurrent optic neuritis. No patients with several optic neuritis attacks in the same eye had normal pattern electroretinogram amplitude. In all patients the latencies of b wave were normal.

Discussion

From the data obtained we can draw the following conclusions: (1) frequently in patients suffering from clinical or subclinical multiple sclerosis optic neuritis the pattern electroretinogram amplitudes appear similar to normal subjects even if the VEPs are considerably impaired (fig 1A). (2) Pattern electroretinogram amplitude reduction can also be found in multiple sclerosis optic neuritis especially when several clinical attacks had impaired the optic nerve (fig 1B and 1C).

Following Arden *et al*,⁵ Vaegan *et al*,⁶ Maffei and Fiorentini,⁷ Seiple *et al*¹² and Fiorentini *et al*¹¹ an

Table 1 Clinical, pattern electroretinogram, and VEP data obtained in patients with multiple sclerosis

Patients	Age (yr)	Sex	Clinical optic neuritis		Optic disc atrophy		Pattern electroretinogram amplitude μV		b wave latency ms		VEP latency ms		VEP amplitude μV	
			LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE
1	28	F	+	-	-	-	3.3	3.6	60	63	146*	128*	8.0	9.0
2	28	M	++	++	-	TP	1.8*	1.7*	70	67	129*	136*	5.0	5.0
3	40	F	-	-	-	-	3.2	3.5	66	66	131*	135*	7.5	12.5
4	27	M	+	-	-	-	3.1	3.5	66	66	153*	126*	3.0	3.7
5	32	F	-	+	-	-	3.2	2.7	50	55	105	120*	11.5	11.5
6	20	F	+	-	TP	-	4.0	3.7	66	66	147*	119*	6.2	5.0
7	37	F	+	-	TP	-	1.1*	2.7	60	57	145*	123*	5.0†	12.5
8	25	F	-	-	-	-	3.8	3.5	55	55	116	136*	7.5	7.5
9	32	M	++	++	P	TP	1.1*	0.9*	62	62	132*	150*	3.5	3.0
10	40	M	-	+	-	-	3.2	3.0	57	57	117	123*	7.5	9.5
11	41	M	+	+	TP	TP	2.2	2.2	60	55	144*	145*	7.5	7.5
12	44	F	-	-	-	-	3.4	3.4	62	62	101	102	12.5	12.5
13	40	F	-	-	-	-	2.8	2.8	57	58	94	96	6.0	6.0
14	37	F	-	-	-	-	2.9	2.3	59	58	102	113†	12.0	12.0
15	30	M	+	++	-	P	2.1	1.5*	60	60	144*	182*	5.5	4.7
16	37	F	-	-	-	-	3.7	2.2†	62	58	135*	143*	12.0	8.5
17	33	F	+	+	-	-	3.0	2.5	56	56	104	150*	3.7	3.7
18	30	M	++	+	P	-	1.8*	2.9	60	60	140*	120*	7.5	10.0
19	41	F	-	-	-	TP	2.6	2.8	56	57	122*	126*	5.5	5.5
20	36	F	++	++	P	P	0.9*	1.2*	60	60	150*	132*	2.2*	3.7

+ one optic neuritis clinical attack; ++ two or more optic neuritis clinical attacks; TP temporal disc pallor; P disc pallor; LE left eye; RE right eye; * abnormal values; † normal values, but significant difference.

optic nerve axonal impairment produces pattern electroretinogram amplitude reduction as a result of retrograde ganglion cell degeneration. In multiple sclerosis optic neuritis is very common and the optic nerve lesion appears to be demyelinating according to Halliday *et al.*¹⁷ Secondary axonal optic nerve lesion can be seen in multiple sclerosis¹⁸ and in the light of this data different pattern electroretinogram patterns in multiple sclerosis may exist as a result of demyelinating or demyelinating and axonal nerve lesions. Arden *et al.*⁵ and Vaegan *et al.*⁶ found pattern electroretinogram amplitude abnormalities in patients suffering from multiple sclerosis optic neuritis as well as in patients affected by other optic neuritides or axonal lesions of optic nerve. Kaufman *et al.*¹³ described normal pattern electroretinogram amplitude in patients with definite multiple sclerosis. Both the above mentioned results appear to agree with our data; we frequently found normal pattern electroretinograms in multiple sclerosis; in some patients, however, a pattern electroretinogram amplitude reduction was detected. Furthermore, it is of interest that all our patients who had had several attacks of optic neuritis showed pattern electroretinogram amplitude abnormalities. It is more likely that these patients also had optic nerve axonal impairment than had patients who had suffered only one or no clinical optic neuritis attack, even if in the latter an optic nerve impairment was found by the VEP analysis. Subnormal flash electroretinogram in

optic nerve lesions have been described by several authors.¹⁹⁻²² Flash electroretinograms and VEPs were used, recently, by Ikeda *et al.*²² as a combined assessment of optic nerve function, in order to localise optic nerve lesions. They found normal flash electroretinograms and delayed VEPs in pure optic nerve demyelinating diseases, and flash electroretinogram amplitude reduction, instead, in axonal or combined axonal and demyelinating lesions of optic nerve. According to these authors the subnormal flash electroretinogram b wave was the result of retrograde transneuronal degeneration of bipolar cells. Our data appear to confirm the possible retinal impairment in axonal lesions of optic nerve as described by Ikeda *et al.*²² even if they used a different electroretinogram stimulus. Since in our selected patients, no flash electroretinogram abnormalities were found, the pattern electroretinogram appears more sensitive than the flash electroretinogram, probably because it is generated in the ganglion cell layer⁷ and, thus, is more specific in detecting this kind of lesion. Another interesting point is the normal b wave latency in our patients, as described by Kaufman *et al.*¹³ this suggests that delay in VEP latency in optic neuritis does not have a contribution from delayed retinal transmission; this observation could have a diagnostic value in retinal lesions able to delay the pattern electroretinogram b wave, but further study is needed to confirm the hypothesis.

We conclude that the pattern electroretinogram in

Fig 1 (A) Normal pattern electroretinograms and abnormal VEPs in patient 1, (B) pattern electroretinograms and VEPs in patient 18. The left eye pattern electroretinogram appears abnormal, (C) bilateral pattern electroretinogram amplitude reduction and abnormal VEPs in patient 2. Pattern electroretinogram up positive; VEP up negative.

multiple sclerosis optic neuritis is useful because pattern electroretinogram recording has become a very simple technique as a result of the technical improvements made by Arden *et al*^{1,2} and Dawson *et al*;³ the pattern electroretinogram gives some information about the anatomical level, be it demyelinating or axonal, of the pathological change in optic neuritis; the pattern electroretinogram evaluation seems to add data to VEP analysis for the differential diagnosis in optic neuritis.

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