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Evoked potentials are useful for diagnosis of neuromyelitis optica spectrum disorder

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ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) has been differentiated from relapsing-remitting multiple sclerosis (RRMS) by clinical, laboratory, and pathological findings, including the presence of the anti-aquaporin 4 antibody. Measurement of evoked potentials (EPs) is often used for the diagnosis of RRMS, although the possibility of applying EPs to the diagnosis of NMOSD has not been investigated in detail. Eighteen patients with NMOSD and 28 patients with RRMS were included in this study. The patients' neurological symptoms and signs were examined and their EPs were recorded. Characteristic findings were absence of visual evoked potentials and absence of motor evoked potentials in the lower extremities in patients with NMOSD, and a delay in these potentials in patients with RRMS. Most patients with NMOSD did not present abnormal subclinical EPs, whereas many patients with RRMS did. None of the patients with NMOSD showed abnormalities in auditory brainstem responses. NMOSD can be differentiated from RRMS by EP data obtained in the early stages of these diseases.

1. Introduction

Neuromyelitis optica (NMO) is an autoimmune inflammatory and necrotizing disease that chiefly affects the optic nerve and spinal cord, and, in past years, has been challenging to differentiate from multiple sclerosis (MS), an autoimmune inflammatory, demyelinating disease of the central nervous system. At present, NMO is recognized as an unquestionably different disease entity from MS, as a result of the identification of its specific association with the anti-aquaporin 4 antibody (AQP4-Ab) [1,2]. On the other hand, the identification of AQP4-Ab has broadened the clinical concept of NMO to the concept of NMO-spectrum disorders (NMOSD), which includes not only optic neuritis and transverse myelitis, but also brainstem syndromes such as intractable hiccups and nausea, hypothalamic syndrome, and brain lesions [3]. In addition, it has been recognized that not all patients with NMOSD have serum AQP4-Ab and certain patients with NMOSD show clinical symptoms and MRI features that are hard to differentiate from MS [4,5]. These points suggest a need for additional diagnostic tools other than AQP4-Ab and MRI by which to more rationally differentiate NMOSD from MS, because these two diseases demand different therapeutic approaches.

The clinical utility of evoked potential recordings (EPs) has already been established for MS [6–8], in which EPs can detect clinically silent lesions in visual, auditory, sensory, and motor pathways [9]. In particular, the abnormal visual evoked potentials (VEP) were a key criterion in the McDonald diagnostic criteria for MS [10]. In addition, several studies have suggested a prognostic value for EPs in MS and an association between EP abnormality and the level of clinical disability [9,11,12]. On the other hand, there have been few reports on EPs in patients with NMO [13,14]. Therefore, in this study, we identified the characteristic features of EPs in patients with NMOSD, and compared them with those of MS to elucidate whether EP analysis adds diagnostic value for differentiating between NMOSD and MS.

2. Materials and methods

2.1. Patients

In this study, we analyzed 44 patients with MS and 27 patients with AQP4-Ab-positive NMOSD, including both classic NMO and limited

Abbreviations: NMOSD, Neuromyelitis optica spectrum disorder; MS, Multiple sclerosis; RRMS, Relapsing-remitting multiple sclerosis; SPMS, Secondarily progressive multiple sclerosis; PPMS, Primary progressive multiple sclerosis; EP, Evoked potential; AQP4-Ab, Anti-aquaporin 4 antibody; EDSS, Expanded disability status scale; VEP, Visual evoked potential; ABR, Auditory brainstem response;; SEP, Somatosensory evoked potential; MEP, Motor evoked potential; UE, Upper extremity; LE, Lower extremity; CSCT, Central sensory conduction time; TMS, Transcranial magnetic stimulation; CMCT, Central motor conduction time; MRI, Magnetic resonance imaging.

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forms of NMO, such as optic neuritis and acute transverse myelitis. Using the McDonald criteria [15], the 44 patients with MS were classified into 34 patients with relapsing-remitting (RR) MS, 5 patients with secondarily progressive (SP) MS, and 5 patients with primary progressive (PP) MS. All patients with MS were AQP4-Ab negative. The patients with SPMS and PPMS were excluded from further analysis. All of the patients with NMOSD were AQP4-Ab positive and fulfilled the diagnostic criteria for NMOSD [3]. Three patients with NMO and 6 patients with RRMS were excluded from the study because more than 5 years had elapsed since their time of onset, and 1 patient with NMOSD was excluded owing to severe spondylotic cervical radiculomyelopathy. The final numbers of patients analyzed were 23 with NMOSD and 28 with RRMS. We examined the initial neurological symptoms of all the patients, and their disability was evaluated with the expanded disability status scale (EDSS) [16]. All the patients underwent neuroimaging and EP testing at the initial medical examination. No ethical approval was obtained because this study did not involve a prospective evaluation.

2.2. Visual evoked potentials

VEPs to black and white pattern-reversal stimuli were recorded at the Oz electrode with reference to the Fz electrode. P100 latencies were measured. VEPs were recorded in 46 eyes of 23 patients with NMOSD and in 48 eyes of 24 patients with RRMS.

2.3. Auditory brainstem responses (ABRs)

ABRs to clicks were recorded in the Cz electrode with reference to the ipsilateral and contralateral ears. The latencies of the main peaks (I, III, and V) and the inter-peak latencies (I–III, III–V, and I–V) were measured. ABRs were examined in 34 ears of 17 patients with NMOSD and in 46 ears of 23 patients with RRMS.

2.4. Somatosensory evoked potentials (SEPs)

Electrodes for recording the SEPs of the upper extremities (UEs) were placed on 3 points: Erb's point, the seventh cervical vertebra, and the postcentral scalp. The reference electrode for Erb's point was placed collaterally to Erb's point. Fz was used as the reference for the other two points. Electrodes for recording the SEPs of the lower extremities (LEs) were placed on the twelfth thoracic vertebra and the central scalp. The reference electrodes were placed on the superior border of the iliac crest and Fz. The UE and LE SEPs were obtained by electrical stimulation of the median nerve at the wrist and the tibial nerve at the ankle, respectively. Peak latencies were measured as N9 (at Erb's point), N13 (at C7) and N20 (over sensory cortex) in the UE tests and as N20 (at Th12) and P37 (over sensory cortex) in the LE tests. The central sensory conduction time (CSCT) was calculated by subtracting the cervical (N13) and lumbar (N20) latencies from the cortical (N20 and P37) latencies, to give the CSCTs for the UEs and LEs, respectively. UE SEPs were examined in 46 limbs of 23 patients with NMOSD and in 56 limbs of 28 patients with RRMS. Similarly, LE SEPs were examined in 44 limbs of 22 patients with NMOSD and in 54 limbs of 27 patients with RRMS.

2.5. Motor evoked potentials (MEP)

The UE and LE MEPs were recorded from the abductor pollicis brevis and abductor hallucis muscles, respectively, after transcranial magnetic stimulation (TMS) of the contralateral motor cortex using a plane, figure-of-eight coil. The intensity of the TMS was set 10% above the MEP threshold in the resting condition. The central motor conduction time (CMCT) was calculated using the formula shown below, based on the F wave.

$$CMCT = MEP\ latency - (M\text{-}wave\ latency + F\text{-}wave\ latency - 1)/2$$

UE and LE MEPs were examined in 28 limbs of 14 patients with NMOSD and in 36 limbs of 18 patients with RRMS. The upper normal limits (means + 3 × SD) of the EP modalities were as follows: P100 of VEP, 121.0 ms; latency of the main peaks (I, III, and V) and the inter-peak latencies (I–III, III–V, and I–V) of ABR, 1.79, 4.13, 5.92, 2.4, 2.2, and 4.5 ms, respectively; CSCT of the median nerve, 7.33 ms; CSCT of the tibial nerve, 21.83 ms; CMCT of the UE MEP, 6.5 ms; and CMCT of the LE MEP, 13.5 ms.

2.6. Statistical analysis

The age of onset, disease duration, EDSS score at diagnosis, and CSF findings were compared between patients with NMOSD and patients with RRMS using the *t*-test. The initial symptoms and the rate of agreement of clinical symptoms with the EP findings were compared between groups using the Fisher exact test. Residual analysis was performed on any EP findings that showed significant intergroup differences by the Fisher exact test. A *P*-value of <0.05 was considered to indicate a significant difference between the two groups.

3. Results

The clinical characteristics of the patients with NMOSD and RRMS are summarized in Table 1. The mean age at onset of the patients with NMOSD was 51.7 years, which was older than that of the patients with RRMS ($P < 0.001$). The ratio of female patients with NMOSD was higher than that with RRMS ($P = 0.044$). The main initial symptoms of both patients with NMOSD and with RRMS were sensory disturbances. The prevalence of visual disturbance and bladder dysfunction was higher in the NMOSD group. Hiccups and bladder dysfunction were found only in patients with NMOSD. Other symptoms did not differ between patients with NMOSD and those with RRMS. The periods from onset to diagnosis were similar between the two groups. However, the mean EDSS score at the first examination of the NMOSD group was higher than that of patients with RRMS ($P > 0.001$). Patients with RRMS had EDSS scores ranging from 1 to 3 at the examination of EPs, whereas patients with NMOSD showed variable clinical symptoms, with EDSS scores ranging from 2 to 8 at the examination of EPs. Analysis of the CSF of the patients demonstrated the presence of the oligoclonal band in 65.2% of patients with RRMS, but only 3 patients with NMOSD were positive for it ($P = 0.002$). Patients with NMOSD who had severe muscle

Table 1
Clinical features and laboratory data of patients with NMOSD and of patients with RRMS.

	NMOSD	RRMS	*P*-value
Number of patients	23	28	
Age at onset[a]	51.7 ± 13.8	29.8 ± 8.9	<0.001**
Sex (men/women)	2/21	10/18	0.044*
Disease duration (months)[a]	10.7 ± 14.2	13.8 ± 17.0	0.48
Initial symptoms			
Visual disturbance	10 (43.5%)	4 (14.3%)	0.029*
Diplopia	1 (4.3%)	6 (21.4%)	0.112
Dysarthria and dysphagia	1 (4.3%)	1 (3.6%)	1.0
Hiccups and nausea	3 (13.0%)	0 (0)	0.085
Hearing difficulty	0 (0)	2 (7.1%)	1.0
Facial nerve palsy	1 (4.3%)	3 (10.7%)	0.617
Muscle weakness	7 (30.4%)	2 (7.1%)	0.061
Sensory disturbance	8 (34.0%)	15 (53.6%)	0.093
Bladder dysfunction	4 (17.4%)	0 (0)	0.035*
EDSS score at diagnosis[a]	4.0 ± 2.2	2.1 ± 0.9	<0.001**
CSF WBC (/mm^3)[a]	24.3 ± 58.7	4.7 ± 5.5	0.098
CSF protein (mg/dL)[a]	50.5 ± 27.8	38.9 ± 21.7	0.113
CSF oligoclonal band	3/20 (15.0%)	15/23 (65.2%)	0.002**

NMOSD, neuromyelitis optica spectrum disorder; RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status scale; CSF, cerebrospinal fluid; WBC, white blood cell.
[a] Mean ± SD.
* $P < 0.05$.
** $P < 0.01$.