Distribution of Spatial Complexity of EEG in Idiopathic Generalized Epilepsy and Its Change After Chronic Valproate Therapy

Istvan Kondakor*, Marton Toth*, Jiri Wackermann†, Csilla Gyimesi*, Jozsef Czopf*, and Bela Clemens‡

Summary: The objective of this study was to investigate the global and regional spatial synchrony of the EEG background activity, and to assess the effect of chronic valproate therapy on spatial synchrony. 15 idiopathic generalized epilepsy (IGE) patients were examined and compared to 16 normal controls. Resting EEG with 19 channels was investigated before and during chronic administration of valproate (VPA). Omega, a single-valued measure of spatial covariance complexity, was calculated to assess the degree of spatial synchrony of EEG. Furthermore, a new parameter was defined to characterize the distribution of spatial synchrony (Antero-Posterior Complexity Ratio, APCR). Global Omega complexity was significantly lower in IGE compared to controls, while regional complexity showed significant differences only in the anterior region: the IGE group showed lower complexity. APCR was significantly lower in IGE. VPA therapy (1) lowered the global complexity, (2) increased regional complexity in the anterior region, but decreased it in the posterior region, and (3) increased APCR. In IGE lower complexity, i.e. enhanced spatial synchrony, was found, especially in the anterior cortical area. VPA modified the distribution of spatial synchrony in IGE patients towards that of normal controls, although the effect is not identical with full normalization of cortical bioelectric activity. Whether the observed change of spatial synchrony distribution may reflect the normalizing effect of valproate on the brain state is worth further investigation.

Key words: Human multichannel EEG; Idiopathic generalized epilepsy; Valproate; Spatial synchrony; Omega complexity; Antero-Posterior Complexity Ratio.

Introduction

Idiopathic generalized epilepsy (IGE) is the most common form of generalized epilepsy, including a number of syndromes (ILAE 1989) highly determined by genetic factors (Berkovic and Scheffer 2001). IGE is classically conceived as "functional disorder" without abnormal neurological and neuropsychological findings (Gastaut 1973). However, in the last two decades several arguments have been published about regional differences using the classical investigational methods. Using histological methods, mild developmental abnormalities of the brain tissue (microdysgenesis) were reported in the last few years (Meencke and Veith 1999). Especially, abnormalities of the frontal cortex (neuronal profile counts in the molecular layer of the frontal cortex and in deep frontal white matter) were found, and they were present in significantly higher number in IGE compared with control subjects (Meencke 1983; Meencke 1985). However, in another study no microscopic or ultramicroscopic histological abnormalities were shown: Opeskin et al. (2000) did not find any differences analyzing the microstructures of nine Brodmann’s areas, putamen and globus pallidus, thalamus and both hippocampi. The assumption that there are morphological differences between several areas of the brain in IGE is also supported by recent quantitative MRI studies, that showed volume and structural abnormalities: a larger gray matter/subcortical volume ratio (Woermann et al. 1998), structural abnormalities in cortical gray matter in patients with juvenile myoclonic epilepsy (Woermann et al. 1999), and elongation of the anterior portion of the brain and a shrinkage of the posterocaudal part in patients with
primarily generalized tonic-clonic seizures (Savic et al. 1998). In addition to morphological alterations, positron emission tomography (PET) studies revealed widespread cortical dysfunction in IGE patients. [11C]Flumazenil (FMZ) PET investigations have demonstrated differences in patients with IGE compared to normal controls: FMZ volume distribution was significantly higher in the cerebral cortex, thalamus and cerebellum in the IGE group which could reflect microdysgenesis and might be related to cortical hyperexcitability (Koepp et al. 1997).

EEG background activity in IGE was generally reported as being within normal limits. However, in recent reviews an admixture of slower frequencies of the background activity was reported in patients with grand mal seizures on awakening (EGMA), juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME) (Wolf 1992a,b,c). The main results of a quantitative EEG study were diffuse delta and theta power excess in these IGE groups, as opposed to controls. The changes were uppermost prominent bilaterally, in the frontal regions (Clements et al. 2000).

In most IGE syndromes the broad-spectrum antiepileptic drug, valproate (VPA) is preferred for pharmacotherapy. The mode of action of clinically effective doses of VPA is uncertain in IGE, but it is likely, that multiple mechanisms are responsible for its anticonvulsant action. Effects of valproate on EEG, particularly on paroxysmal activity, are well-known: it reduces the 3 cps spike and wave activity, showing a clear correlation with the control of absence seizures, while no significant changes were found in the background activity (Villareal et al. 1978; Brunii 1980). Moderate slowing of background activity (Sackellares et al. 1980) and increase of diffuse slow frequencies have been noted (Gram et al. 1977), while another study reported that chronic VPA therapy nearly normalizes the power spectra of background EEG (Clements and Barta 1999).

Numerous methods, linear as well as non-linear, were developed to assess "complexity" or "dimensionality" of brain electrical activity (e.g., Rapp et al. 1989). These measures may reflect the degree of co-operation of the processes generating the electric field of the brain (Friston 1996) and are thus of particular relevance for studies in epilepsy. It has been also claimed that these methods may be helpful in localization of epileptogenic areas in different cerebral regions, even during seizure-free intervals, and also in monitoring of anti-epileptic therapy and in forecasting of epileptic seizures (Lehnertz 1999). The measure used in this study, Omega complexity, belongs to the class of linear measures (Wackermann 1999; see also Appendix) and characterizes the spatial synchrony of the multichannel signal: the lower the value of Omega, the higher the spatial synchrony, and vice versa. The method has been shown to reflect mental activity, vigilance levels and medication effects very sensitively (Szelenberger et al. 1996a; Kondakov et al. 1997; Yagyui et al. 1997; Saito et al. 1998; Stancak and Wackermann 1998; Kondakov et al. 1999). There are, however, no reports on effects of antiepileptic drugs like valproate on spatial synchrony of EEG.

The objective of this study was to investigate the global and regional spatial synchrony of the EEG in IGE patients, before and during chronic VPA therapy, and to compare the results with normal controls. The hypothesis that chronic administration of valproate influences brain functional complexity was tested.

Methods

Subjects

Fifteen patients with newly diagnosed IGE participated in the study (mean age: 18.9 years, S.D. = 3.4; 4 male, 11 female). The patient group showed the following distribution: 5 juvenile absence epilepsy (JAE, mean age: 19.0 years, S.D. = 4.4), 5 juvenile myoclonic epilepsy (JME, mean age: 17.4 years, S.D. = 3.4) and 5 patients with epilepsy with grand mal (generalized tonic-clonic) seizures on awakening (EGMA, mean age: 20.4 years, S.D. = 2.4). Patients were enrolled on a prospective, quasi-random basis. All patients were free of antiepileptic medication. Structural neuroimaging (MRI) was obligatory in EGMA but not in JAE and JME patients. Diagnoses were made or revised by the senior author (B.C.). Concerning diagnosis, internationally accepted diagnostic guidelines were respected (Commision 1989; Wolf 1992a,b,c). Exclusion criteria were as follows: neurological or mental symptoms indicative of brain pathology or psychiatric disease, use of any drug (including all therapeutic agents, alcohol, recreational or other compounds except oral contraceptives), any concomitant complaint or medical condition that could influence brain activity and EEG, and a major (convulsive) seizure in the 5 days before EEG investigation. After the diagnostic examinations, including EEG, when the diagnosis of IGE was established, a plan of valproate therapy was elaborated by the senior author (B.C.) who also followed the patients during the therapy. The drug was administered orally in capsule form, with individual dosage varying from 10 to 30 mg/kg. The second EEG recording was carried out 3 months later, when all patients were free of seizures and had no drug-related adverse events. The study design was approved by the Local Ethics Committee of the Hospital.

Sixteen non-paid healthy persons (mean age: 20.5 years, S.D. = 4.0; 4 male, 12 female) served as normal control in the study recruited from the medical staff, relatives and friends of the staff, and from medical students. Control persons had not had any CNS-affecting items in