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Cortical inhibitory dysfunction in epilepsia partialis continua: A high frequency oscillation somatosensory evoked potential study

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HIGHLIGHTS

- Sensory evoked potentials localize thalamocortical dysfunction of epilepsia partials continua.
- Epilepsia partialis continua shows attenuation of median P24 wave and post-synaptic cortical HFO.
- Gabaergic dysfunction of somatosensory cortex maintains epilepsia partialis continua.

ABSTRACT

Objective: The pathophysiology of epilepsia partialis continua (EPC) is still unclear, a thalamo-cortical circuit dysfunction has been hypothesized.

The aim of present study is the functional evaluation of the thalamo-cortical network in EPC by means of the study of low- and high-frequency somatosensory evoked potentials (LF-SEP and HF-SEP).

Methods: Median LF-SEP and HF-SEP were recorded in 3 patients with EPC and in 2 patients with rolandic lesions without EPC (non-EPC). Recording electrodes were placed on P3, C3, F3 and P4, C4, F4 of scalp regions. HF-SEP were obtained by an offline 400–800 Hz filtering of P3-F3 and P4-F4 traces.

Results: In EPC patients, we found a significant suppression of post-synaptic HF-SEP burst and an amplitude reduction of the P24 wave of the LF-SEPs. Both these components are related to cortical inhibitory interneuron activity. HF-SEP and LF-SEP were normal in non-EPC patients.

Conclusion: The different results obtained in patients with a rolandic lesion with and without EPC supports the hypothesis that EPC might be correlated to a dysfunction of gabaergic interneurons of a cortical sensory-motor network.

Significance: Our results might contribute to the understanding of the physiological basis of the cortical dysfunction causing epilepsia partialis continua.

1. Introduction

Epilepsia partialis continua (EPC), a continuous seizure type (Engel, 2001), characterizes by continuous and prolonged rhythmic muscle jerks, arising from abnormal excitation of sensorimotor cortex. EPC is usually caused by rolandic cortex lesions. However, motor cortex lesions are not always associated with EPC, thus, the pathophysiology of EPC is still unclear. Cortical rhythmic paroxysmal activity, myoclonus activated by a reverberant activity through a thalamo-cortical loop, or both mechanisms, have been proposed as the possible pathophysiological mechanisms underlying EPC. Whatever the case, EPC manifests through an involvement of sensory-motor cortex and thalamocortical projections (Guerrini, 2009).

Clinical neurophysiology can help in understanding the pathophysiological background of EPC. In particular, the study of high frequency components (>400 Hz) of somatosensory evoked potentials (HF-SEP) is very useful in exploring thalamo-cortical circuits and early inhibitory cortical responses. The study of HF-SEP allows isolating potentials with several different generators, including the thalamus and the cortical somatosensory Broadmann area 3b (Gobbelé et al., 1998). Two distinct components of HF-SEP can be easily recorded; an early burst and a late burst in respect of the peak latency of the low-frequency SEP (LF-SEP) N20 potential. The early burst of HF-SEP, which precedes N20 peak, is generated

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by a presynaptic activity of the final part of the thalamo-cortical tract, whereas the late subcomponent, which follows N20 peak, is a post-synaptic response related to the activity of inhibitory GABAergic interneurons in superficial layers of primary sensory cortex (for a review see Ozaki and Hashimoto, 2011).

We present a case-control series study with the description of LF-SEP and HF-SEP features in 3 consecutive patients with epilepsia partialis continua and in 2 cases of rolandic non-epileptic lesions.

2. Material and methods

2.1. Patients

In the period 2001–2010, we recorded LF-SEP and HF-SEPs in 3 consecutive patients (2 females, 1 male) during EPC and two patients (2 females) with non-epileptogenic lesions of the primary sensorimotor cortex (Non-EPC).

The study was approved by the local ethic committee and patients signed a written informed consent.

2.2. SEP recording technique

For SEP recording, subjects lay on a couch in a warm and semi-darkened room. Both median nerves were alternatively stimulated; stimuli (0.2 ms duration) were delivered by skin electrodes at the wrist, with intensity slightly above the motor threshold. The stimulation rate was 5.1 Hz. SEP were recorded from disk recording electrodes (impedance below 5 kΩ) placed at 6 scalp locations: (i) the parietal region omo- and contra-lateral to stimulation (P3/P4), (ii) the central regions (C3/C4) and the frontal regions (F3/F4). The reference electrode was placed on the auricular lobe ipsilateral to the stimulation. The ground electrode was positioned over the stimulated arm. The analysis time was 50 ms, with a sampling rate of 20000 Hz. The amplifier bandpass was 3–3000 Hz (12 dB roll-off). Two averages of 1000 trials each were obtained.

2.3. LF-SEP

SEP were identified on the basis of latency, polarity and scalp distribution. Peak amplitudes and latencies were measured on the average of the 2 trials. Amplitudes of the surface SEP components were measured from the baseline.

2.4. HF-SEP

In order to study the high-frequency responses selectively, we reconstructed, by means of off-line subtraction, P3-F3 and P4-F4 traces; this array allowed us to obtain the best derivation to detect the pre and postsynaptic HF-SEP bursts (Restuccia et al., 2007a). These traces were submitted to time-frequency analysis based on a Morlet wavelet transformation (AutoSignal 3.1, Systat Software, Inc.). After identification and evaluation of LF-SEPs, frequency spectrum was estimated by means of autoregressive (AR) modelling. The used algorithm was the SVD (singular value decomposition) least-squares method. AR frequency spectra within the whole latency window (0–50 ms) revealed a main peak with a mean frequency of around 600 Hz. Therefore, the scalp traces were filtered by a 400–800 Hz bandpass.

3. Results

3.1. EPC patients

Case 1: an 81 years-old female presented to the emergency department with continuous jerks of the right hand with rare diffusion to the ipsilateral arm and face. Two months earlier, she had a mild traumatic brain injury. MRI revealed a thin subdural hematoma in the left hemisphere and a hypointensity of the pre-rolandic and post-rolandic circumvolutions in long-TR MR images. EEG recording showed repetitive monomorphic bursts of beta activity on scalp left centro-parietal regions. EPC stopped after seven days of frequent recurrent episodes. In the left (affected) hemisphere, the LF-SEP analysis revealed the absence of P24, while HF-SEP analysis revealed a preserved early burst, but no reliable late (post-synaptic) responses were identifiable. In the right hemisphere, both the LF-SEP and HF-SEPs were normal (Fig. 1).

Case 2: an 81 years-old male with a previous haemorrhagic stroke and a residual right hemiparesis presented, 7 days after a mild traumatic brain injury, continuous jerks of the left hand with rare diffusion to the arm. Computerized Tomography (CT) showed a right rolandic sub-arachnoideal haemorrhage and a thin subdural left hygroma. EEG showed polymorphic delta waves with intermingled spiky waves in the right central area. EPC lasted 12 days. During EPC, he underwent SEP recordings. In the right affected hemisphere, the broadband analysis revealed a reduction of P24 amplitude, while HFO analysis revealed a preserved early HF-SEP burst with desynchronized late responses. No abnormalities were found in LF-SEP and HF-SEP of the left unaffected hemisphere (Fig. 2).

Case 3: a 79 years-old female, two days after a mild traumatic brain injury, developed a left arm paresis. After 24 h, she manifested continuous rhythmic clonic movements of the left hand and arm. Brain CT showed a subarachnoideal haemorrhage in the right rolandic sulcus. EEG showed polymorphic theta waves with intermingled spiky waves in the right central area. EPC stopped after 10 days. During EPC, she underwent SEP recording. In the affected right hemisphere, the LF-SEP analysis revealed the absence of P24, while HF-SEP analysis revealed a preserved early HFO burst with desynchronized late responses (Fig. 2).

In EPC case 1, case 2 and case 3, SEP were recorded between the 5th and 7th day after EPC onset, in a resting state, between two episodes of EPC and during endovenous administration of Phenytoin (300 mg/die) and diazepam (20 mg/die) and intramuscular administration of Fenobarbital (200 mg/die).

3.2. Non-EPC patients

Case 4: an 80 years-old female with an acute stroke of right pre-rolandic cortex (brain CT, Fig. 2) with moderate paresis of left hand. Three days after symptom onset, we assessed SEP recordings. No alterations of both stroke and normal side LF-SEP and HF-SEP responses were found (Fig. 2).

Case 5: a 47 years-old female arrived at the emergency department with a Jacksonian seizure of the right hand. Intramuscular injection of phenobarbital (100 mg/die) stopped seizures. MRI showed a multiform glioblastoma occupying sensorimotor left cortex. After 5 days of hospitalization, we recorded SEP. HF-SEP and the P24-N30 complex were higher in amplitude in the affected hemisphere (Fig. 2).

4. Discussion

We found changes in the cortical somatosensory components of both the LF-SEP and the HF-SEP, which were consistent across three patients affected by EPC (cases 1, 2 and 3). These findings were specific for the affected hemisphere, while normal responses were recorded in the unaffected hemisphere.

EPC is a form of cortical myoclonus. The cortical myoclonus has been physiologically classified into six types, according to the origin (cortical sensory, motor or sensory-motor) and elicitability

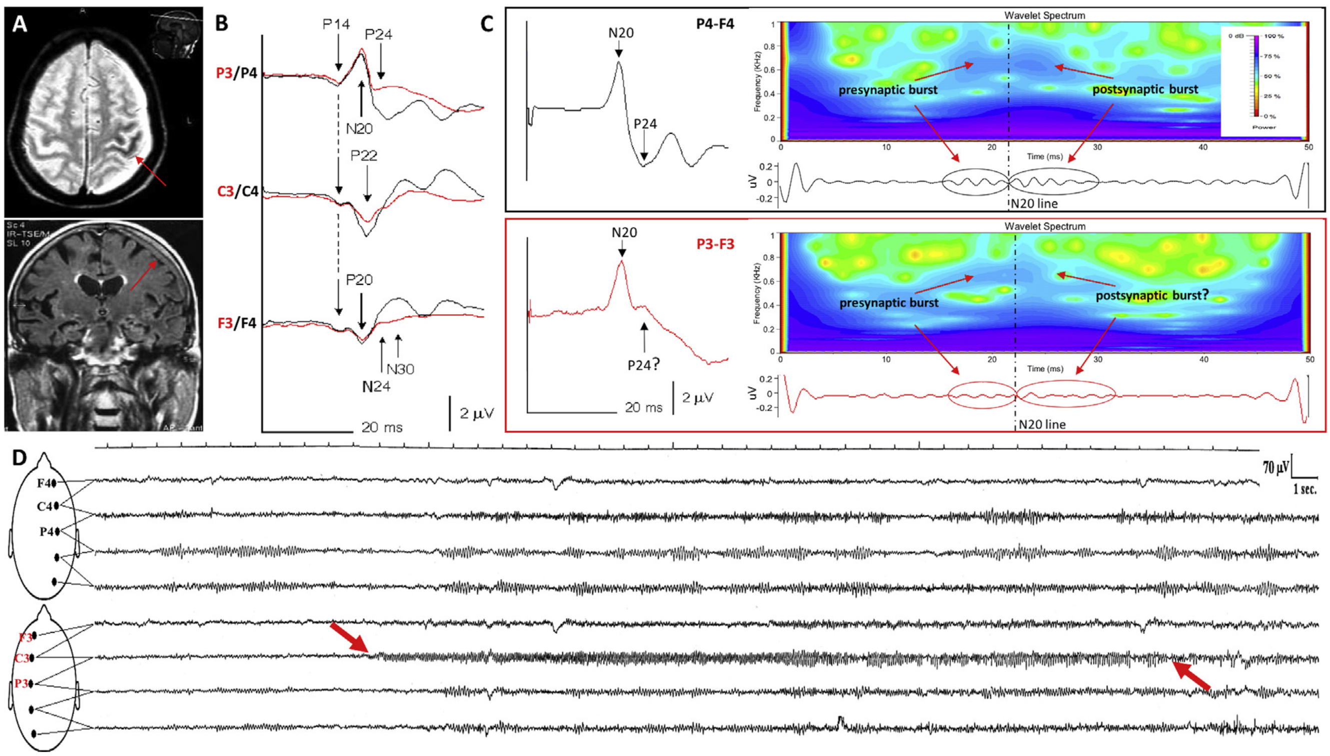

Fig. 1. A. Up: Axial T2 Magnetic resonance image demonstrating a sufferance of pre-rolandic and post-rolandic cortices (hypointense signal, red arrow); Down: Coronal FLAIR magnetic resonance image demonstrating the left subdural haematoma (red arrow). B. Superimposed wide band somatosensory evoked potentials (SEP) as recorded by different scalp electrodes with contralateral auricular reference (red, affected hemisphere; black, unaffected hemisphere). C. Left: wide band cortical SEP (P4/P3 electrodes with F4/F3 reference). Note the P24 absence in the affected hemisphere. Right: up, wavelet spectrum clearly shows, in the frequency band 400–800 Hz, two band power peaks corresponding to the high frequency components of SEP, a pre-synaptic burst (before the peak of N20) and a post-synaptic burst (after the peak of N20, absent in the affected hemisphere). Time–frequency analysis of SEPs recorded from the scalp. Power is expressed as decibels (normalized to 0 for time–frequency node with maximum power). Power changes are represented by a color change of the contour according to the color scale on the right. Any color gradient represents 1 dB difference in the spectrum; down, 400–800 Hz filtered waves. Note a pre-synaptic burst and a post-synpatic burst. The post-synaptic burst is desynchronized in the affected hemisphere. D. A scalp EEG of the same patient showing a paroxysmal beta frequency discharge over centro-parietal left regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(spontaneous or reflex). The myoclonus of EPC patients is physiologically classified as a motor cortical spontaneous myoclonus. Actually, it is usually reported in patients with motor cortex hyper-excitability, as revealed by transcranial magnetic stimulation, and with normal SEP recovery cycle and absence of the long-loop reflex. However, several findings suggest the involvement of sensory cortex as a possible cause of motor cortex hyper-excitability. Nakatani-Enomoto et al. (2009) reported a patient with EPC and a pure sensory cortical lesion. In another patient with EPC, an ictal single photon emission computed tomography (SPECT) study revealed a parietal lobe epileptic focus within the superior segment of the postcentral gyrus (Matthews et al., 2006). Moreover, Cowan et al. (1986) described an EPC patient in whom a parietal cortical resection definitively suppressed seizures. Thus, even if EPC is primarily caused by an hyperexcitability of the motor cortex, the sensory cortex plays a pivotal role in sustaining the EPC and, sometimes, can be also the origin of the disorder. According to this, the role of sensory and motor cortex connectivity seems extremely relevant as also suggested by the observation of EPC in a patient with progressive multifocal leukoencephalopathy (Berciano et al., 2003), a demyelinating disorder primarily affecting the white matter. One possible explanation is that the demyelination of U fibers underneath the motor-sensory areas can isolate the motor cortex from surrounding areas, and this in turn leads to motor cortex hyperexcitability with EPC. This is in line with the neurophysiological literature demonstrating that an abnormality in the excitability of the motor cortex results in abnormal excitability of the sensory cortex and viceversa (e.g. Rushton et al., 1981; Seyal et al., 1992; Rossi et al., 1998; Ishikawa et al., 2007).

4.1. HF-SEP

In EPC patients, we found a desynchronization of post-synaptic HF-SEP when compared with non-EPC patients with rolandic lesions (case 4 and case 5). Post-synaptic HF-SEP are 3–4 wavelets that start at around the latency of the N20 cortical potential (Nakano and Hashimoto,1999; Haueisen et al., 2000) and last up to 7–10 ms. Experimental data demonstrated that cortical injection of glutamatergic receptors antagonists (Ikeda et al., 2002) or propofol anesthesia (Klostermann et al., 2000) abolish the HF-SEP burst. Furthermore, SEP recovery cycle studies with scalp (Emori et al., 1991) and subdural cortical recordings (Urasaki et al., 2002) demonstrated the late burst HF-SEP disappearance after median nerve paired stimulation at very short (3–6 msec) inter-stimulus intervals, thus confirming the cortical polysynaptic inhibitory nature of late HF-SEP waves. Our previous studies on "gating phenomenon" demonstrated that movement, which mostly affects post-synaptic responses through an inhibitory mechanism (Insola et al., 2004, 2008, 2015; Valeriani et al., 2017), reduces HF-SEP amplitude. This post-synaptic burst of HF-SEP is thought to reflect a gabaergic intra-cortical activity, which immediately follows the arrival of the stimulus to the 3b area of primary somato-sensory cortex. However, the cortical mechanism generating the post-synaptic waves of HF-SEP is still controversial; it is unclear whether they are produced directly by activities of inhibitory interneurons or indirectly by the activation of gabaergic interneurons by excitatory pyramidal neurons (Ozaki and Hashimoto, 2005). Actually, the inhibitory interneuron hypothesis for late HF-SEP burst origin is based on two possible mechanisms:

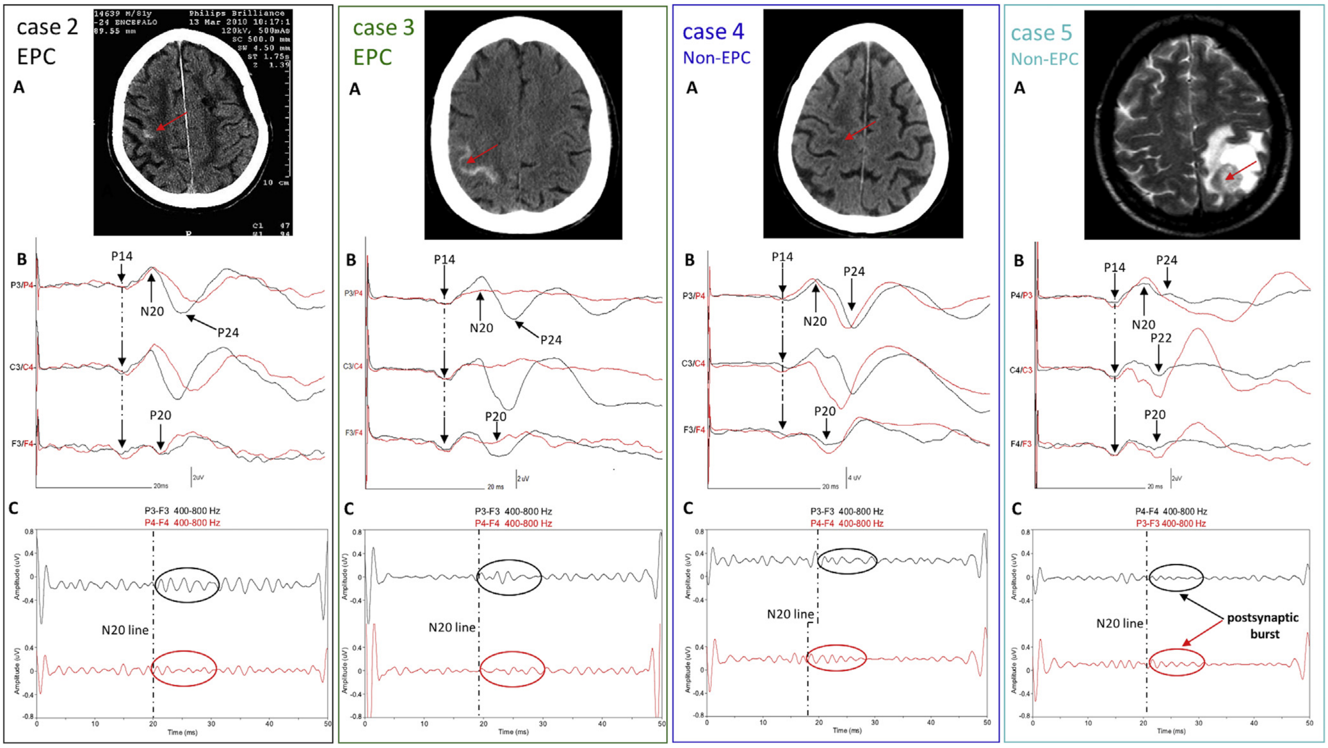

Fig. 2. A: Axial neuroimaging. Case 2 and case 3 (epilepsia partialis continua) CT scan showing right peri-rolandic subarachnoideal haemorrhage (hyperdensity, red arrow); case 4, right pre-rolandic ischemic stroke (hypodensity, red arrow); case 5, T2-weighted magnetic resonance imaging showing left peri-rolandic multiform glioblastoma with oedema. B. Superimposed wide band somatosensory evoked potentials (SEP) as recorded by different scalp electrodes with contralateral auricular reference (red, affected hemisphere; black, unaffected hemisphere). Please note the reduction of amplitude of P24 in case 2 and the absence of P24 in case 3 (epilepsia partialis continua). C. 400–800 Hz filtered somatosensory evoked potentials. In circles (red affected, black unaffected) the post-synpatic bursts. The vertical dotted line indicates the latency of the N20 component, possibly coincident with the arrival of the afferent volley to the somatosensory cortex. Please note a highly desynchronized post-synaptic burst in the affected hemisphere of case 2 and case 3. EPC: epilepsia partialis continua. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a feedforward and a feedback inhibitory pathway. Human studies favor a feedforward inhibitory hypothesis in which the late burst is generated by inhibitory interneurons that regulate the activity of the pyramidal neurons by a feedforward inhibition. Gabaergic drug lorazepam can induce a slight but significant decrease of N20 amplitude, while do not modify at all HF-SEP (Restuccia et al., 2002a), suggesting that the late burst wavelets of HF-SEP are not directly evoked by gabaergic receptor activation. On the opposite hand, GABA receptor antagonist bicuculline administration, at subconvulsive concentrations, produces a clear increase in the duration of HF-SEP together with an enlargement of LF-SEP. Taking together these findings into consideration, Jones and Barth (2002) proposed that the late HF-SEP burst results from spiking of a population of excitatory pyramidal neurons, modulated by gabaergic interneurons. The administration of slow repetitive TMS, which is known to inhibit cortical excitability, on primary sensory area increases the amplitude of the whole response of HF-SEP with preserved LF-SEP (Restuccia et al., 2007a), corroborating the post-synaptic origin of HF-SEP and suggesting their origin from a complex cortical inhibitory network (for a review see Ozaki and Hashimoto, 2011). The possible role of a cortical inhibitory pathway is also supported by the findings in HF-SEP studies in epileptic patients. Restuccia and colleagues (Restuccia et al., 2007b) demonstrated that, in patients affected by idiopathic generalized epilepsies, HF-SEP are sensitive to the seizure frequency and, in particular, HF-SEP were increased in seizure free patients as to suggest that the increase of HFO represents a protective mechanism against seizures. In seizure-free patients affected by childhood absence epilepsy, the same authors recorded a lack of reduction of HF-SEP during NREM sleep when compared with controls, thus strengthening the link between HF-SEP and convulsive predisposition (Restuccia et al., 2005). These experiments are in line with our results, in our EPC patients the reduction of HFO might represent a deficit in a cortical inhibitory network controlling seizures.

4.2. LF-SEP

Present data on LF-SEP also support this hypothesis. An absence/reduction of the P24 wave amplitude was consistently observed in all EPC patients together with the late HF-SEP burst desynchronization, while it was not observed in non-EPC patients with rolandic lesions. The amplitude of P24 is related to gabaergic cortical responses as demonstrated in pharmacological experimental and human studies. Restuccia et al. (2002b) administered tiagabine, a powerful inhibitor of GABA reuptake, to healthy subjects and obtained a significant increase of the P24/N24 complex amplitude. Furthermore, the high sensitivity of the N24/P24 potential to stimulation at high frequencies, which entails a pronounced suppression of this wave (Valeriani et al., 1998), supports the hypothesis that the inhibitory circuitry contributes to the shaping of these SEP components, indeed, cortical inhibitory neurons are more sensitive to higher stimulus rates (Nacimiento et al., 1964). Human studies demonstrated that patients with Angelman's syndrome, caused by a deletion of GABA-A receptors and characterized by frequent seizures, present a less pronounced post-synaptic response of median somatosensory evoked field in magnetoencephalographic recordings, thus strengthening the hypothesis that the post-synaptic SEP components are related to the GABA activity (Egawa et al., 2008). Furthermore, a decreased P24 response was reported contralaterally to the lesioned hemicerebellum in patients with a lesion of the cerebellum (Restuccia et al., 2001), a structure that physiologically inhibits the sensory-motor cortex (Miller et al., 1993; Kros et al., 2015).

The pre-synaptic component of HF-SEP was not affected in EPC, suggesting that thalamo-cortical projections are not functionally impaired in EPC. These data corroborate the hypothesis that EPC is mainly sustained by an intra-cortical network functional impairment. A cortical lesion, actually, might not suffice to generate and sustain EPC, as it is also demonstrated by the two case-controls that we reported who had normal HF-SEPs. It is worth noting that in the non-EPC patient with cerebral tumor (case 5) LF-SEP and HF-SEP were increased in the affected hemisphere, as previously reported by other authors (Ooba et al., 2010) and attributed to a presumed hyperexcitability in the thalamocortical pathway.

Valeriani et al. (1997) found giant P24/N24 components in 3 cases of cortical myoclonus of varying causes. These results seem in contrast with our finding of a reduction of P24 in EPC patients. However, pathophysiological backgrounds subtending the myoclonus of the two groups of patients could be significantly different. It should be considered that patients reported by Valeriani and co-workers were affected by genetic/degenerative disorders with a paroxysmal myoclonus resulting in hyperpolarization, following the postsynaptic excitatory potentials responsible for the early giant components. On the opposite hand, our patients were affected by pure focal lesions of the rolandic cortex with a continuous myoclonus, probably due to an impairment of gabaergic tonic inhibition in the sensori-motor cortex, as suggested by the P24 reduction.

The main limitation of our study is the small sample. We are aware that 3 patients are not enough to provide a statistical analysis allowing to achieve a high degree of scientific reliability. However, it should be considered that EPC is extremely rare (Cockerell et al., 1996) and it appears worth analysing consistent data even if obtained in a small number of patients because the findings can be clinically significant and can provide insights in the pathophysiology of the disorder.

5. Conclusion

In conclusion, our data on SEP support the hypothesis that EPC origins from a cortical rolandic dysfunction due to an impairment of inhibitory intra-cortical network activated by spared thalamo-cortical projections. In this light, our data suggest a possible rational approach to the drug treatment of EPC, where gabaergic drugs should be preferred to compensate gabaergic interneurons dysfunction.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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