The role of evoked potential and MR imaging in assessing multiple sclerosis: a comparative study

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ABSTRACT

Introduction: The role of evoked potential (EP) in evaluating multiple sclerosis (MS) has changed with the advent of magnetic resonance (MR) imaging. Given the possibly varied nature and distribution of pathologic lesions in Asian MS, this study compared the diagnostic usefulness of EPs to that of MR imaging among Chinese subjects.

Methods: This was a retrospective study of MS patients treated at the Kwong Wah Hospital, Hong Kong, between June 2004 and June 2009. The visual (VEPs), brainstem auditory (BAEPs), somatosensory (SEPs) and trigeminal (TSEPs) EPs were compared with MR imaging for correlation and usefulness using the chi-square test. Sensitivities and specificities were calculated.

Results: The results showed that abnormalities were detected in the three modalities of EP among the 17 patients studied (VEP 82 percent, median and tibial SEP 65 percent, BAEP 47 percent). Compared with MR imaging, VEP was far more useful at detecting optic nerve lesions, while SEP was less sensitive at detecting cord lesions. BAEP was able to localise lesions along the auditory pathways at a rate that was almost similar to that of MR imaging (non-inferiority). Both TSEP and MR imaging for trigeminal nerves were negative in the two patients with trigeminal neuralgia. In some instances, EPs yielded abnormalities that were undetected by conventional MR imaging, and the sensitivity increased with the number of EP modalities.

Conclusion: EP may be considered in clinical situations in which MR imaging is negative or cannot be performed. They may also be performed when evaluating treatment response, long-term prognosis and nonspecific changes on MR imaging.

Keywords: Chinese, comparative study, evoked potentials, MR imaging, multiple sclerosis

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Table I. Distribution of MR imaging lesions among the 17 patients with MS or possible MS.

MR imaging finding	No. (%)
1 Gd-enhancing lesion or 9 T2 hyperintense lesions if no Gd-enhancing lesion	15 (88)
≥ 1 infratentorial lesions	8 (47)
≥ 1 juxtacortical lesions	13 (76)
≥ 3 periventricular lesions	15 (88)
Cord lesions	17(100)
Optic nerve lesions	1 (6)

MR: magnetic resonance; MS: multiple sclerosis; Gd: gadolinium

INTRODUCTION

In multiple sclerosis (MS), it is essential to find a surrogate marker that is linked to the underlying disease process, in order to ensure a more rational approach to assessing therapy apart from clinical assessment.[1] The role of evoked potential (EP) in the evaluation of MS has changed over the last decade, largely due to advancements in imaging techniques. Magnetic resonance (MR) imaging can provide useful information for dissemination in time and space, although the nature of the lesions visualised is not specific to MS but rather, reflects changes in the water content and gliosis of tissue. Similarly, the abnormalities detected with EPs may appear sufficiently characteristic to be reliable, if not specific, for diagnosing the disease. EPs are still useful in locating clinical evidence of lesions of the central nervous system (CNS).

The prevalence rate of MS in Asian populations is significantly lower than in Caucasian populations.[2,3] Opticospinal MS and neuromyelitis optica are common among Asians with demyelinating disorders.[4-7] Some studies have suggested that there are recognisable differences in pattern between Asian and Western MS patients;[8] severe spinal cord involvement is even regarded as a universal feature of Asians with MS.[9] Given the possibly varied nature and distribution of pathologic lesions in Asian MS, it is timely to evaluate the value of EPs in Asian MS.[10-13] This study evaluated the diagnostic usefulness of commonly used EPs, namely visual (VEP), brainstem auditory (BAEP),

Table II. Correlation of the VEP abnormalities with optic nerve abnormalities on MR imaging.

Correlation	No. (%)
Abnormal MR imaging of orbits; VEP	1 (6)
Abnormal MR imaging of orbits; normal VEP	0 (0)
Abnormal VEP; normal MR imaging of orbits	13 (76)
Normal MR imaging of orbits; VEP	3 (18)

$X^2 = 20.16$, df = 1, $p < 0.01$
VEP: visual evoked potential; MR: magnetic resonance

Table III. The BAEP patterns of the eight patients with MS.

BAEP pattern	No. (%)
Absence of all waves	0 (0.0)
Increased I–III IPL	2 (25.0)
Increased III–V IPL; decreased IV/V amplitude	5 (62.5)
Increased I–III IPL, III–V IPL, I–V IPL	1 (12.5)

BAEP: brainstem auditory evoked potential; MS: multiple sclerosis; IPL: interpeak latency

somatosensory (SEP) and trigeminal (TEP) EPs, in comparison with that of MR imaging.

METHODS

A total of 17 Chinese patients with MS or possible MS treated at the Kwong Wah Hospital, Hong Kong, between June 2004 and June 2009 were included in the study. Out of these, 15 were women (mean age 33.9 [range 17–57] years) and two were men (mean age 35 [range 29–41] years). MR imaging using Achieva XR, magnet field strength 1.5 Tesla (Philips, Eindhoven, North Brabant, The Netherlands) was performed for all the patients, and the findings contributed to the diagnosis and determination of lesion dissemination. The MR imaging sequences included proton density and T2 spin echo in addition to fluid-attenuated inversion recovery (FLAIR) for the identification of hyperintense lesions and gadolinium-enhanced T1 imaging. In order to increase the specificity of MR imaging interpretation, the findings were classified according to the revised diagnostic criteria for MS.[14] Supportive investigations including cerebrospinal fluid (CSF) analysis and VEPs were performed as an additional requirement for making a diagnosis. In addition, BAEPs and SEPs were performed as they may help to obtain a better understanding of abnormalities in demyelination. The neurologists who reported the EP findings were blinded to the MR imaging findings and the definite diagnosis, although brief clinical summaries were usually provided on the request forms.

The VEPs were obtained by monocular checkerboard pattern reversal stimulation.[15] Recording electrodes were placed at Oz and Fz, and the bandpass was 1–100 Hz. The SEPs were elicited by stimulating the median and posterior tibial nerves at the wrist and ankle, respectively. Single stimulation was employed. The responses were recorded using bipolar-cephalic montages, with electrodes placed at C3' and C4' referred to Fpz for median nerve stimulation, and at Cz referred to Fpz for tibial nerve stimulation. BAEPs were obtained by click delivering as the stimulus, with recording electrodes placed at A1/2-Cz. The time-base was 10 ms. Potentials were classified as abnormal if they were absent, and the latencies were measured following the identification of their morphology. All the EPs were performed using a VikingSelect System (NeuWake Medical Solutions, Madison, WI, USA).

The abnormal findings obtained from MR imaging and VEPs, BAEPs and SEPs were compared for their association and usefulness using the chi-square test. A p-value < 0.01 was considered to be statistically significant. Sensitivity and specificity were calculated for the three modalities of EP and for oligoclonal bands positivity in the CSF analysis.

RESULTS

The classified MR imaging abnormalities found in the 17 patients are listed in Table I. A total of 14 (82%) patients had either an absence of VEP or prolonged P100 latency, (mean 133.7 [range 112–188.5] ms). The amplitude of the visual evoked responses for prolonged P100 latencies was 1.7–12.9 uV, with a mean of 6.2 uV. MR imaging detected an optic nerve lesion in only one (6%) patient. The analysis showed that the detection of optic neuritis was test dependent ($X^2 = 20.16$, df = 1, $p < 0.01$), and that VEP was far more sensitive than MR imaging at detecting abnormalities (Table II).

The BAEP abnormalities detected are listed in Table III. MR imaging detected abnormalities in seven (41%) patients (Table IV). Hence, MR imaging and BAEP were equally useful at detecting brainstem abnormalities ($X^2 = 0.119$, df = 1, $p > 0.1$). Tibial SEP was abnormal in 11 (65%) patients, and median SEP in seven (41%) patients. Hence, abnormalities in either the tibial or median SEP, or both, were present in 11 (65%) patients. The abnormalities consisted of prolonged latency, reduced amplitude, altered morphology and an absence of response. Combined abnormalities were common occurrences. There

Table IV. The correlation of BAEP abnormalities with brainstem abnormalities on MR imaging.

	No. (%)
Abnormal MR imaging of brainstem; BAEP	5 (29)
Abnormal MR imaging of brainstem; normal BAEP	2 (12)
Abnormal BAEP; normal MR imaging of brainstem	3 (18)
Normal MR imaging of brainstem; BAEP	7 (41)

$X^2 = 0.119$, df = 1, $p > 0.1$
BAEP: brainstem auditory evoked potential; MR: magnetic resonance

Table V. Correlation of the median and tibial SEP abnormalities with MR imaging abnormalities.

	No. (%)
Abnormal MR imaging; SEP	11 (65)
Abnormal MR imaging; normal SEP	6 (35)
Abnormal SEP; normal MR imaging	0 (0)
Normal MR imaging; SEP	0 (0)

$X^2 = 7.29$, df = 1, $p < 0.01$
SEP: somatosensory evoked potential; MR: magnetic resonance

was a 24% higher incidence of SEP abnormalities found upon testing the lower limbs in comparison to the upper limbs, probably due to the greater length of white matter traversed and the larger extent of neuraxis screened.

MR imaging detected cord lesions in all the 17 patients. The detection of spinal cord abnormalities was test dependent (Table V); MR imaging was more sensitive and useful than SEP for this purpose ($X^2 = 7.29$, df = 1, $p < 0.01$). The pathways studied were not very well defined, as the patients presented with incomplete mixed motor and sensory abnormalities. 13 (76%) patients had abnormal VEP amid normal orbits and optic nerves with MR imaging, and three (18%) had abnormal BAEP amid normal brainstem with MR imaging (Table VI). Two MS patients had trigeminal neuralgia, but their trigeminal SEPs and MR imaging of trigeminal nerves were normal. Neuromyelitis optica-IgG (NMO IgG) was found to be negative in all the patients. Oligoclonal bands were positive in CSF analysis in ten (59%) patients.

The sensitivity and specificity of the tests were in the following order: VEP (sensitivity 100%, specificity 100%), BAEP (sensitivity 80%, specificity 100%), SEP (sensitivity 64.7%), oligoclonal band (sensitivity 58.8%). Of the 17 MS patients, one had an optic nerve abnormality detected by both MR imaging and VEP, five had brainstem abnormalities detected by both MR imaging and BAEP, and 11 had cord lesions detected by both MR imaging and SEP. In evaluating the correlation of EP measures with MR imaging abnormalities (Table VII), the analysis did not uncover the superiority of any particular EP ($X^2 = 0.593$, df = 2, $p = 0.7433$).

DISCUSSION

Abnormalities were detected with the three modalities of EP (82% with VEP, 65% with median and tibial SEP, 47% with BAEP). Interestingly, this occurred more often at the visual pathways, making VEP far more sensitive (i.e. superior) than MR imaging at detecting optic neuritis. Clinically silent lesions were also more readily detected with VEP than with MR imaging. Therefore, VEP may help provide evidence of a second lesion in MS patients and in patients with suspected myelopathy secondary to demyelinating disease.

BAEP localises lesions along the auditory pathway, and the BAEP abnormalities in MS are either unilateral or bilateral.[15] Increased I wave latency is seen when the most distal portion of the acoustic nerve is affected. Increased I–III interpeak latency indicates a defect in the pathway from the proximal eighth nerve into the inferior pons. Increased III–V interpeak latency indicates a defect in conduction between the caudal pons and the midbrain. Increased I–III and III–V interpeak latency signifies that the lesion is affecting both the brainstem above the caudal pons and either the caudal pons or the acoustic nerve. In this study, BAEP localised lesions along the auditory pathways at a similar rate to that of MR imaging, but it could not differentiate multifocal lesions as in MR imaging. For evaluating cord lesions, SEP was clearly less sensitive (i.e. inferior) than MR imaging. This occurred despite the fact that the spinal pathway is longer and is expected to be involved more frequently if lesions are randomly distributed throughout the neuraxis, and central conduction times may be prolonged with brainstem lesions of the lemniscal pathway and thalamocortical radiations. Furthermore, SEP is not very sensitive to small cord lesions. As long as there are sufficient centrally conducting fast fibres, the onset of response will still be normal.

It was noted that there were circumstances in which the EPs were abnormal despite obtaining normal MR images for the relevant regions. This made up 76% of the patients in the VEP group and 18% of those in the BAEP group (Table VI). This finding may have significant implications on the choice of the proper test for investigation, since MR imaging was not shown to

Table VI. Normal MR imaging but abnormal EPs of the related regions among the 17 MS patients.

	No. (%)
Abnormal VEP; normal MR imaging of orbits	13 (76)
Abnormal BAEP; normal MR imaging of brainstem	3 (18)
Abnormal Median and tibial SEP; normal MR imaging	0 (0)

MR imaging: magnetic resonance imaging; EP: evoked potential; MS: multiple sclerosis; VEP: visual evoked potential; BAEP: brainstem auditory evoked potential; SEP: somatosensory evoked potential

Table VII. Correlation between MR imaging abnormalities and abnormalities of VEP, BAEP and SEP.

	No. (expected counts)			Total
	VEP	BAEP	SEP	
Abnormal MR + abnormal EP	1 (0.68)	5 (4.76)	11 (11.56)	17
Abnormal MR + normal EP	0 (0.32)	2 (2.24)	6 (5.44)	8
Total	1	7	17	25

$X^2 = 0.593$, df = 2, p = 0.7433

MR; magnetic resonance; EP: evoked potential; MS: multiple sclerosis; VEP: visual evoked potential; BAEP: brainstem auditory evoked potential; SEP: somatosensory evoked potential

be able to replace EPs completely in the assessment. With regard to how often the tests would be positive in detecting abnormalities, the following sensitivities have been noted: VEP 100%, BAEP 80%, SEP 64.7% and oligoclonical band in CSF analysis 58.8%. In terms of the ability of both EP and MR imaging to detect abnormalities, SEP has the highest yield, with 11 out of 17 (65.7%) patients identified, followed by BAEP and VEP, which identified five out of 17 (29.5%) and one out of 17 (5.9%) patients, respectively.

Conventional MR imaging, which measures alterations in tissue water content and dynamics by proton excitation, is used for diagnosing MS, for excluding other pathologies such as neoplasms and malformations, for detecting disease activity, prognostication and CNS atrophy, as well as for assessing the effectiveness of therapies. While proton density, T2 and FLAIR sequences are extremely sensitive in detecting MS lesions,[16] advanced imaging techniques can detect pathologic changes occurring in CNS that are not visible on conventional MR images. Diffusion tensor tractography is a recently developed technique that enables the assessment of the magnitude and directionality of water diffusion in tissue (i.e. anisotropy).[17] MR spectroscopy, which investigates proton-containing metabolites such as N-acetylaspartate and myoinositol, can be used to study their concentration levels in CNS lesions.[18] Functional MR imaging enables the study of neuronal mechanisms from changes in blood oxygenation levels as a result of neuronal activation.[19]

Nonetheless, both conventional and nonconventional MR imaging are not without their problems. They may be unavailable or unable to be performed, and further, maynot address certain unresolved issues such as the definition of the actual features underlying diffusion changes in MS. There are limitations to MR imaging in monitoring treatment response in view of the existence of a poor correlation between clinical status and MR imaging measures. The long-term prognostic value of MR imaging has yet to be proven. Thus, a clinician may wish to relate nonspecific changes on MR imaging with EP abnormalities, and evaluate the long-term prognosis through the additional use of EPs. One significant problem with correlating between MR imaging and EPs in this study was the unconfirmed specificity of the lesions. Effort was made to exclude connective tissue disease, NMO, syphilis, Lyme's disease, the human immunodeficiency virus, human T-cell lymphotropic virus type 1 and other viruses. The number of patients in the project was small as the prevalence rate of MS in the population is low. A large patient sample size is desirable to improve the effect size of the correlation. Measures were taken to restrict the analysis to objective EP measures such as the latencies of clearly defined components, and to avoid the transformation of continuous evoked potential data to ordinal data.

In conclusion, the importance of EPs has declined with the advent of MR imaging. However, MR imaging and EPs are complementary techniques for the detection of MS lesions. Statistical analysis of our findings did not show the superiority of any particular modality of EP when correlating the EP measures with MR imaging abnormalities. In the evaluation of MS, the choice depends on the clinical circumstance. VEP was far more sensitive than MR imaging at detecting optic neuritis, while SEP was less useful than MR imaging in evaluating myelitis. On the other hand, MR imaging and BAEP were somewhat equally sensitive at detecting brainstem abnormalities. The EPs were similar to MR imaging in that they yielded clinically undetected lesions in patients who were referred for suspected MS, and the sensitivity increased with the number of EP modalities. EPs should therefore be indicated where MR imaging is negative or cannot be performed. As there are still unresolved issues with regard to MR imaging, including the definition of

the actual features underlying diffusion changes, EPs are the electrophysiological tools that should be considered in the evaluation of nonspecific changes on MR images, treatment effectiveness and long-term prognosis.

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