Serial Pattern Shift Visual Evoked Potentials in Multiple Sclerosis

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SUMMARY: Forty patients with MS initially tested in our laboratory were recalled for repeat PSVEP testing approximately two years later. Twelve normal controls were tested in a similar manner approximately two years apart. The PSVEP positive peak latency changed little in the 24 control eyes (mean 1.4 msec, range 0-6) over the study interval. Most MS patient eyes also showed little change in PSVEP latency over the two year study interval. Fifty-eight eyes changed 8 msec or less. Eighteen eyes showed a PSVEP latency increase of 10 msec or more. Six of these eighteen eyes were symptomatic (attack of clinical optic neuritis), twelve asymptomatic during the study interval. Symptomatic eyes tended to have greater latency increases during the study interval than asymptomatic eyes.

Significant latency increases occurred with equal frequency in previously normal eyes (normal PSVEP on first test) and abnormal eyes (abnormal PSVEP on first test or previous clinical optic neuritis). Significant latency increases occurred with greater frequency in patients with a mixed or progressive course than in patients with a remitting-relapsing course, and in patients with greater disability ratings (Kurtzke 3-7) than in patients with lower disability ratings (Kurtzke 0-2). Bilateral latency increases occurred during the study interval more frequently than expected by chance. Patient age and disease duration did not significantly influence the number of PSVEP latency increases seen during the study interval.

Four eyes *decreased* in latency by 10 msec or more during the study interval. All these eyes had had an episode of acute optic neuritis which began in the 5 weeks immediately preceding the 1st PSVEP test.

In our MS patients, 13% of eyes per year developed latency increases of 10 msec or more. These may represent new demyelinating lesions. If so, one-third of these lesions were clincally symptomatic.

RÉSUMÉ: Nous avons réexaminé après 2 ans 40 patients souffrant de sclérose en plaques (SEP) à l'aide du test PSVEP (potentiels évoqués sensitifs). Douze témoins normaux furent aussi examinés de nouveau après un intervalle de 2 ans. Le pic de latence positive du PSVEP ne changea pratiquement pas en 2 ans dans les 24 yeux témoins (moyenne 1.4 msec, fourchette 0-6). La plupart des cas de SEP ne montrèrent pas de changements après 2 ans. Ainsi une modification de 8 msec ou moins fut trouvée pour 58 yeux. Cependant celle-ci dépassait 10 msec chez 18 yeux, dont 6 étaient symptomatiques (névrite optique clinique). L'augmentation de la latence était plus grande dans les yeux symptomatiques.

Les augmentations de latence se retrouvent également chez les yeux qui étaient antérieurement normaux ou anormaux. Elles sont plus importantes et plus fréquentes chez les patients dont l'évolution est mixte ou progressive comparés à ceux qui ont des rémissions. Elles sont également plus importantes chez les patients plus atteints (Kurtzke 3-7) que chez les moins atteints (Kurtzke 0-2). Une augmentation bilatérale de la latence se retrouve plus souvent que par simple effet du hasard. L'âge et la durée de la maladie n'ont aucun effet sur les résultats obtenus.

Chez 4 yeux, il y eut une diminution de la latence dépassant 10 msec. Dans tous les cas un épisode aigu de névrite optique avait précédé le premier test d'au plus 5 semaines.

Chez nos patients souffrant de SEP, 13% des yeux par année augmentent la latence de réaction de 10 msec ou plus. Il peut donc s'agir de nouvelles lésions démyélinisantes, dont seulement un tiers furent symptomatiques.

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Pattern shift visual evoked potentials (PSVEP) are frequently abnormal in patients with multiple sclerosis (MS) (Halliday et al., 1973; Asselman et al., 1975). Some of these PSVEP abnormalities are thought to reflect asymptomatic (or subclinical) central nervous system lesions, and thus may aid in the diagnosis of MS (Zeese, 1977; Shahrokhi et al., 1978). In patients with definite MS, Chiappa (1980) found the PSVEP to be abnormal in 90% of 83 patients with a history of optic neuritis.

PSVEP studies may well indicate additional information about the natural history of MS. If further increases in PSVEP latency represent new demyelinating lesions, the PSVEP may give some indication when during the patient's course and at what rate new plaques are formed in visual pathways. Tabulation of clinical relapses and monitoring of increasing patient disability have yielded much information about the natural history of MS (Confavreux et al., 1980), but clinical review may both underestimate and overestimate disease activity (Poser, 1980). Repeated PSVEP studies in MS patients might contribute by providing an objective even if only a partial monitor of demyelination, both symptomatic and asymptomatic, in visual pathways. Among evoked response studies, the PSVEP is particularly suited for this purpose because it is one of the simplest to perform,

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requires the least time, and because optic nerve involvement is so common in MS. In an autopsy study of 70 MS patients, Ikuta and Zimmerman (1976) found optic nerve lesions in 99%.

Many recent studies have detailed the incidence of evoked response abnormalities in patients with MS (Chiappa, 1980; Kjaer, 1980; Purves et al., 1981) but relatively few attempts have been made to delineate the rate of appearance of new PSVEP abnormalities in MS patients over time. Matthews and Small (1979) performed serial PSVEP studies in 51 patients with MS. 27% of eyes tested showed a PSVEP latency prolongation of over 10 msec during the mean study interval of 18 months. 25% showed a latency reduction of over 10 msec, but it is not stated how many of these patients had had onset of acute optic neuritis shortly before the first PSVEP test. No normal control group is mentioned, so it is not clear how much PSVEP latency variation from test to test results from factors other than new demyelination, such as measuring error and normal variability. Diener and Scheibler (1980) performed serial PSVEP tests in MS patients, with a mean time interval of 34 days between recordings. In this short time interval, most patients without recent optic neuritis showed no change in PSVEP latency. Of 24 patients with actue optic neuritis, 58% showed a reduction in latency of over 10 msec during the study period, while 29% showed a further latency prolongation. Walsh et al. (1982) did PSVEP recordings twice 31 months apart in 56 patients with MS. They reported a PSVEP latency change of 5 msec or more in 58% of eyes. However, no normal control group is mentioned. It is doubtful that 5 msec represents a significant change.

The present study was done to define the changes in PSVEP latency occurring over time in MS patients and to determine to what extent serial PSVEP tests might contribute information on the natural history of MS. To this end, serial PSVEP tests were done under carefully controlled conditions in 12 normal controls and 40 MS patients.

Methods

PSVEP Testing Procedure

All PSVEP tests were done in the same air conditioned room using a Nicolet CA 1000 signal averager coupled to a NIC 1006 Color Visual Stimulator. Bandpass was 1 Hz to 30 Hz, and recording montage was 0_z-C_z (International 10-20 System). The patient was seated one meter from the television screen. The visual stimulus was a black and white checkerboard pattern reversing at 1.88 Hz. Each pattern check subtended a visual angle of 27.5′ of arc, and the total stimulus field subtended 16° of visual angel at 1 meter. Luminance of the light squares was 275 cd/m^2, and of the dark squares was 3 cd/m^2. Contrast was 0.98.

Each eye was tested separately with the opposite eye occluded. Evoked responses to 2 runs of 100 stimuli each were averaged for each eye. PSVEP waveforms were displayed and latency measurements for the major positive peak (P 100) made from an oscilloscope screen. A permanent record was also made with an X-Y plotter (Hewlett Packard 7010B) for later comparison.

PSVEP testing was done in an identical manner in patients and normal controls. The upper limit of normal for the PSVEP latency in our laboratory, based on 48 control eyes, is 116 msec (Mean + 3 SD). The maximum normal inter-eye latency difference of our laboratory is 6 msec (Mean + 3 SD). A PSVEP latency was considered abnormal if it exceeded 116 msec, or if it exceeded the latency of the opposite eye by 6 msec or more.

Patient Studies

A) PSVEP testing was done daily (excluding weekends) for five days on three patients with MS to determine how much the PSVEP latency would vary from day to day. All three patients had prolonged PSVEP latencies bilaterally, but had well formed positive peaks.

B) From patients with clinically suspected or definite MS initially referred to our clinical evoked response laboratory for evaluation, 40 were recalled for repeat PSVEP testing approximately two years afer their first test. To be eligible for recall, patients had to show well developed and easily measured positive peaks on their initial PSVEP test. On the basis of their initial PSVEP test, three categories of patients were recalled for repeat testing:

1. Twenty patients with a normal PSVEP latency in one eye, and an abnormal PSVEP latency in the other eye.
2. Ten patients with abnormal PSVEP latencies in both eyes.
3. Ten patients with normal PSVEP latencies in both eyes.

Patients were recalled for repeat PSVEP testing without knowledge of their intervening clinical course. This may have resulted in the exclusion of patients with more aggressive MS who may have been referred back to our laboratory more frequently for PSVEP testing because of increasing symptoms and signs, as such patients would not have been entered into our study.

All patients were examined neurologically at the time of their second PSVEP test by the same neurologist (W.B.). Disability was assessed (Kurtzke, 1965) and the patients assigned a clinical diagnostic category (McDonald and Halliday, 1977). 21 patients had clinically definite, 8 early probable, 1 suspected, 7 progressive probable and 3 progressive possible MS. All eyes studied had a visual acuity of 20/60 or better.

Most eyes had normal acuity. Mean patient age was 33 years (range 22 to 52).

Twelve normal control subjects were studied in a manner identical to our patients. Mean age for the controls was 38 years (range 26-56).

Results

All 80 MS patient eyes showed easily measured PSVEP peaks on their second study. At study completion, 10 eyes showed a PSVEP latency of over 150 msec, 16 eyes showed a latency between 130 and 150 msec, and 54 eyes showed a latency of under 130 msec.

A) **PSVP Latency Variability from Day to Day in MS patients** Table 1 shows the PSVEP latency measured on five consecutive days in three patients with MS. The PSVEP latency varied little from day to day, but over the five measurements done for each eye, maximum and minimum latency measurements varied as much as 7 msec. These differences likely reflected variability inherent in our PSVEP testing and measuring method, as well as possible variability in neural conduction and processing time for the visual stimulus. From these results, it was doubtful that any latency increase of less than 10 msec could confidently be

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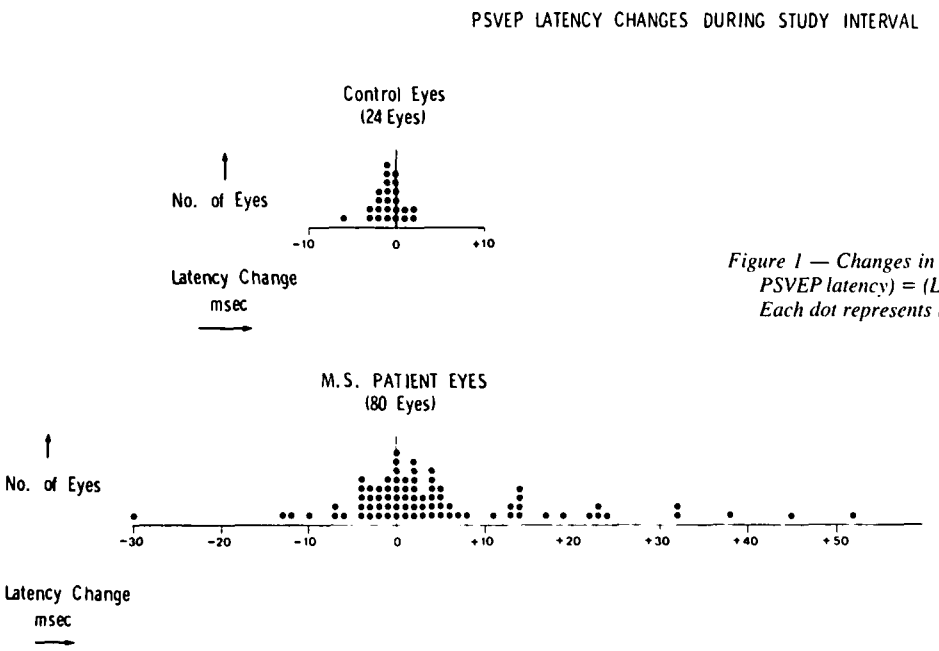

Figure 1 — Changes in PSVEP latency [(Final PSVEP Latency) — (Initial PSVEP latency) = (Latency Change)] occurring during the study interval. Each dot represents the latency change in one eye.

considered evidence for new optic nerve or other CNS damage.

b) **PSVEP Latency Changes Over Time in MS Patients and Controls**

PSVEP latency changes occurring during the study interval are shown in Figure 1. Each dot represents the latency change measured in a single eye [(Final PSVEP Latency) — (Initial PSVEP Latency) = (Latency Change)]. For controls, the mean study interval was 23 months (range 12-39). For MS patients, the mean study interval was 21 months (range 4-36).

Latency changes occurring in the 24 normal control eyes are shown in the upper part of the Figure. Changes occurring in the 80 MS patient eyes are shown in the lower part. The mean PSVEP latency change in the control eyes was 1.4 msec (SD 1.3 msec). In the MS patient eyes, the mean latency change was 8.1 msec (SD 10.7 msec).

Figure 2 shows an example of two serial PSVEP tests in a patient with MS, demonstrating a PSVEP latency increase during the study interval in both eyes.

Because of the data already discussed, and shown in Table 1, PSVEP latency changes of less than 10 msec were not considered significant. Our control data likewise suggested that certainly latency changes of 6 msec or less were not significant. The PSVEP latency changes in the 80 MS patient eyes were therefore analyzed by dividing them into three groups:

Group I (18 eyes) — *These showed PSVEP latency increases of 10 msec or more during the study interval (mean 25 months). These latency increases occurred in 13 patients, as 5 patients had bilateral latency increases.*

Group II (58 eyes) — *These showed no significant latency changes during the study interval (mean 20 months).*

Group III (4 eyes) — *These showed latency reductions of 10 msec or more during the study interval (mean 20 months).*

C) **Patient Clinical Parameters and Likelihood of PSVEP Latency Increase**

Correlations between PSVEP increase of 10 msec or more and various patient clinical parameters are shown in Table 2. Eyes in patients with progressive probable MS had more PSVEP latency increases then eyes in patients with early probable MS, (Fisher exact test, $P < 0.005$). Differences between other clinical classification groups were not statistically significant. Patient age and disease duration did not significantly influence the number of eyes which showed PSVEP latency increases during the study interval. Eyes in patients with a mixed or progressive course showed more latency increases than eyes in patients with a remitting-relapsing course ($P < 0.05$, chi-square test). Likewise, patients with greater disability from MS had significantly more eyes with PSVEP latency increases than those with milder disability ($P < 0.02$, chi-square test).

D) **Previous Optic Nerve Disease and New PSVEP Latency Increases**

As shown in Table 3, remote prior clinical optic neuritis did not predispose to new PSVEP latency increases during the study interval. Likewise, PSVEP latency increases occurred with equal frequency in eyes with a normal PSVEP latency on their first test, as in eyes with a prolonged PSVEP latency on their first test.

Table 1: PSVEP Latency: day to day variability

Patient	Eye	PSVEP Latency Measurements (msec)					Maximum PSVEP Latency Variation
		Day 1	Day 2	Day 3	Day 4	Day 5	
1	Left	124	118	117	123	123	7
	Right	117	115	111	118	118	7
2	Left	150	148	147	148	145	5
	Right	137	141	138	135	139	6
3	Left	140	139	138	143	141	5
	Right	142	140	142	145	141	5

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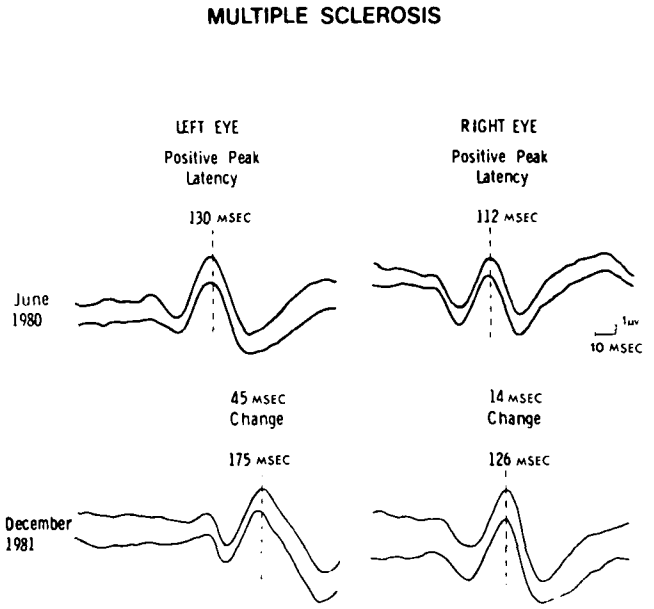

Figure 2 — Serial PSVEP studies done 18 months apart in a patient with MS. Both eyes showed a PSVEP latency increase during the study interval. Recording montage: O_z - C_z (International 10-20 system). Upward deflection is positive.

Table 2: Patient clinical features and PSVEP latency increases

		No. of Patients Studied	No. of Eyes with Latency Increases of 10 msec
Disease Classification	Clinically Definite	21	11
	Early Probable	8	0
	Progressive Probable	7	6
Patient Age (years)	Under 35	24	13
	35 and Over	16	5
Disease Duration (years)	5 Years and Under	16	8
	Over 5 years	24	10
Patient Course	Remitting - Relapsing	22	6
	Mixed and/or Progressive	18	12
Patient Disability (Kurtzke Scale)	K - 0 to K - 2	25	7
	K - 3 to K - 7	15	11

Table 3: Previous optic nerve disease and probability of PSVEP latency increases

		No. of Eyes Studied	No. of Eyes Within Latency Increases of 10 msec or more
Remote Previous Clinical Optic Neuritis Prior to First PSVEP test	No	62	16
	Yes	18	2
Initial PSVEP Latency	Normal	40	8
	Prolonged	40	10

Table 4: Increases in PSVEP latency and clinical optic neuritis during study interval

		No. of Eyes	Latency Change (msec)	
			Mean	Range
PSVEP LATENCY CHANGE of 10 msec or More	Eyes with Clinical Optic Neuritis during Study Interval	6	34	13-52
	Eyes Asymptomatic During Study Interval	12	18	11-32

E) **Bilateral PSVEP Latency Increases**

Of the 18 eyes with latency increases in our study, 10 were in pairs, occurring in five patients. These bilateral latency increases occurred more frequently than expected by chance ($P < 0.05$, by normal approximation to binomial). This suggests that active demyelination occurring in one optic nerve is associated with a greater likelihood of demyelination occurring in the opposite optic nerve either at the same time or in the near future.

F) **PSVEP Latency Increases and Clinical Symptoms of Optic Neuritis**

18 eyes in our MS patients showed a PSVEP latency increase of 10 msec or more. Of these, 6 or approximately one-third were clinically symptomatic during the study interval between tests with acute or sub-acute visual blurring and transient loss of visual acuity. The other 12 eyes with PSVEP latency increases were clinically asymptomatic. As shown in Table 4, although there was much overlap, latency increases tended to be more marked in those patients with clinical symptoms of optic neuritis during the study interval. Mean latency changes for the two groups were significantly different ($P < 0.05$. Wilcoxon rank sum test for unpaired samples).

G) **PSVEP Latency Reductions**

As seen in Figure 1, 4 eyes in patients with MS had latency reductions of 10 msec or more during the study interval. It is of interest that all four of these patients had clinical optic neuritis with onset within five weeks (range 1-5 weeks) prior to the first PSVEP test.

Discussion

The PSVEP positive peak P100 results from activation of the extrastriate visual cortex (Jeffreys and Axford, 1972b) and therefore the latency of this peak gives some indication of transmission time from retina to occipital cortex, including initial processing time in the occipital cortex.

A review of the relevant anatomy supports this concept. The human optic nerve contains approximately 1,100,000 myelinated nerve fibers (Kupfer et al., 1967) and the vast majority have a total fiber diameter (axon plus myelin sheath) of 2 microns or less (Potts et al., 1972a). These nerve fibers would be expected to conduct at a maximum rate of approximately 6 m/sec (velocity in m/sec = 3.2 x diameter in microns) (Ogden and Miller, 1966). This agrees well with physiological studies in monkeys, where measured conduction velocities in optic nerve fibers range from 1.3-20 m/sec with one large group of fibers conducting at 4 m/sec., and a second large group at 8 m/sec (Ogden and Miller, 1966).

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Our PSVEP test used a relatively small check size (27.5′ visual angle) and a total stimulus field of 16°. Most available evidence suggests that the PSVEP in response to small check size stimulation is mediated primarily by the central retina (Harter, 1970; Hennerici et al., 1977). The optic nerve fibers serving the macular area are generally of small diameter and occupy the lower end of the optic nerve fiber size spectrum (Potts et al., 1972b), and would be expected to conduct at 5 m/sec or less.

The distance taken by the visual pathways from the posterior eye globe to the occipital cortex as measured in the skull is approximately 17.5 cm. Conduction time over this distance at 5 m/sec would be 35 msec. The intra retinal optic nerve fibers conduct much more slowly at 0.5-1 m/sec (Ogden and Miller, 1966), and over a 0.5-1 cm distance would add another 10 msec to the conduction time. The time required for activation of optic nerve fibers by the retina after light stimulation is considerable, and varies with the luminance of the light stimulus (Kuffler, 1953; Gouras and Link, 1966). A 20-30 msec retinal delay would appear reasonable in the generation of the PSVEP. A cortical processing time of 25 msec or more leading up to P100 would appear likely as the earlier components of the PSVEP (65-80 msec) also have a cortical origin (Jeffreys and Axford, 1972a).

While much shorter conduction times from retina to occipital cortex have been described for flash visual evoked responses (Cracco and Cracco, 1978), the following approximate time frame appears reasonable for the events underlying the PSVEP P100 latency.

Retinal Processing	30 msec
Conduction Time:	
Intraretinal Optic Nerve Fibers	10
Optic Nerve, Tract, Radiation	35
Synaptic Processing, etc:	
Lateral Geniculate Body and Occipital Cortex	25
	100 msec

The normal PSVEP latency approximates what might be expected from known anatomical and physiological mechanisms. Known pathological processes can likewise explain the abnormally prolonged PSVEP latency commonly seen in patients with MS.

Complete demyelination of previously meylinated ventral root nerve fibers in rats slows conduction velocity, if conduction block does not occur, to approximately 2 to 5% of the normal conduction velocity expected for that fiber (Bostock and Sears, 1978). Although the resultant slowing might be somewhat less in the smaller optic nerve myelinated fiber (Waxman and Bennett, 1972) demyelination of a 1 cm segment of optic nerve could increase conduction time through that segment from 2 msec at 5 m/sec to 20 msec at 0.5 m/sec. McDonald (1977) in a study of 20 optic nerve plaques at postmortem found the average length of individual plaques to be 10.5 mm (range 3-30 mm), and calculated that slowed conduction through the demyelinated area might well account for the delayed PSVEP in MS, although other factors might also contribute. Ikuta and Zimmerman (1976) found optic nerve plaques larger than 1 cm in 79% of their 70 autopsied MS patients. Gartner (1953) found such extensive demyelination in many optic nerves in MS at autopsy that he questioned whether this demyelination had all occurred in one attack. Such large areas of demylination may account for the extremely long PSVEP latencies seen in some patients with MS.

New visual pathway demyelinating lesions, whether symptomatic or asymptomatic, could account for the new PSVEP latency increases seen in some of our patients during our study interval. A monocular increase in PSVEP latency most likely represents an optic nerve lesion, for beyond the optic chiasm visual pathways carry visual input from both eyes, and intact conduction through one optic tract and radiation is enough to produce a normal PSVEP latency upon sitmulation of either eye (Asselman et al., 1975).

Could factors other than new demyelination account for the changes in PSVEP latency observed over time in our study? Certainly changes as large as 7 msec likely are not significant, as the latency may fluctuate this much from day to day (Table 1). In our control subjects, the greatest observed variation in PSVEP latency over time was 6 msec, but Meienberg et al., (1979), using different stimulus parameters, observed variations in PSVEP latency in normal controls of up to 12 msec on serial testing. Clearly, attaching significance to PSVEP latency changes of 5 msec as some authors have done (Walsh et al., 1982) is highly questionable.

It is unlikely small fluctuations in body temperature accounted for our observed PSVEP changes. Increases in temperature do not cause conduction slowing but do tend to cause conduction block in demyelinated fibers (Rasminsky, 1973). Matthews et al. (1979) raised the oral temperature by 1° in 14 patients with MS. PSVEP latency did not change, but the amplitude fell. Persson and Sachs (1978) and Bajada et al. (1980) had similar results.

Small fluctuations in the luminance of our visual stimulus likewise are unlikely to have resulted in significant PSVEP latency changes. Cant et al. (1978) showed that changes in the luminance of the white checks in the pattern stimulus did affect the PSVEP latency, and this effect was more marked in some MS patients than in normal controls. However, these changes were most marked at quite low luminance levels, and the changes in luminance required to produce latency changes of 10 msec in even the occasional patient were quite large (20 cd/m^2). Hennerici and Wist (1982) found only small changes in PSVEP latency with substantial changes in luminance in MS patients with a checkerboard pattern stimulus.

If a PSVEP increase of 10 msec or more indicates new demyelination, then 18 of the 80 eyes in our MS patients developed detectable new lesions in visual pathways over a mean time interval of 21 months. This translates to 13% of eyes per year.

One third of these PSVEP latency increases were clinically symptomatic. Although we cannot tell from our study whether latency increases measured during symptomatic intervals occurred in one episode at the time of clinical symptoms, or whether asymptomatic increases in latency were added before or after the episode of clinical optic neuritis, mean latency increases during symptomatic intervals were significantly greater than mean latency increases occurring during asymptomatic intervals. There was considerable overlap, however, and quite severe episodes of clinical optic neuritis at times would leave only short permanent latency increases. In other patients, very long latency increases had apparently occurred asymptomatically — perhaps in a stepwise manner by the addition of multiple small increments over time. More closely spaced repetitive PSVEP tests would help define this further.

Four of our MS patient eyes showed a PSVEP latency reduction of 10 msec or more, but all of these patients had had the onset of acute clinical optic neuritis in the five weeks preceding their first PSVEP test. In three of the four eyes, PSVEP latency values returned to within normal limits. Bynke (1980) has also reported considerable normalization of PSVEP latency after actue optic neuritis.

In our study, significant latency reductions seem most unusual in patients who are clinically stable, although one would suspect they might occur if the first PSVEP test was done shortly after an asymptomatic latency increase. Whatever the factors leading to these latency reductions are, they seem operative primarily in the weeks or months following a new demyelinating lesion. Although resolution of edema and inflammation may play a part, other mechanisms may also be involved.

Remyelination has been shown to occur in the cat spinal cord and optic nerve after demyelination induced by compression or lysophosophatidyl choline injection (Harrison and McDonald, 1977; Gledhill and McDonald, 1977; Clifford-Jones et al., 1980). By two to three weeks after injury, remyelination was beginning, and by 2-3 months most nerve fibers had undergone remyelination. Central remyelination in cat spinal cord after lysophosphatidyl choline injection has also been shown to restore conduction, with recovery of conduction in some fibers beginning at two weeks (Smith et al., 1981).

Although some remyelination does appear to occur in MS (Prineas and Connell, 1979), this would appear to be limited. However, a small amount of remyelination could make a large difference to nerve conduction through a demyelinated area (Waxman and Brill, 1978).

The PSVEP may be totally absent after acute optic neuritis. Mechanisms other than remyelination might also explain the reappearance of the PSVEP after a short time interval. Even without remyelination, conduction has been shown to recover in demyelinated rat ventral nerve root six days after lysophosphatidyl choline induced demyelination. Rearrangement of sodium channels along the denuded nerve cell membrane may well be the mechanism responsible for recovery of conduction (Smith et al., 1982). Morphological evidence for reorganization of Na^+ channels after demyelination also exists (Foster et al., 1980). Mechanisms therefore exist for the restoration of conduction through a demyelinated area after an initial period of conduction block, and possibly also for some increase in conduction velocity through the damaged area over time.

The PSVEP may be reflecting some of these changes.

The PSVEP may help define the natural history of the disease. For example, only one-third of the latency increases in our patients were symptomatic. Latency increases during our study period were more common in patients with greater disability than in patients with lesser disability, and more common in patients with a mixed or progressive course than in patients with a remitting relapsing course.

Interestingly, evidence of prior optic nerve disease (previous clinical optic neuritis or prolonged PSVEP latency on initial test) did not seem to predispose to further demyelinating lesions in the same optic nerve. New latency increases occurred just as frequently in the apparently normal optic nerves. Demyelination in one optic nerve was, however, associated with demyelination in the other optic nerve of the same patient during the same study interval. The study intervals were, however, often quite long. More closely spaced PSVEP studies would be required to determine whether the demyelination was occurring simultaneously in both optic nerves. Alternatively, if one optic tract or radiation had a lesion, a second lesion in the other optic tract or radiation might result in simultaneous bilateral PSVEP latency prolongation.

Undoubtedly, carefully done studies with more closely spaced PSVEP tests involving larger numbers of patients, coupled with careful clinical correlation, will be able to tell us much about the natural history of MS. Some MS patients, however, have no measurable PSVEP positive peak, and other have poorly developed unstable peaks which vary in latency even during a single recording session. This will limit the useful information which PSVEP studies can give us. Such patients were excluded from the present study.

Although they sample only a limited part of the nervous system, the objective nature of serial PSVEP measurements in patients with well developed positive peaks might also make them useful in comparing treatment and control groups in therapeutic trials in MS.

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