Seizure 23 (2014) 213–221

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Uppermost synchronized generators of spike–wave activity are localized in limbic cortical areas in late-onset absence status epilepticus

Palma Piros [a], Szilvia Puskas [b], Miklos Emri [c], Gabor Opposits [c], Tamas Spisak [c], Istvan Fekete [b,*], Bela Clemens [a]

[a] Department of Neurology, Kenezy Gyula Hospital, Bartok Bela ut 2-26, H-4031 Debrecen, Hungary
[b] Department of Neurology, Medical and Health Science Center, University of Debrecen, Moricz Zsigmond krt. 22, H-4032 Debrecen, Hungary
[c] Department of Nuclear Medicine, Medical and Health Science Center, University of Debrecen, Nagyerdei krt. 98, H-4032 Debrecen, Hungary

ARTICLE INFO

Article history:
Received 14 April 2013
Received in revised form 25 November 2013
Accepted 27 November 2013

Keywords:
Absence status epilepticus
LORETA
LORETA Source Correlation

ABSTRACT

Purpose: Absence status (AS) epilepticus with generalized spike–wave pattern is frequently found in severely ill patients in whom several disease states co-exist. The cortical generators of the ictal EEG pattern and EEG functional connectivity (EEGfC) of this condition are unknown. The present study investigated the localization of the uppermost synchronized generators of spike–wave activity in AS.
Method: Seven patients with late-onset AS were investigated by EEG spectral analysis, LORETA (Low Resolution Electromagnetic Tomography) source imaging, and LSC (LORETA Source Correlation) analysis, which estimates cortico-cortical EEGfC among 23 ROIs (regions of interest) in each hemisphere.
Results: All the patients showed generalized ictal EEG activity. Maximum *Z*-scored spectral power was found in the 1–6 Hz and 12–14 Hz frequency bands. LORETA showed that the uppermost synchronized generators of 1–6 Hz band activity were localized in frontal and temporal cortical areas that are parts of the limbic system. For the 12–14 Hz band, abnormally synchronized generators were found in the antero-medial frontal cortex. Unlike the rather stereotyped spectral and LORETA findings, the individual EEGfC patterns were very dissimilar.
Conclusion: The findings are discussed in the context of nonconvulsive seizure types and the role of the underlying cortical areas in late-onset AS. The diversity of the EEGfC patterns remains an enigma. Localizing the cortical generators of the EEG patterns contributes to understanding the neurophysiology of the condition.

1. Introduction

Long-lasting ictal epileptic conditions with deranged higher-order cerebral functions but not major convulsions are labeled as nonconvulsive status epilepticus (NCSE). NCSE with generalized spike–wave pattern is usually called absence status (AS). AS may appear as a complication of idiopathic and symptomatic epilepsies[1] and may be precipitated by acute cerebral disorders, metabolic-toxic conditions, neuroactive drugs, a few antibiotics, hormonal changes, fever and sleep deprivation.[2–4] AS may occur in severely ill patients in whom several pathological conditions co-exist.[5,6] The diagnosis of AS may be suspected on clinical grounds but should be confirmed by an ictal EEG record.

NCSE was at first subdivided into generalized (absence status, spike–wave stupor) and focal (psychomotor status, complex partial status epilepticus) groups. This rigid dichotomy has been challenged by a lot of observations. Well-documented reports revealed that ictal EEG activity frequently starts focally and becomes bilateral and synchronous later, in the course of AS.[7,8] Conventional analysis of the EEG potential field only allows raw topographical estimation of the cortical generators when the ictal patterns are bilateral. Furthermore, it is not known what sort of abnormal EEG functional connectivity (EEGfC) of the brain is associated with the derangement of higher cerebral functions in AS. Neurophysiological exploration of the severely ill patients with AS has not been carried out yet. EEG source analysis may be

Abbreviations: AS, absence status; BOLD, blood-oxygen-level-dependent; EEGfC, EEG functional connectivity; LORETA, Low Resolution Electromagnetic Tomography; LSC, LORETA Source Correlation; NCSE, nonconvulsive status epilepticus; ROI, region of interest; VNB, very narrow band.

* Corresponding author. Tel.: +36 52 415 176; fax: +36 52 453 590.
E-mail addresses: pirospalma@freemail.hu (P. Piros), prof.fekete@yahoo.com (I. Fekete).

1059-1311/$ – see front matter © 2013 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2013.11.017

Table 1
Main relevant clinical data, laboratory and cranial CT abnormalities of the patients. LH = left hemisphere; RH = right hemisphere.

Pt. no.	Age (sex)	Main clinical data
1	51 (M)	Past history: schizophrenia, moderate mental retardation, rare convulsive seizures. Recent history: upper airway infection with high fever, not specified changes in psychiatric drug treatment, repeated convulsive seizures. Generalized rigidity, somnolence, psychomotor slowing. Findings: CT: mild bilateral temporal-insular atrophy. Mildly elevated blood glucose level. Chronic treatment: carbamazepine but subtherapeutic serum level. Acute drug treatment: no neuroactive drugs before EEG registration.
2	82 (M)	Past history: hypertension, cardiomyopathy, RH ischemic insult, a single acute symptomatic seizure. Recent history: cranial trauma, RH contusion, subdural hematoma. Two days after evacuation of the hematoma disorientation, followed by motionless, areactive state, the lack of any cooperation. Findings: CT: small RH intracerebral hematoma, overall cortical atrophy. No significant laboratory alterations. Chronic treatment: no neuroactive drugs. Acute drug treatment: no neuroactive drugs before EEG registration.
3	69 (F)	Past history: schizophrenia, ischemic lesion in the LH, three convulsive seizures, diabetes (treated). Recent history: headache, disoriented state, a few hours later motionless, areactive state. Findings: CT: moderate cerebral atrophy. Moderately elevated blood glucose. Chronic treatment: no neuroactive drugs. Acute drug treatment: no neuroactive drugs before EEG registration.
4	82 (F)	Past history: hypertension, ischemic cardiomyopathy, diabetes, focal epilepsy with LH focus. Recent history: right facio-brachial motor seizures, 10 mg diazepam intravenously, followed by motionless, unresponsive state. Findings: CT: Diffuse cortical atrophy and multiple small ischemic lesions in both hemispheres. Moderately elevated blood glucose. Urine analysis indicated purulent uroinfection. Chronic drug treatment: gabapentin, daily dose: 1200 mg. Acute drug treatment: no neuroactive drugs before EEG registration.
5	32 (F)	Past history: childhood absence epilepsy, in terminal remission. Later depression, alcohol abuse and suicide attempt. Diabetes with hypoglycemic episodes and situation-related convulsive seizures. Recent history: upper airway infection, a convulsive seizure, thereafter decreased level of vigilance, no spontaneous movements. Findings: normal cranial CT and laboratory findings. Chronic treatment: no neuroactive drugs. Acute drug treatment: no neuroactive drugs before EEG registration.
6	42 (M)	Past history: no significant disease events. Recent history: high fever, non-purulent encephalitis, several convulsive seizures, disoriented in the intervals. Phenytoin given intravenously abolished the motor seizures but the patient remained confused and areactive. Findings: cranial CT was normal, analysis of the cerebrospinal fluid confirmed aseptic meningitis. Chronic treatment: no neuroactive drugs. Acute drug treatment in the 2 days before EEG registration: intravenous phenytoin, therapeutic serum levels.
7	56 (M)	Past history: long-lasting alcohol abuse and dependence, cerebral and cerebellar atrophy, frontal lobe symptoms. Recent history: hypertonic crisis, left faciobrachial convulsion, benzodiazepine and phenytoin treatment followed by decreased ventilation. Moderately elevated temperature. Confused state and fluctuating level of vigilance. Findings: cranial CT: left temporal hypodense abnormality of unknown origin. No significant laboratory findings. Chronic treatment: no neuroactive drugs. Acute drug treatment a few hours before EEG registration: intravenous diazepam and phenytoin.

performed in the time and frequency domains. However, the former approach does not refer to EEG frequencies and frequency bands. Investigating the frequency domain is of interest in all brain states because brain functions are organized by oscillations at specific frequencies that are strongly interrelated. With these facts in mind we performed EEG source analysis in the frequency domain. Functional connectivity analysis is a particularly important approach because it demonstrates normal and abnormal interrelatedness among parts of a neuronal system or network. Network analysis is a promising tool to realize abnormal functions and clinical symptoms in terms of network dynamics.[9] As to address these issues, we analyzed the ictal EEG activity of seven, severely ill patients with AS.

2. Patients and methods

2.1. Patients and EEG recording

Patients with AS were enrolled into this retrospective study. Using the search words "generalized" and "NCSE" we detected 14 patients in the database of our EEG Laboratory in the 2005–2010 time period. Out of them, seven, non-consecutive patients fulfilled the inclusion criteria for this study: a correct patient file; a good quality EEG record that allows quantitative EEG analysis; the reviewed case had to fit the diagnostic criteria of AS.[10] The presence of active, idiopathic generalized epilepsy was an exclusion criterion. Relevant events of the patients' medical history, clinical, laboratory and cranial CT findings, neuroactive medication and a brief description of the patients' behavior during AS are briefly summarized in Table 1. As far as it is known from the patient's records their medications were not change during the last few days prior to the occurrence of AS.

Six patients had at least two neurological disorders in their past history. Five of them had focal epilepsy or acute symptomatic seizures. Their recent history was very diverse, including some of the following items: recently acquired cerebral lesion, upper airway infection, primary cerebral infection, elevated blood glucose, changes in neuroactive drug regimen, convulsive epileptic seizures. The core symptoms of the AS were very similar in five patients: motionless, unresponsive state, the lack of verbal and nonverbal communication. However, some degree of arousability was preserved. One of the remaining patients had psychomotor slowing and decreased responsiveness (Patient 1), while the other showed fluctuating somnolence and confusion (Patient 7).

All the EEG records and the clinical data were reviewed by one of us, a board-certified expert in neurology and clinical