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Giant early components of somatosensory evoked potentials to tibial nerve stimulation in cortical myoclonus

Francesca Anzellotti[a], Marco Onofrj[a,b], Laura Bonanni[a,b], Antonio Saracino[a], Raffaella Franciotti[b,c,*]

[a] Department of Neurology, SS Annunziata Hospital, Chieti, Italy
[b] Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University and Aging Research Centre, Ce.S.I., "G. d'Annunzio" University Foundation, Chieti, Italy
[c] ITAB, "G. d'Annunzio" University Foundation, Chieti, Italy

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ABSTRACT

Enlarged cortical components of somatosensory evoked potentials (giant SEPs) recorded by electroencephalography (EEG) and abnormal somatosensory evoked magnetic fields (SEFs) recorded by magnetoencephalography (MEG) are observed in the majority of patients with cortical myoclonus (CM). Studies on simultaneous recordings of SEPs and SEFs showed that generator mechanism of giant SEPs involves both primary sensory and motor cortices. However the generator sources of giant SEPs have not been fully understood as only one report describes clearly giant SEPs following lower limb stimulation. In our study we performed a combined EEG-MEG recording on responses elicited by electric median and tibial nerve stimulation in a patient who developed consequently to methyl bromide intoxication CM with giant SEPs to median and tibial nerve stimuli.
SEPs wave shapes were identified on the basis of polarity-latency components (e.g. P15-N20-P25) as defined by earlier studies and guidelines. At EEG recording, the SEP giant component did not appear in the latency range of the first cortical component for median nerve SEP (N20), but appeared instead in the range of the P37 tibial nerve SEP, which is currently identified as the first cortical component elicited by tibial nerve stimuli. Our MEG and EEG SEPs recordings also showed that components in the latency range of P37 were preceded by other cortical components. These findings suggest that lower limb P37 does not correspond to upper limb N20. MEG results confirmed that giant SEFs are the second component from both tibial (N43m-P43m) and median (N27m-P27m) nerve stimulation. MEG dipolar sources of these giant components were located in the primary sensory and motor area.

1. Introduction

Cortical myoclonus (CM) can be defined as involuntary brief muscle jerks originating from an abnormal discharge in the cerebral cortex: electroencephalographic (EEG) changes (positive spikes, spike and wave complexes or negative sharp waves) over the contralateral sensorimotor cortex are reported to precede CM (Obeso et al., 1985). By means of magnetoencephalography (MEG), Uesaka et al. (1996) identified 3 types of CM: cortical reflex myoclonus, sensorimotor cortical reflex myoclonus and motor cortical myoclonus. The first 2 types generate from the sensory cortex and result in both reflex and spontaneous myoclonus. Both were considered to be essentially stimulus-sensitive, and the spontaneous myoclonus probably results from unnoticed somatosensory inputs. Cortical reflex and sensorimotor cortical reflex myoclonus depend on abnormal enhancement of sensory and sensorimotor cortices excitability. The motor cortical myoclonus was thought to be primarily generated by spontaneous discharges in the motor cortex (Celesia et al., 1994; Uesaka et al., 1996). Postcentral cortex is considered the source of pre-myoclonus cerebral activity (Hitomi et al., 2006), despite earlier, challenging, reports (Mima et al., 1998).

Since the initial studies by Dawson (Dawson, 1946), which described somatosensory evoked potentials (SEPs) in humans, it is known that one of the main characteristics of the CM is the presence of very high-amplitude SEPs (giant SEPs) (Hallett et al., 1979; Rothwell et al., 1984; Shibasaki et al., 1978).

The majority of studies showed evidence of giant SEPs only to median nerve stimulation: these giant SEPs consisted of increased amplitude of the components appearing after the N20, which is thought to represent the first cortical postsynaptic activation corresponding to afference in primary idiotipic postrolandic cortex (Desmedt and Cheron, 1980; Desmedt et al., 1987; Mauguiére et al., 1983).

The giant SEPs to median nerve stimulation were characterized by normal amplitude of P14 and N20 and by appearance of high amplitude complexes in the latency range of P25-N30. The P25-N30 complex of normal SEPs is thought to represent activity of perirolandic cortex, possibly supplementary motor area (SMA) and associative somatosensory cortex, areas 2–3 (Desmedt and Cheron, 1980; Desmedt et al., 1987; Mauguiére et al., 1983). The giant SEPs in the latency range of P25-

* Corresponding author at: Department of Neuroscience, Imaging and Clinical Science, "G. d'Annunzio" University, Via dei Vestini 33, 66013 Chieti, Italy.
E-mail address: raffaella.franciotti@itab.unich.it (R. Franciotti).

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N30 are thought to be dependent on the activation of new generators (Ikeda et al., 1995; Valeriani et al., 1997) or simply to an increase in the amplitude of the P25-N30 components of the normal response (Kakigi and Shibasaki, 1987a).

While there is agreement on the features (i.e. latency, topography) of giant SEPs to median nerve stimuli, there are only two studies showing that also SEPs to stimuli of lower limbs nerves might be giant (Hitomi et al., 2006; Kakigi and Shibasaki, 1987b). This is probably because the diseases inducing CM and giant SEPs appear with different involvement of peripheral nerves and CM to lower limb stimulation could be concealed by coexisting neuropathy (Fournier-Goodnight et al., 2015). In the present report we describe SEP and somatosensory evoked field (SEF) by means of MEG recordings, and their topography in a patient affected by CM of upper and lower limbs. The study allowed a comparison of the giant components of the upper and lower limbs and a discussion of possible generators.

A previous electrophysiological study from our Institution (Uncini et al., 1990) described a case of myoclonus after methyl bromide intoxication. The authors found that myoclonus, which was characterized by myoclonic jerks of the upper and lower limbs, belonged to the cortical reflex myoclonus type. In the patient presented in that report, CM persisted despite several pharmacological treatments attempts. Thus, we could record several years later, giant SEPs and SEFs following median and tibial nerve stimulation in the same patient.

2. Materials and methods

2.1. Patient and control group

Previously, we described (Uncini et al., 1990) a 13-year-old girl that had slept one night in a warehouse for wheat which had been sprayed a few hours before with methyl bromide as an insect fumigant. The morning after she woke up with headache, dizziness and nausea. At lunch time she was found unconscious in bed and was admitted to the intensive care unit where she developed generalized seizures. After 3 days her level of consciousness gradually improved and myoclonic jerks, at times generalized, appeared. The patient was initially unsuccessfully treated with phenobarbital 250 mg/day and acute i.v. administration of phenytoin (1000 mg). No reduction of frequency and intensity of myoclonic jerks was noted. Four weeks later, the patient, who was at the time oriented and cooperative, was transferred to our department. We ineffectively attempted to treat the patient with sodium valproate (up to 60 mg/Kg) and L-5-hydroxytryptophan (800 mg/day) with carbidopa (100 mg/day) or chlorimipramine (50 mg/day) were also unsuccessfully administered to the patient. During her two-month stay in our department we observed periodic gradual increase of myoclonic jerks culminating on at least 2 occasions in a grand mal attack.

We had the chance to observe the same patient 20 years later: at rest, frequent myoclonic jerks of the limbs were present and myoclonus was also induced by somatosensory stimuli as touching or tendon tapping. Any attempt of voluntary limb movements or passive displacement of limbs provoked a series of jerks and often gave rise to generalized jerks involving the entire body. Myoclonic jerks disappeared only when the patient was sleeping or floating in a swimming pool. Gait was wide-based, continuously hampered by myoclonus and impossible without assistance. Speech was dysarthric. Muscle tone was normal. Plantar responses were in flexion. There were no sensory abnormalities. Cerebral CT and MRI were normal. Through time, several attempts were made to reduce myoclonus, by introducing Clonazepam, Clobazam, Piracetam, Levetiracetam, Lamotrigine, Carbamazepine, Etosuccimide, Topiramate, Felbamate, Perampanel, Amantidine, Memantine, Gammahydroxybutirate, all attempts to treatment were unsuccessful. When SEPs and SEFs were recorded, her treatment consisted of 6 mg/day of clonazepam, 4000 mg/day of levetiracetam and 100 mg/day of Phenobarbital, as attempts to reduce these treatments resulted in increased frequency of generalized seizures.

SEP and MEG recordings were separately performed on the patient following left and right median and tibial nerve stimulations.

A control group consisting of 10 female healthy subjects (mean age 35 ± 4 years, ranging from 29 to 41 years) and mean height of 165 ± 5 cm) was selected from our neurophysiology laboratory. SEPs were recorded on the control group following left and right median and tibial nerve stimulations for comparison with the patient. The patient and all the control subjects signed a written informed consent to the study. The investigation was carried out according to the Declaration of Helsinki and subsequent revisions (Declaration of Helsinki, 1997).

2.2. Stimulation and recording

Somatosensory electrical stimuli were rectangular pulses with a repetition rate of 0.3 Hz. Stimuli were unilaterally delivered to right or left median nerve at the wrist or to the left and right tibial nerve at the medial malleolus. Intensities of stimulation were settled at a level producing a painless, clearly visible thumb opposition or foot flexion. The duration of the stimuli was set at 200 μs for the upper limbs and at 800 μs for the lower limbs. Stimuli were delivered by means of a pair of nonmagnetic, 3-cm-spaced, Ag-AgCl disk electrodes filled with conductive gel, via a twisted and shielded pair of wires for MEG recordings.

SEPs after median and tibial nerve stimulation were recorded with Ag/AgCl disk electrodes placed on 19 derivations corresponding to the International 10–20 system. Reference was at the linked earlobes (A1 + A2). 130 artifact-free responses were separately recorded for each of the four stimulation sessions. Then, responses were averaged in a period of 100 ms from the onset of the stimuli to obtain SEPs for each recording session. The amplitude of each SEPs was calculated with respect to the amplitude at the onset of the stimuli.

EEG and MEG were recorded in separate session. During MEG recording, the patient was seated inside a magnetically shielded room. SEFs were recorded at 1025 Hz sampling rate using the whole-head MEG system consisting of 165 dc SQUID integrated magnetometers (Della Penna et al., 2000).

Before and after each stimulation session, the position of the head with respect to the sensor was determined by localizing five coils placed on subject's head. The locations of the coils and of three anatomical landmarks on the subject's head were digitized by means of a 3D digitizer (Polhemus, 3Space Fastrak).

A high-resolution structural volume was acquired with a Philips scanner at 3 T via a 3-D T1-TFE (Turbo Field Echo) sequence to provide the anatomical reference for the MEG recordings.

For each of the four stimulation sessions (left and right median nerve stimulation, left and right tibial nerve stimulation) MEG data were preprocessed to subtract the heart signal and to remove noisy trials. Thus the first artifact-free 130 responses were averaged in a period of 150 ms, including a 50 ms prestimulus time. The amplitude of SEFs was calculated with respect to a baseline level chosen as the mean value of the 10–15 ms post-stimulus baseline (Torquati et al., 2002). The SEFs were analyzed in the interval 18–120 ms post-stimulus. Data analysis was performed using the equivalent current dipole (ECD) as source model of the SEFs. Only dipolar source configurations with explained variance >90% were accepted. Source waveforms were estimated by multiple source analysis using the BESA-BrainVoyager software in the 0–100 time interval. For each dipolar source the greatest intensity and the latency of peak activity were estimated in order to compare the strength among sources. Then the intensity of the sources was normalized with respect to the source intensity of the first component. ECDs were superimposed on structural MRI images transformed into the Talairach space using a piecewise affine and continuous transformation to evaluate the location of the sources.