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Blink reflex in progressive myoclonic epilepsies

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ABSTRACT

Purpose: Progressive myoclonic epilepsies (PME) include a heterogeneous group of disorders. The brainstem is involved in these disorders, as demonstrated by neuroimaging and autopsy studies. The blink reflex (BR) is characteristically elicited after supraorbital electrical stimulation. The BR has two components, an ipsilateral R1 and bilateral R2 (R2 and R2c). The central generator of the BR is the brainstem. In this study, we aimed to investigate the functional status of the brainstem using the BR in PME cases with different etiological factors.

Methods: We prospectively included 17 patients with a diagnosis of PME (8 male, 47.1%) who were examined between June 2009 and June 2012. For comparison, we included 41 healthy volunteers (18 male 43.9%) who did not have any neurological or systemic diseases. We recorded responses bilaterally over the orbicularis oculi muscles after supraorbital stimulation in all participants.

Results: The R1 and R2 components of the BR were obtained in all healthy subjects with normal latencies, whereas abnormalities in the R2 and R2c components were observed at significantly higher rates in the PME patients. The mean latencies of the bilateral R2 and R2c components were significantly prolonged, and the amplitudes were diminished in the PME patients. Disease duration and the use of multiple antiepileptic drugs were related to abnormal R2s.

Conclusion: The abnormalities of the R2 and R2c components of the BR confirmed the inhibition of the reticular formation. The findings are probably related to disease processes and partially due to the use of multiple antiepileptic drugs.

1. Introduction

Progressive myoclonic epilepsies (PMEs) include a heterogeneous group of rare disorders that are generally transmitted via autosomal recessive inheritance and present with myoclonus as the core symptom accompanied by other types of seizures, progressive neurocognitive decline, ataxia, and systemic features [1]. Miscellaneous etiological factors may lead to PME, some of which include Unverricht–Lundborg disease (ULD), Lafora disease (LD), myoclonus epilepsy with ragged-red fibers (MERRF), sialidosis, dentato-rubro-pallido-luysian-atrophy (DRPLA) and neuronal ceroid lipofuscinosis (NCL).

Widespread pathologies of the central nervous system have been shown in PME; however, evidence regarding the involved pathways in the brainstem is still limited. DRPLA typically involves the brainstem, and pathological studies have confirmed the loss of acetylcholinergic neurons in the pedunculopontine nucleus [2]. Magnetic resonance imaging (MRI) and spectroscopy findings support the loss of neurons in the pons, medulla and cerebellum in PME due to other causes [3,4].

Among the electrophysiological investigations that have been conducted, brainstem-evoked potentials have been applied, and the results have revealed reduced or absent brainstem components as well as prolonged latencies and central transmission periods [5,6]. In contrast, the blink reflex (BR) has been studied in MERRF and found to be suppressed [7]. The BR is characteristically elicited after supraorbital electrical stimulation via an afferent pathway through the trigeminal nerve and an efferent pathway through the facial nerve. Two components of the BR, the ipsilateral R1 and bilateral R2, have central generators in the brainstem and are modulated by supratentorial and basal ganglia structures [8]. The BR reflects the integrity of the brainstem circuits or at least the

Abbreviations: PME, Progressive myoclonic epilepsy; ULD, Unverricht–Lundborg disease; LD, Lafora disease; MERRF, Myoclonus epilepsy with ragged-red fibers; DRPLA, Dentato-rubro-pallido-luysian-atrophy; NCL, Neuronal ceroid lipofuscinosis; MRI, Magnetic resonance imaging; BR, Blink reflex; AED, Antiepileptic drugs; EEG, Electroencephalography; SEP, Somatosensory evoked potentials; GTCS, Generalized tonic-clonic seizures.

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circuits specific to the BR and the excitability of the related segmental and suprasegmental structures to some extent.

In this study, we aimed to investigate BR circuit in PME patients with different etiological factors.

2. Subjects and methods

2.1. Subjects

We prospectively included 17 patients with diagnoses of PME (8 male, 47.1%) who were examined in our epilepsy outpatient clinic between June 2009 and June 2012. The diagnoses of PME were based on clinical findings and electroencephalography. Cognitive performance was tested via a clinical interview and the mini-mental state examination.

The inclusion criteria were as follows:

i. presence of cortical myoclonus confirmed by electrophysiological investigations,
ii. presence of any type of drug-resistant seizures,
iii. accompanying neurological findings, such as cognitive decline and truncal or extremity ataxia,
iv. age >5 years or <55 years.

The exclusion criteria were as follows:

i. presence of any other diagnosis for myoclonus,
ii. presence of any other neurological disorder (e.g., cerebrovascular disease, multiple sclerosis, organic brain disease, etc.),
iii. presence of any contraindication for electrophysiological investigations.

For comparison, we included 41 healthy age- and gender-matched volunteers (18 male, 43.9%) who did not have any neurological or systemic diseases.

This study was approved by the local ethical committee. Regarding the healthy subjects, all participants provided informed consent. Regarding the PME group, both the patients and their family members provided informed consent.

2.2. Clinical and routine electrophysiological evaluation

The age at onset, seizure semiology, detailed clinical history, antiepileptic drug (AED) use, family history, findings from electroencephalography (EEG) and MRI, and the presence of giant somatosensory evoked potentials (SEP) were noted. Axillary sweat gland biopsies and muscle biopsies were performed to determine the specific subtypes. Selected cases were referred for genetic analysis. The PME patients without specific diagnoses despite the extensive evaluations were classified as probable PME.

3. Methods

3.1. Blink reflex

The electrophysiological recordings were performed using Ag–AgCl cutaneous EMG recording electrodes (Neuropack Σ-MEB-5504K, Nihon Kohden Corporation, Tokyo, Japan) according to standard techniques [9]. The active electrode was placed on the lower eyelid, the reference electrode was placed on the lateral orbital margin, and the ground electrode was positioned on the sternum. The trigeminal nerve was percutaneously stimulated on the supraorbital margin. Single electrical stimuli of 0.2 ms in duration and an intensity of three times the R2 threshold (8–14 mA) were applied. Five consecutive responses were recorded with random inter-stimulus intervals of at least 20 s. Reflex responses were defined as deflections of at least 50 μV from the baseline. The filter settings were 3 kHz high-cut and 20 Hz low-cut. The analysis time was 10 ms/div, and the sensitivity was 200 μV.

The onset latencies, durations and amplitudes of responses were measured using cursors. The amplitudes were calculated peak-to-peak.

3.2. Statistical analysis

The data analyses were performed using the SPSS 15 statistical software package (SPSS Inc., Chicago, IL, USA).

The mean onset latencies, durations and amplitudes of the responses were compared between the patients and healthy subjects using independent *t*-tests for quantitative data and chi-square tests for qualitative data.

The mean onset latencies, durations and amplitudes of the responses were also compared between the patients with and without specific diagnoses using independent *t*-tests for quantitative data and chi-square tests for qualitative data.

Prolonged latencies and absences of responses were categorized as abnormal.

Clinical and demographical features, such as age, gender, disease duration, seizure types, neurological examination findings, AEDs, SEP findings, and MRI findings were compared between the patients with normal and abnormal R2s using independent *t*-tests for quantitative data and chi-square tests for qualitative data.

The correlation between disease duration and R2 latency was analyzed using a Pearson correlation test.

Regression analyses were performed using the variables of generalized tonic-clonic seizures (GTCSs), absence seizures, automatisms, age at seizure onset, disease duration and use of AEDs, to understand the effects of these variables on the abnormal R2s.*p* values ≤ 0.05 were accepted as significant. All values are presented as the mean ± the SD.

4. Results

4.1. Clinical evaluation

GTCS were the second most frequent seizure type after myoclonic seizures ($n = 16$, 94.1%). Absence seizures were present in 6 patients (35.3%) and two patients had automatisms (11.8%). The neurological examinations revealed cognitive decline in 13 patients (76.5%), gait difficulties in 9 (52.9%), pyramidal findings in 6 (35.3%), extrapyramidal findings in 5 (29.4%), speech problems in 7 (41.2%), nystagmus in 4 (23.5%), extremity ataxia in 5 (29.4%) and cranial nerve palsy in 1 patient (5.9%). There were no patients with mental retardation. The cognitive deficits were mild and involved executive, planning and memory functions.The clinical, electroencephalography and neuroimaging findings are presented in Table 1.

Ten patients had definitive diagnoses of specific PME subtypes including the following: 5 patients with Lafora disease, 3 patients with adult-onset NCL and 2 patients with ULD. Genetic analysis revealed EPM2A gene mutation in two LD patients and homozygous mutations of the CLN6 gene in siblings with NCL. The remaining patients ($n = 7$) did not have specific diagnoses and were classified as probable PME.

Twelve patients (70.6%) were using multiple AEDs. The medications included valproic acid (76.5%), levetiracetam (47.1%) and clonazepam (11.8%). One patient was using all three drugs. Clonazepam was the only add-on treatment. Three patients were using only levetiracetam because valproic acid had to be discontinued due to side effects. Three patients had previously