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Neurophysiological activity underlying altered brain metabolism in epileptic encephalopathies with CSWS

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Summary We investigated the neurophysiological correlate of altered regional cerebral glucose metabolism observed in children with epileptic encephalopathy with continuous spikewaves during sleep (CSWS) by using a multimodal approach combining time-sensitive magnetic source imaging (MSI) and positron emission tomography with [¹⁸F]-fluorodeoxyglucose (FDG-PET).

Six patients (4 boys and 2 girls, age range: 4–8 years, 3 patients with Landau—Kleffner syndrome (LKS), 3 patients with atypical rolandic epilepsy (ARE)) were investigated by FDG-PET and MSI at the acute phase of CSWS.

In all patients, the onset(s) of spike-waves discharges were associated with significant focal hypermetabolism. The propagation of epileptic discharges to other brain areas was associated with focal hypermetabolism (five patients), hypometabolism (one patient) or the absence of any significant metabolic change (one patient). Interestingly, most of the hypometabolic areas were not involved in the epileptic network per se.

This study shows that focal hypermetabolism observed at the acute phase of CSWS are related to the onset or propagation sites of spike-wave discharges. Spike-wave discharges propagation can be associated to other types of metabolic changes, suggesting the occurrence of various

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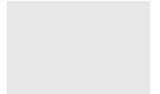
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Abbreviations: CSWS, continuous spike-waves during sleep; EEG, electroencephalography; FDG-PET, positron emission tomography with [18F]-fluorodeoxyglucose; MSI, magnetic source imaging; MRI, magnetic source imaging; MEG, magnetoencephalography; LKS, Landau—Kleffner syndrome; ARE, atypical rolandic epilepsy; SWI, spike-wave index; SWD, spike-wave discharge; ECD, equivalent current dipole; EEG-fMRI, electroencephalography combined with functional magnetic resonance imaging.

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neurophysiological mechanisms at the cellular level. Most of the hypometabolic areas are not involved in the epileptic network as such and are probably related to a mechanism of remote inhibition. These findings highlight the critical value of combining FDG-PET with time-sensitive functional neuroimaging approaches such as MSI to assess CSWS epileptic network when surgery is considered as a therapeutic approach.

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Introduction

Epileptic encephalopathies are pediatric epileptic conditions in which cognitive, sensorial, behavioral or psychomotor functions deteriorate as a consequence of epileptic activity (Dulac, 2001; Engel, 2001; Nabbout and Dulac, 2003). The epileptic encephalopathies with continuous spike-waves during sleep (CSWS) are considered as a prototype of epileptic encephalopathies (Holmes and Lenck-Santini, 2006). They are indeed age-related peculiar conditions in which epileptic EEG activity occurring almost exclusively during sleep and for prolonged periods of time leads to heterogeneous neuropsychological impairment and behavioral disorders (Tassinari et al., 2009). This EEG pattern is therefore also frequently referred to as electrical status epilepticus during slow sleep (Tassinari et al., 2009).

Previous positron emission tomography with [18F]fluorodeoxyglucose (FDG-PET) studies performed during the awake state at the acute phase of CSWS have demonstrated the existence of long lasting changes in brain function characterized by the association of focal increases and decreases in neuronal activity in distinct brain areas, with heterogeneous location of the metabolic abnormalities across patients (for reviews, see De Tiège et al., 2009; Van Bogaert et al., 2012). Several experimental evidences suggest that these metabolic abnormalities observed during the awake state are in fact related to the intense epileptic activity occurring during sleep (De Tiège et al., 2004, 2008b; Maguet et al., 1995). One pathophysiological model proposed to explain these findings is based on the "surrounding and remote inhibition theory", which suggests the existence of epilepsy-induced inhibition of neurons that surround or are remote from the hypermetabolic epileptic focus but connected with it via cortico-cortical or polysynaptic pathways (De Tiège et al., 2009). This model was initially elaborated to account for the anatomical relationship found between localizations of CSWS focus on EEG on one hand and sites of metabolic changes on awake FDG-PET on the other hand. This relationship indeed appeared to be tighter for hypermetabolic than for hypometabolic areas (De Tiège et al., 2004). The evidence of altered effective connectivity between hyper- and hypometabolic areas further suggested that the level of metabolic activity in hypometabolic areas is related to the epilepsy-induced metabolic changes in the hypermetabolic ones (De Tiège et al., 2004, 2008b). Finally, the complete or almost complete parallel regression of awake hypermetabolic and hypometabolic abnormalities at recovery from CSWS is an additional clue for a causal relationship between these opposite metabolic changes in remote brain regions (De Tiège et al., 2008b). On a clinical point of view, metabolic data suggest that sustained perturbation of neurophysiological processes through the sleep-wake cycle might account for the cognitive and behavioral regressions observed at the acute phase of CSWS. These data also incite to attribute the neurological regression not only to the neuronal impairment at the epileptic focus site, but also to epilepsy-induced neurophysiological changes in distant and connected brain areas (De Tiège et al., 2004, 2008b, 2009). Although the previous metabolic studies contributed to the understanding of the epileptic encephalopathy with CSWS, and of the impact of epileptic activity on normal brain function in general, interpretation of the awake FDG-PET abnormalities suffered from a lack of information on the exact pathophysiological relationship between the intense epileptic activity occurring during sleep and altered neuronal metabolism observed during the awake state.

Here, we applied a multimodal approach combining magnetic source imaging (MSI) and FDG-PET to investigate in six children with epileptic encephalopathy with CSWS the neurophysiological correlate of altered regional cerebral glucose metabolism observed during the awake state at the acute phase of CSWS. MSI localizes on a structural cerebral magnetic resonance imaging (MRI) the electrical sources at the origin of magnetic fields recorded by magnetoencephalography (MEG) with a temporal resolution at the level of the millisecond and a spatial resolution of a few millimeters (Hämäläinen et al., 1993). The combination of MSI and FDG-PET takes advantage of both methods (neurophysiological signal, excellent temporal and good spatial resolutions for MSI; neurometabolic signal, poor temporal and good spatial resolutions for FDG-PET) to better characterize the neurophysiological mechanisms accounting for the long-lasting metabolic repercussions of CSWS activity in this disorder. The main objective of this study was to find common pathophysiological mechanisms across children with CSWS despite the clinical and metabolic heterogeneity characterizing this epileptic condition.

Methods

Patients and control subjects

Among the population of patients studied by FDG-PET in the context of presurgical evaluation for focal epilepsy between May 2008 and April 2010, six children (4 boys and 2 girls, 4—8 years) were retrospectively selected based on the following inclusion criteria: (1) epileptic encephalopathy with CSWS, (2) normal structural cerebral MRI, (3) FDG-PET and MEG performed concomitantly at the acute phase of CSWS, and (4) significant local hypermetabolism on FDG-PET data. None of these patients had been included in previous studies on FDG-PET in CSWS. Patients' clinical data were retrieved

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