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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.

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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

Table 1
Demographical and clinical features of participants.

	Patients	Healthy subjects	*p*
Mean age (±SD), years	26.2 (±9.6)	31.0 (±11.6)	0.132
Age range, years	13–54	11–58	
Gender M/F (%)	8/9 (47.1/52.9)	18/23 (43.9/56.1)	0.826
Age at seizure onset, years	18.3 (±12.6)	–	
Age at diagnosis, years	15.1 (±11.1)	–	
Seizure types, *n* (%)			
GTCS	16 (94.1)	–	
Absence	6 (35.3)	–	
Automatisms	2 (11.8)	–	
Neurological examination, *n* (%)			
Cognitive decline	13 (76.5)	–	
Gait difficulty	9 (52.9)	–	
Dysarthria	7 (41.2)	–	
Pyramidal findings	6 (35.3)	–	
Extrapyramidal findings	5 (29.4)	–	
Extremity ataxia	5 (29.4)	–	
Nystagmus	4 (23.5)	–	
Cranial nerve palsy	1 (5.9)	–	
Electroencephalography			
Generalized ED	7 (41.2)	–	
Focal/multifocal ED	6 (36.3)	–	
Bioelectrical disorg.	5 (29.4)	–	
Fotic sensitivity	3 (17.6)	–	
Brain MRI			
Normal	15 (88.2)	–	
Cortical atrophy	1 (5.9)	–	
Cerebellar atrophy	1 (5.9)	–	
SEP			
Giant SEP	10 (58.8)	–	
Medications			
Multiple	12 (70.6)	–	
Vaproic acid	13 (76.5)	–	
Levetiracetam	8 (47.1)	–	
Clonazepam	2 (11.8)	–	

M, male; F, female; GTCS, generalized tonic clonic seizures; ED, epileptiform discharges; disorg., disorganization; MRI, magnetic resonance imaging; SEP, somatosensory evoked potentials.

used carbazepine and topiramate, which were stopped due to ineffectiveness before the electrophysiological investigation. No patient was receiving vagal nerve stimulation.

4.2. Electrophysiological findings

The R1 and R2 components were obtained in all of the healthy subjects. The mean latencies are presented in Table 2. In contrast, the R1 component was not obtained on one side in one patient (5.9%). The R2 and R2c components were not recorded in two patients (11.8%). Both of these patients had Lafora disease, and they were 23 and 17 years old. Both of these patients were using multiple AEDs. One had cranial nerve and cerebellar involvement whereas the other had a cognitive deficit. The mean latencies of the bilateral R1s were similar in patients and healthy subjects. The mean latencies of the bilateral R2 and R2c components were significantly longer in the patients than in the healthy subjects (Table 2). The durations of the R2 responses were similar between groups, whereas the amplitudes of the bilateral R2 responses were diminished in the patients compared with the healthy subjects. In 7 patients (58.8%), the R2 was abnormal; it was bilaterally prolonged in six patients and absent in one patient. The R2c was also prolonged in 5 patients and absent in two.

The mean latencies of all of the components of the BR and the amplitudes and durations of the R2s were similar between the patients with specific diagnoses and the patients with probable PME. The subgroups of PME patients also did not exhibit any differences regarding these parameters. However, R2 and R2c abnormalities were more common in the patients with specific diagnoses (R2: 60.0% vs 14.3%, $p = 0.059$; R2c: 66.7% vs 14.3%, **p = 0.036**).

In the group with R2 abnormalities, the use of multiple AEDs (100% vs 50%, **p = 0.026**) was more frequent than among those with normal R2s. The disease durations were also longer in the group with abnormal R2s (7.9 ± 5.8 vs 15.8 ± 10.0, **p = 0.050**). Age, gender, other seizure types, the use of each AED, and the giant SEPs were not different between the groups with normal and abnormal R2s (Table 3). As the disease duration increased, the latencies of both the right and left BR R2 components were prolonged (Pearson correlation, right: 0.514, left: 0.549, **p right = 0.050**, **p left = 0.034**). However, disease duration was not correlated with either the right or left R2c latency (Pearson correlation, right: 0.106, left: 0.093, *p* right = 0.744 and *p* left = 0.762).

Although this difference was not significant, the patients who were using multiple AEDs had longer disease durations.

The regression analysis revealed that the disease duration (**p = 0.028**) and the use of multiple AEDs (**p = 0.013**) were independently related to abnormal R2s (Table 4).

5. Discussion

The major findings of this study are the significantly prolonged latencies of the R2 and R2c components of the BR and the reduced amplitudes of the R2 despite normal R1 responses. The use of multiple AEDs was more frequent, and the disease durations were longer among the patients with abnormal R2s.

Table 2
Parameters of blink reflex in patients and healthy subjects.

	Patients	Healthy subjects	*p*
R R1 latency, ms	10.5 ± 0.9	10.1 ± 1.7	0.400
L R1 latency, ms	10.5 ± 0.9	10.3 ± 0.9	0.560
R R2 latency, ms	39.4 ± 7.5	31.8 ± 3.7	**0.000***
L R2 latency, ms	38.7 ± 8.0	31.6 ± 3.4	**0.000***
R R2 amplitude, μV	248.0 ± 149.9	362.5 ± 143.7	0.064
L R2 amplitude, μV	287.8 ± 127.7	412.0 ± 105.2	**0.021****
R R2 duration, ms	57.2 ± 10.5	53.0 ± 12.0	0.748
L R2 duration, ms	50.5 ± 13.1	53.8 ± 13.1	0.856
R R2C latency, ms	41.1 ± 7.4	31.9 ± 3.8	**0.000***
L R2C latency, ms	40.7 ± 7.7	32.1 ± 3.8	**0.000***
Abnormal R2, %	58.8	0	**0.000***
Abnormal R2C, %	58.8	0	**0.000***

R, right; L, left.
* $p < 0.001$.
** $p < 0.050$.

Table 3
Comparisons of clinical findings between patients with abnormal R2 and normal R2.

	Patients with abnormal R2s *n* = 7	Patients with normal R2s *n* = 10	*p*
Age, years	24.3 ± 8.5	23.4 ± 6.2	0.180
Gender, M/F, *n* (%)	3/4	5/5	0.581
Use of multiple AEDs, *n* (%)	100	50	**0.026****
Disease duration, years	15.8 ± 10.0	7.9 ± 5.8	**0.050****
Presence of automatisms, *n* (%)	0	2 (20.0)	0.331
Presence of GTCS, *n* (%)	7 (100)	9 (90.0)	0.588
Use of valproic acid, *n* (%)	5 (71.4)	8 (80.0)	0.682
Use of levetiracetam, *n* (%)	5 (71.4)	3 (30.0)	0.117
Cognitive deficit, *n* (%)	5 (71.4)	8 (80.0)	0.559
Abnormal MRI findings, *n* (%)	1 (14.3)	1 (10.0)	0.700
Giant SEP	5 (71.4)	5 (50.0)	0.354

M, male; F, female; AED, antiepileptic drugs; MRI, magnetic resonance imaging; SEP, somatosensory evoked potential.
** $p < 0.050$.

Table 4
Analysis of effect of clinical features on abnormal R2s.

	Beta	Sig.
Absence seizure	−0.142	0.505
GTCS	−0.216	0.206
Automatism	−0.357	0.093
Disease duration[a]	**0.422**	**0.028****
Use of multiple AEDs	**0.527**	**0.013****

[a] Disease duration was grouped as 0–5 years, 5–10 years, >10 years.
GTCS, generalized tonic clonic seizure; AEDs, antiepileptic drugs.
** $p < 0.050$.

The BR is an established electrophysiological investigation that is used to examine the functions of the brainstem in routine clinical practice. The BR is most frequently elicited by supraorbital electrical stimulation. The afferent and efferent pathways of both the R1 and R2 components are the ophthalmic branch of the trigeminal nerve and the facial nerve, respectively. The central generator of the R1 is located in the pons, whereas the R2 pathway involves numerous synapses bilaterally in the brainstem reticular formation from the pons to the medulla. Therefore, the latency of the R1 is shorter, and this response is unilateral. The latency and characteristics of the R1 do not change with repeated stimulation because the number of synapses is limited [9]. The latencies and presences of the R1 and R2 reflect the integrity of the related circuits. Thus, we can conclude that the reflex circuitry of the R1 was intact in all of our patients. Our results support the integrities of the afferent and efferent pathways and the motor neurons in the pons that innervate the orbicularis oculi muscle because the R1 was normal in all of the patients with the exception of one in whom the R1 could not be obtained on one side.

In contrast, the number of synapses and interneurons in the R2 pathway are high, which leads to responses with longer latencies, longer durations, and multiple phases. The characteristics of the response also change after each stimulus. Consequently, the R2 is more affected by the modulatory effects of the rostral brainstem, specifically the superior colliculus, raphe nucleus and basal ganglia [10,11]. The latency and presence of the R2 also reflects the integrity of the related circuit. Longer latencies may suggest a structural lesion or a functional inhibition in the pathway. There are different methods to investigate the excitability of the BR pathway [12]. The amplitude, area and duration of the R2 may indicate the excitability of its pathway and the related rostral structures. Therefore, the abnormal findings regarding the R2 parameters observed in our study suggest the suppression of the interneuronal network in the reticular formation of the brainstem and impairments of the suprasegmental control mechanisms.

The excitability of the BR has been used to monitor the functional status of the brainstem in various neurodegenerative diseases [12]. Increased activity of the superior colliculus suppresses the excitability of the R2 [11]. For example, in Huntington's disease, the loss of striatal neurons has been hypothesized to increase collicular activity and lead to a hypoexcitable BR [13]. Additionally, direct inhibition of the brainstem interneurons in the reticular formation due to either functional or structural changes may also result in the suppression of the R2. Koutroumanidis et al. [7] demonstrated suppressed R1 and R2 components in patients with histochemically and genetically confirmed mitochondrial myopathies, and two of these patients had diagnoses of myoclonic epilepsy with ragged red fibers syndrome. These authors attributed the results from their patients, including those with apparently pure myopathy, to clinically silent brainstem impairments. Although our patients did not have any brainstem or basal ganglia lesions, there were significant abnormalities of the R2 and R2c components, which support the idea of Koutroumanidis et al. [7] that brainstem involvement can be functionally observed in cases of PME even without neuroimaging findings.

A previous report indicated that gender does not affect the BR [14], and we also observed no effect of gender. The observed increases in abnormalities with longer disease durations were not surprising because degeneration probably increases over years. The use of valproic acid or levetiracetam did not seem to have any effect; however, the use of multiple AEDs was associated with abnormally suppressed R2s. The absences of the R2 and R2c were probably related to the use of multiple AEDs. AEDs have been shown to suppress the polysynaptic pathway of the R2 [15], which is not surprising because AEDs may affect the levels of dopamine and GABA, which are the main neurotransmitters in the modulatory pathways of the BR.

Accompanying neurological findings, such as ataxia, are features in myoclonic epilepsies with poor prognoses which are related to the pathological involvements of different parts of brain [16]. As we previously mentioned, neuroimaging and autopsy studies have also suggested brainstem involvement. Therefore, we believe that the inhibition of the R2 is most likely related to degenerative changes in the brainstem and rostral structures that are beyond the imaging capacity of MRI.

Regarding the clinical courses, the patients with LD exhibited more severe neurological symptomatology and more intractable seizures. However, we did not find any differences between the patients with specific diagnoses, which could be a consequence of the major limitation of this study; i.e., the entire group was rather heterogeneous, and the subgroups included small numbers of patients. Additionally, the electrophysiological abnormalities were less remarkable in the patients with probable PME, which represents a second limitation. Although the patients who were categorized as probable PME had all of the features specific to PME, clinical classification is associated with the problem of including patients without PME. Nevertheless, the statistical analyses that were performed after excluding this group confirmed the presence of abnormal R2 findings in PME.

In conclusion, the abnormalities of the R2 and R2c components of the BR confirmed the inhibition of the reticular formation in PME, and this inhibition probably was primarily due to the disease process and partially due to the use of AEDs.

Conflict of interest statement

The study was not supported by a corporate sponsor and the authors did not have any financial interests in this study.

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