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SHORT COMMUNICATION

Brainstem reflexes in neuro-Behçet disease

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Summary We hypothesized that brainstem responses may allow detection of functional brainstem changes in patients with neuro-Behçet Disease (NBD). Thus, we recorded electrically-induced blink reflex (eBR), auditory blink reflex (aBR) and electrically-induced masseter inhibitory reflex (eMIR) in 16 patients with NBD. However, these neurophysiological tests proved to have a poor overall sensitivity compared to neuroimaging for the diagnosis of brainstem lesions. They also showed low sensitivity for the differential diagnosis of focal pontine lesion versus diffuse brainstem disease in NBD.

Introduction

Behçet disease is a multisystem, inflammatory disorder. In the central nervous system, neuro-Behçet disease (NBD) most frequently involves brainstem and diencephalon [4,11]. Although brain magnetic resonance imaging (MRI) is strongly diagnostic, brainstem responses may provide an alternative way to monitor functional changes in the brainstem [6]. For example, increased gain of the vestibulo-ocular reflex in darkness was suggested to show a latent brainstem abnormality in NBD [13]. Another study showed that brainstem auditory evoked potentials with MRI were useful in detecting the presence and assessing the degree of neurological involvement in patients with NBD [9].

Brainstem reflexes are neurophysiological tools to assess brainstem functions [1]. Blink reflex (BR) elicited by electrical stimulation of trigeminal nerve (eBR) [1,5,10] or by sound (auditory BR, ABR) [7] and masseter inhibitory reflex (eMIR) by electrical stimulation of mentalis nerve [1,2] have generators in the brainstem. Disorders associated with facial and trigeminal nerves as well as pontine and medullary lesions may affect BR responses [5]. A possible reflex pathway of the ABR includes the ventral cochlear nucleus, the superior olivary complex, the lateral lemniscus nuclei, and the caudal colliculus [3]. The masseter inhibitory reflex (eMIR) consists of two phases of suppression (suppression period 1 and 2; SP1 and SP2). The SP1 response, which is more sensitive, is mediated by the ipsilateral trigemi-

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nal nucleus through a mono- or oligosynaptic circuit. The SP2 response is elicited by a more caudally located polysynaptic chain of interneurons [1,2]. In this study, we aimed to investigate the functional changes in brainstem using eBR, ABR, and eMIR in NBD patients with radiologically confirmed brainstem lesions and to compare the results based on groups with lesions at different brainstem levels.

Methods

Patients

We enrolled 16 consecutive patients with NBD and an MRI-documented brainstem lesion without a supratentorial or extraparenchymal lesion. The diagnosis of NBD was based on consensus criteria [4]. All participants gave informed consent and the local ethics committee approved the study protocol.

Clinical assessment

The following data were recorded for each subject: age, gender, MRI findings and neurological examination findings at the time of electrophysiological examination, duration till last follow-up, last available outcome (stabilized clinical condition vs. progressive neurological involvement), and medications used at last follow-up.

Electrophysiological assessment

Electrophysiological recordings were performed using Ag-AgCl cutaneous EMG recording electrodes (Neuropack Σ-MEB-5504 K, Nihon Kohden Corporation, Tokyo, Japan) according to standard techniques [1].

Electrically-induced blink reflex

Surface electrodes were placed bilaterally on orbicularis oculi (O.oc) muscles. The ground electrode was on the forehead. The supraorbital nerve was randomly stimulated where it exited from the supraorbital foramen using an electrical square wave pulse with a duration of 0.2 ms. The stimulus intensity was five times R1 threshold.

Auditory Blink Reflex

Electrode placement was the same as in the recording of eBR. The 105 dB, single click bursts were delivered bilaterally through earphones.

Electrically-induced masseter inhibitory reflex

Surface electrodes were placed on bilateral masseter muscles. The electrical stimulus up to 20 mA and 0.2 ms in duration was applied over the mentalis nerve while participants were asked to maintain contraction.

Studied variables

Onset latencies of eBR (R1 and R2), ABR, and eMIR responses were measured. Latencies were considered prolonged when they were longer than the mean latency + 2 standard deviations (SDs) of normal values of the laboratory. Response asymmetry was accepted when response of one side was normal and response of the other side was absent or prolonged or when there was a latency difference of more than 2 SDs.

Statistical Analysis

Data were analyzed using SPSS 20.0 for Windows. The presence of abnormal electrophysiological findings was compared between patients with focal pontine vs. diffuse brainstem lesion using the chi-square test. Latencies of eBR (R1 and R2) were compared using the Mann—Whitney test. The level for statistical significance was $P \leq 0.05$.

Results

Clinical findings

Eight patients had pontine lesions and six had diffuse brainstem lesions. Two patients had mesencephalic involvement. Ten patients had long-term follow-up after the electrophysiological recordings (range 2—12 years). Among them, four patients had a progressive course. All 4 patients with a progressive course were being treated with infliximab at last follow-up, whereas other patients were on azathioprine and prednisolone.

Electrically-induced blink reflex

Responses were absent in 2 patients, and early and late responses were abnormal in 2 patients. Among patients with pontine involvement, one had no R1 response whereas one with diffuse involvement had asymmetric findings (Table 1). The abnormal findings regarding R2 and R2c were similar between patients with pontine or diffuse brainstem involvement.

Auditory blink reflex

Three patients had no response (18.8%) whereas two patients had abnormally long latency (26.3%). The number of patients with pontine or diffuse brainstem lesions was similar between patients with normal or abnormal ABR findings (Table 1).

Electrically-induced masseter inhibitory reflex

Among patients, one had no eMIR-SP1 (6.2%) and ten had delayed responses. eMIR-SP2 did not develop in five patients and one had a delayed eMIR-SP2. In total, 93.7% of patients had abnormal eMIR (delayed, asymmetric or no response). The number of patients with isolated pontine or diffuse

Table 1 Electrophysiological findings in patients with focal pontine vs. diffuse brainstem involvement.

	Focal pontine involvement ($n=8$)	Diffuse brainstem involvement ($n=6$)	*P*-value
R1, n (%)			0.352
No response	1 (12.5)	0	
Delayed latency	0	0	
Asymmetric responses	0	1 (16.7)	
R2, n (%)			0.540
No response	1 (12.5)	0	
Delayed latency	0	1 (16.7)	
Asymmetric responses	1 (12.5)	1 (16.7)	
R2c, n (%)			0.664
No response	1 (12.5)	0	
Delayed latency	1 (12.5)	2 (33.4)	
Asymmetric responses	1 (12.5)	1 (16.7)	
R1 latency (ms), mean (SD)			
Right	10.9 (0.9)	10.6 (1.5)	0.653
Left	11.0 (0.8)	11.3 (3.4)	0.847
R2 latency (ms), mean (SD)			
Right	31.6 (3.8)	33.5 (8.8)	0.622
Left	32.4 (1.9)	33.1 (6.1)	0.801
R2c latency (ms), mean (SD)			
Right	31.1 (2.5)	36.5 (13.5)	0.317
Left	30.1 (5.2)	35.7 (8.1)	0.191
ABR, n (%)			0.531
No response	2 (25.0)	1 (16.7)	
Delayed latency	0	1 (16.7)	
Asymmetric responses	1 (12.5)	0	
eMIR-SP1, n (%)			0.406
No response	0	0	
Delayed latency	5 (62.5)	5 (83.3)	
Asymmetric responses	0	0	
eMIR-SP2, n (%)			0.215
No response	4 (50.0)	1 (16.7)	
Delayed latency	1 (12.5)	0	
Asymmetric responses	0	0	

R1, R2, R2c: ipsilateral (R1, R2) and contralateral (R2c) responses of electrically-induced blink reflex. ABR: auditory blink reflex. eMIR-SP1, eMIR-SP2: first and second silent periods of the, masseter inhibitory reflex.

brainstem involvement was similar between patients with normal or abnormal eMIR findings.

Discussion

In this study, the major findings were that eMIR was the most abnormal test in NBD, but abnormalities of eBR, ABR or eMIR were less frequent than MRI lesions, and were similar between patients with pontine or diffuse brainstem involvement.

Results from a previous study indicated that eBR may help in the evaluation of the affected brainstem areas in NBD [10]. Our results showed no latency change of R1 or R2 in most patients with NBD. However, on an individual basis, we found two patients with absent R1 response and another two with asymmetrical or delayed latencies. Abnormalities of ABR were also observed; however, abnormal eMIR was more common. The eMIR abnormalities are clearly not specific to NBD. However, eMIR may be a useful means of exploring functional changes in brainstem in NBD. In the literature, auditory or motor evoked potentials were also previously shown to be helpful in distinguishing subclinical disease activity in NBD and providing objective measures to predict response to treatment [8,12].

All patients in this study had abnormal MRI showing brainstem lesions related to NBD. Therefore, we should emphasize that electrophysiological findings in this study are not more sensitive than MRI in NBD, since the present study included cases with MRI-confirmed brainstem involvement that had normal electrophysiological findings.

On the other hand, the most commonly reported MRI finding regarding brainstem parenchymal involvement in NBD concerns lesions at the mesodiencephalic junction [6] whereas in this study, pontine changes were predominant. Therefore, we assessed whether the type of abnormal reflexes reflected the affected brainstem region and varied with the anatomical site of involvement. However, eBR, ABR or eMIR did not allow distinction between diffuse brainstem and pontine involvement in the present study.

Some limitations must be acknowledged. Patients' outcome was assessed retrospectively and could not be ascertained in all cases, and in addition sample size was small. Finally, eMIR may be absent in healthy individuals, especially in elderly people.

In conclusion, neurophysiological recordings of brainstem reflexes have a poor overall sensitivity compared to MRI for the diagnosis of brainstem lesions, and also poor sensitivity for differential diagnosis of focal pontine lesions versus diffuse brainstem disease in NBD.

Disclosure of interest

The authors declare that they have no competing interest.

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