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Research paper

Enhanced blink reflex recovery in juvenile myoclonic epilepsy

Melek Kandemir[a,*], Ayşegül Gündüz[b], Nurten Uzun[b], S. Naz Yeni[b], Meral E. Kızıltan[b]

[a] Department of Neurology, Bayindir Hospital Icerenkoy, Ali Nihat Tarlan Cad. Ertas Sok. No: 17, 34752, Atasehir, Istanbul, Turkey
[b] Department of Neurology, Istanbul University, Cerrahpasa School of Medicine, 34098, Fatih, Istanbul, Turkey

HIGHLIGHTS

- Blink reflex recovers easily and quickly in juvenile myoclonic epilepsy (JME).
- R2 components have longer durations and higher amplitudes in JME.
- Latencies of R2 are normal in JME.
- There is an enhanced excitability in the brainstem blink reflex circuitry in JME.

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ABSTRACT

Juvenile myoclonic epilepsy (JME), which has been attributed to the dysfunction of cortico-thalamic pathway, has been considered to be one of the system epilepsies. However, electrophysiological and functional neuroimaging techniques have revealed the functional involvement of various parts of the central nervous system, also. Here, we aimed to analyze the role of brainstem circuits in JME by using the blink reflex recovery cycle (BRrc).

Electrophysiological recordings of 18 JME patients together with age and gender matched 18 healthy subjects were made during single and paired supraorbital stimulation. Constant current paired stimuli were delivered at interstimulus intervals (ISI) of 200 and 400 ms. Amplitudes of R2 responses were measured on the non-dominant side, and percentages of the recovery cycles were calculated.

All participants had normal and similar R1 and R2 components of blink reflex (BR). At ISI of 400 ms, R2 recoveries were significantly higher in the JME group compared to healthy subjects ($p = 0.040$). There was no correlation between R2-BRrc and ages of JME patients, disease duration and daily dosage of valproic acid.

We suggest that in JME, the integrity of BR circuit is preserved while the excitability of the brainstem BR circuitry is enhanced.

1. Introduction

Juvenile myoclonic epilepsy (JME) is an epileptic syndrome, which is characterized by bilateral, arrhythmic myoclonic jerks and generalized tonic-clonic seizures (GTCS) [1]. Using back-average techniques, myoclonic jerks have been shown to originate from cortex [2]. Paired-pulse transcranial magnetic stimulation has indicated impaired intracortical inhibition suggesting GABA A mediated dysfunction [3]. It has also been suggested that JME is attributed to the dysfunction of the cortico-thalamic loop secondary to abnormal excitation of reticular thalamic neurons [4].

Although there may be a role of cortico-thalamic circuitry in mediating the generation of epileptic activity from the cortex, various functional and structural abnormalities including decreased number of anterior horn cells at multiple spinal levels without any clinical findings have been reported [5]. Likewise, impaired dopamine uptake in the midbrain was verified in JME patients using dopamine transporter imaging techniques [6]. Moreover, regional blood flow in bilateral thalami, red nucleus, midbrain, pons, left hippocampus, and in the cerebellumwas demonstrated to be reduced in JME [7]. It seems clear that there exist abnormalities in the brainstem and related structures of JME patients, which leads to a new question of whether there is a change in the brainstem circuits also.

Blink reflex (BR), which is obtained by various modalities of stimuli, is generated at the brainstem and reflects its functions.

* Corresponding author. Fax: +90 2165757937.
E-mail addresses: melekkandemir@gmail.com (M. Kandemir), draysegulgunduz@yahoo.com (A. Gündüz), nurtenzn@yahoo.com (N. Uzun), naz441@gmail.com (S.N. Yeni), meralekiziltan@yahoo.com (M.E. Kızıltan).

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BR after electrical stimulation of trigeminal nerve has two components: The R1 component, which is a short-latency, monosynaptic reflex, is not observed clinically. R2 is a relatively long-latency and polysynaptic reflex because there are interneurons operating in this component, and it is seen as the clinical blink response [8]. The recovery of the blink reflex (BRrc) after paired stimulation is the occurrence of BR after a stimulus and reflects the excitability of BR and its circuit It was shown to be under dopaminergic control, and is enhanced in various movement disorders [9–12,14,15]. It still draws attention in conditions with supposed dopaminergic dysfunction [13]. BRrc is mainly calculated using parameters related to R2 component and it may also be referred as R2-BRrc. Based upon this information, we aimed to analyze whether R2-BRrc shows any changes in JME.

2. Patients and methods

2.1. Participants

Eighteen patients who were diagnosed to have typical JME and followed up by a senior neurologist experienced in epilepsy between October 2009 and May 2011 were included in this study. Exclusion criteria were the coexistence of any other neurological or systemic diseases, age younger than 10 years or older than 60 years, history of peripheral facial palsy, and any drug use except antiepileptic drugs (AEDs). The control group consisted of age and gender matched 18 healthy volunteers who did not have any neurological or systemic diseases and no use of any drug.

The study was approved by the local ethical committee of Istanbul University Cerrahpasa School of Medicine and all participants or their parents gave informed consent.

2.2. Clinical evaluation

Medical records including detailed interviews, neurological examinations, routine biochemical analysis, and electroencephalography investigations were reviewed and were repeated when required. AEDs which have been used at the time of investigation were noted.

2.3. Electrophysiological recordings

All electrophysiological recordings were performed with surface silver–silver chloride electrodes using Neuropack MEB-9000, Nihon Kohden Medical, Tokyo, Japan.

2.4. Blink reflex

BR was obtained over orbicularis oculi (O.oc) muscle on the nondominant side by stimulating via bipolar electrode supraorbitally while subjects were sitting. The recording electrode was placed on the lower eyelid with a reference electrode located on the lateral orbital margin. The ground electrode was on the forehead. The duration of the stimulus was 0.1–0.2 ms and the stimulus intensity was set to three times the sensory threshold that corresponded to 8–14 mA in our subject group. The instrument was set with a sweep ranging from 10 ms per division. The gain was 200 μV per division. Filter settings were 20Hz–3 kHz. Recordings were repeated 5 times at random intervals of at least 20 ms. Measurements above 50 μV were defined as the reflex responses.

2.5. Blink reflex recovery

To obtain BRrc, electrodes were placed as described in the BR methodology, and constant current, paired stimuli with the same stimulus characteristics as the single stimulus were delivered at interstimulus intervals (ISIs) of 200 and 400 ms. Analysis time was adjusted as 50 ms/div during stimulation with ISI of 200 ms and as 100 ms/div during stimulation with ISI of 400 ms. Recordings were repeated 5 times at random intervals of at least 20 ms for each ISI interval.

The amplitudes (μV) of R2 responses were measured following both the first stimulus (conditioning) and the second stimulus (test). R2-BRrc was calculated using the following formula: 100 × (amplitude of R2 response to test stimulus)/(amplitude of R2 response to conditioning stimulus).

2.6. Statistical analysis

Data analyses were performed using the SPSS 17.5 software statistical package (SPSS Inc., Chicago, IL, USA). Onset latency, duration, and peak-to-peak amplitude of the responses were measured using cursors. Data were pooled to obtain mean values and standard deviations.

Mean values of latencies and amplitudes of BR responses to single stimulus as well as R2-BRrc at ISIs of 200 and 400 ms were compared between the JME group and healthy subjects. As the distribution of these groups was heterogeneous, the nonparametric Mann–Whitney *U* test was used for this comparison.

We performed one way ANOVA to investigate the change of R2-BRrc between ISI of 200 ms and ISI of 400 ms in both groups.

Relationships between each of R2-BRrc at ISIs of 200 ms and 400 ms versus age of JME patients, disease duration and daily dosage of VPA were tested using Pearson correlation test. Patients were also grouped according to their usage of AEDs (no AED, single AED or multiple AEDs), and we performed comparisons of R2-BRrc at ISIs of 200 ms and 400 ms between three groups using Kruskal–Wallis test.

p Value $\leq$0.050 was considered as significant. As there were two groups and two ISI values, p value $\leq$0.012 was accepted as significant for pairwise comparisons of R2-BRrc.

3. Results

3.1. Clinical findings

Mean ages of JME and control groups were 24.8 ± 7.1 years (age range: 15–38 years) and 23.1 ± 5.9 years (age range: 11–31 years), respectively (p = 0.400). Male gender constituted 33.3% of the JME group and 44.4% of the control group (p = 0.500)

All patients had history of myoclonus and 88.9% had history of GTCS. Neurological examination was normal in all participants. Mean age at seizure onset was 15.2 ± 3.1 years (range: 9–23 years). Mean duration from the diagnosis was 9.7 ± 6.6 years (range: 1–22 years).

Three patients (16.7%) did not use any medications at the time of electrophysiological examinations. AEDs usedwerevalproic acid(VPA) (n = 11, 61.1%), VPA and lamotrigine (n = 3, 16.7%), and levetiracetam (n = 1, 5.5%). Table 1 shows the demographical and clinical findings in JME patients and healthy subjects.

3.2. Electrophysiological recordings

Latencies of R1 and R2 components of BR were normal in both groups, whereas the duration of R2 was longer and the amplitude of R2 was higher in the JME group (Table 2). At ISI of 200 ms, mean R2-BRrc was 9.6 ± 20.2% in healthy subjects whereas it was significantly higher in the JME group (32.8 ± 32.9%, p = 0.011). At ISI of 400 ms, mean R2-BRrc was still significantly higher in the JME group compared to healthy subjects (57.9 ± 34.8% vs 21.3 ± 22.9%, p = 0.000). Oneway ANOVA demonstrated that R2-BRrc was significantly enhanced in the JME group at ISI of 400 ms compared to