Objective: To monitor the difference in conversion rates to multiple sclerosis (MS) in 46 patients with optic neuritis between patients with multifocal visual evoked potential latency delay and those with normal latency.

Design: Prospective case series.

Setting: Metropolitan neuro-ophthalmology clinic.

Participants: Forty-six patients with optic neuritis who did not have a diagnosis of MS on enrollment in the study.

Main Outcome Measures: Conversion to MS according to the McDonald criteria.

Results: Analysis revealed that only 22 subjects had multifocal visual evoked potential latency delay. Over 1 year, 36.4% of patients with optic neuritis with latency delays progressed clinically to MS compared with 0% of those with normal latencies ($P = .03, \chi^2$).

Conclusion: This may indicate that multifocal visual evoked potential latency delay can assist in predicting progression to future MS.

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Optic neuritis affects 3 in 100,000 otherwise healthy individuals aged 20 to 30 years. Using full-field conventional visual evoked potentials (cVEPs), Halliday et al. demonstrated that a diagnostic confirmation of optic neuritis (ON) could be made. The significance of ON lies with a 25% to 35% associated risk of developing multiple sclerosis (MS), and studies show that latency delays with a preserved waveform in cVEP are a hallmark of established MS. Despite much research, it has been shown that an abnormal cVEP does not provide additional prognostic information for the development of MS, nor does it alter the treatment plan in patients with a single episode of ON. On the other hand, magnetic resonance imaging (MRI) studies have shown that 31% to 82% of patients with ON and some changes on MRI scans will progress to MS within 2 years compared with only 13% to 16% with normal MRI. The McDonald criteria for the diagnosis of MS require the presence of white-matter lesions on MRI consistent with the Barkhof criteria to show dissemination in space and time or multiple clinical neurological attacks. According to these criteria, a cVEP is used to confirm MS only in those with insidious neurological progression.

The new multifocal VEP (mVEP) techniques allow for the detection of multiple individual VEP signals across the visual field up to eccentricity of 20° to 30°. It has been shown that the changes of ON are more diffuse than originally thought based on standard perimetry. The cVEP, however, is predominated by the central few degrees of vision and may not fully assess peripheral parts of the optic nerve that can provide additional prognostic information. By providing much more information than the cVEP, the mVEP may be able to bridge the gap between tests easily performed in a routine clinic and the diagnostic capabilities of MRI. Thus, the aim of this study was to determine whether there was a potential role for mVEP in MS diagnostics.

METHODS

Sixty-eight patients were enrolled. Each patient had a confirmed diagnosis of ON (unilateral visual loss, afferent papillary defect, pain on eye movement). Patients with any other ocular pathologic abnormalities were excluded. All patients had completed a 3-day course of intravenous methylprednisolone at 1 g per day and a 2-week oral taper of steroids.
To determine whether delayed mVEP latency after a diagnosis of ON could represent an increased probability of progression to MS, these patients were monitored for 1 year. A neurologist reviewed all patients without a diagnosis of MS at the time of the mVEP with repeat clinical examination and MRI scans. Patients who developed MS (according to the McDonald criteria) were recorded.

Multifocal VEP testing was performed using the Accumap (version 2.1, ObjectiVision Pty Ltd, Sydney, Australia) employing standard stimulus conditions12-16 consisting of a cortically scaled dartboard pattern with 38 segments (eccentricity up to 24°) and a central 1° fixation target. Each segment contained a 4 x 4 black-and-white grid with reversing patterns according to a pseudorandom sequence. Luminance of the white check was 146 candela (cd) per m² and luminance of the black check was 1.1 cd/m² (Michelson contrast, 99%). Usually, 8 runs (54 seconds each) achieved a good signal-to-noise ratio.

Subjects were seated 30 cm from the screen with refraction for near vision. Four gold-cup electrodes (Grass-Telefactor, WestWarick, RI) were used for bipolar recording: 2 electrodes 4 cm either side of the inion, 1 electrode 2.5 cm above, and one 4.5 cm below the inion in the midline. Electrical signals were recorded along 4 channels: as the difference superior to inferior, anterior, left to right, and obliquely between horizontal and inferior electrodes.

Visual evoked responses were amplified 1 x 10⁵ times and band-pass filtered 1 to 20 Hz. Opera software (ObjectiVision Pty Ltd) correlated the pattern reversal sequence with the electrical signals recorded, and an averaged evoked response for each segment of the stimulated visual field was obtained. For every segment, the largest peak-trough amplitude within the interval of 60 to 180 milliseconds was determined for each channel. The wave of maximal amplitude from each segment was automatically selected by the software to create a combined topographic map.12,13 Latency analysis was performed using average waveforms (amplitudes >60 nV) from the 4 sectors of the visual field that produced signals of similar morphology.13 A latency deviation z score was derived for each sector by comparison with results from 25 age-matched controls. Each patient’s z scores were averaged with a final score greater than 2 classified as latency delay. A coefficient of variation for sectoral latency z scores, as calculated by testing the same normal patients twice (with a 1-month interval), was 0.2%±1.9%. Other measures of visual function, including Snellen visual acuity, Ishihara 24-plate color vision test, and relative afferent pupillary defect, were also recorded.

Statistical analysis was performed using StatsSoft (StatsDirect, Cheshire, England). Differences between the 3 groups were tested using analysis of variance (ANOVA). To test for the significance and interaction of other confounding factors that might influence latency differences, such as age, sex, treatment, and the number of ON recurrences, a multiple linear regression analysis was performed. An equation to describe the latency z scores and confounding factors for each group was determined. On subsequent linear regressions, the factor with the least significance was removed from the equation and the effect of this alteration was analyzed. Procedures followed the tenets of the Declaration of Helsinki.

The 68 subjects with ON were classified according to the McDonald criteria as either “not MS” (17 subjects), “possible MS” (29 subjects), or “MS” (22 subjects). The mean time from onset of ON to testing in each group was 12 months (range, 15 days to 4 years). There was no statistically significant difference between the ages or sexes of the patient groups (P=.5, ANOVA).

Of the other routine visual tests, latency delay was only associated with a better visual acuity at the time of testing (P=.007, ANOVA). The mean latency z score for patients with vision of 20/40 (6/12) or better was 3.9 (95% confidence interval, 1.4-3.2) for those with worse vision.

The quantitative analysis of the latency deviation for each group, based on the sectoral mVEP waveforms, revealed a statistically significant difference in the latency z scores between each group (P<.001, ANOVA). All 22 patients with definite MS demonstrated significant latency delay (average±SD z score, 5.8±1.0; range, 3.9-7.6). All patients classified as not MS had normal latency (average±SD z scores, 0.5±0.6; range, −0.7 to 1.6). The patients classified as possible MS were shown to have a bimodal distribution of latency results: some (7 patients) had no latency delay, similar to the normal controls and not-MS patients, whereas others (22 patients) had long latency delays, similar to those with MS (Figure 2).

To test for the significance and interaction of other confounding factors that might influence latency differences, such as age, sex, treatment, and the number of ON recurrences, a multiple linear regression analysis was performed. There was no significance or interaction due to any of the confounding factors (P=.01; F=167; r²=0.86, multiple linear regression). Following the removal of confounding factors, the Kruskal-Wallis test and post hoc analyses were repeated. This demonstrated that all groups were still significantly different from each other (P<.01, respectively).

Over 1 year, 8 patients from the possible-MS group progressed to definite MS. All 8 patients had latency delay on initial mVEP testing. Thus, 36.4% of those with mVEP latency delays progressed to MS, whereas none with normal latency from the same group progressed. This difference in conversion rates was statistically significant (P=.03, χ²). None of the patients in the not-MS group converted to MS.
Basic statistical analysis does not reveal any significant difference within the possible-MS group between these 8 patients and the remaining 21 based on age, sex, or time from onset of ON ($P/H_11022$ ANOVA). However, numbers are too small for robust analysis. Longer follow-up and larger patient numbers are required to determine if these results are consistent over time.

**COMMENT**

Because MS is typically diagnosed in the third and fourth decades of patients’ lives, it results in significant functional and work-related disability in what should be the most productive years. The 10-year data from the Optic Neuritis Treatment Trial has shown that the overall risk for MS following ON is 38%, but that this increases to a 56% risk in those with 1 or more typical lesions on the baseline MRI (possible MS). However, numbers are too small for robust analysis. Longer follow-up and larger patient numbers are required to determine if these results are consistent over time.

![Figure 2. Sectoral traces are derived from averaged multifocal visual evoked potential (mVEP) waveforms corresponding to areas of the visual field with VEPs of a similar morphology. A, Visual field color coded and showing sectors. Red indicates upper horizontal; green, upper vertical; blue, lower horizontal; pink, lower vertical. B, Sectoral traces for a normal patient. C, Sectoral traces for a patient with optic neuritis (ON) with magnetic resonance imaging (MRI) abnormalities suggestive of demyelination but not diagnostic for multiple sclerosis with normal sectoral latency values. D, Sectoral traces for a patient with ON with MRI abnormalities suggestive of demyelination but not diagnostic for multiple sclerosis with delayed sectoral latency values. E, Sectoral latency values for each sample patient in milliseconds.](https://www.archneurol.com/)

![Figure 2](https://www.archneurol.com/)

Stringent MRI criteria for eligibility as set out by Barkhof (9 or more white-matter lesions with at least 1 gadolinium-enhancing lesion), the treatment with interferon conferred a 66% reduction in risk for MS over 3 years. Thus, to better target this treatment, clinicians need to be able to distinguish those patients at the highest risk of future MS from all those who presented with ON and MRI changes.

Studies using the MRI evidence of dissemination of lesions in space and time, as set out in the McDonald criteria, have shown that the new McDonald criteria lead to more than double the number of patients with a diagnosis of MS at 1 year compared with the use of the Poser criteria. In addition, the American Academy of Neurology guidelines on MRI report that once alternative diagnoses are excluded at baseline, the finding of 3 or more white-matter lesions on T2-weighted MRI is a sensitive predictor ($>80\%$) of the subsequent development of MS. This pilot study in patients with ON suggests for those patients with abnormal MRI findings (who still do not fulfill the McDonald criteria for a diagnosis of MS) that a sectoral latency delay on mVEP may correlate to an increased rate of progression to MS over the following year compared with the patients with normal mVEP latencies. However, the authors do acknowledge that even in...
patients diagnosed as not MS with normal MRI scans, there is still a small risk of MS.\(^1\)

The potential for earlier recognition of those more likely to develop MS from patients with an initial MRI scan suggests but not diagnostic for MS would allow clinicians to closely monitor this subset of patients with a view to more targeted prescription of interferon beta-1a. This finding represents a new development in the diagnosis of MS because mVEP is noninvasive and inexpensive and can be performed as part of a routine examination.

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Correspondence: Clare Fraser, MBBS, Department of Electrophysiology, Save Sight Institute, Sydney Eye Hospital Campus, 8 Macquarie St, Sydney, NSW 2000, Australia (manuscript@clarefraser.com).

Author Contributions: Study concept and design: Fraser, Klistorner, Graham, Billson, and Grigg. Acquisition of data: Fraser, Garrick, and Grigg. Analysis and interpretation of data: Fraser, Klistorner, Garrick, and Grigg. Drafting of the manuscript: Fraser. Critical revision of the manuscript for important intellectual content: Klistorner, Graham, Garrick, Billson, and Grigg. Administrative, technical, and material support: Klistorner and Grigg. Study supervision: Graham, Garrick, Billson, and Grigg.

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REFERENCES