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Sleep-potentiated epileptiform activity in early thalamic injuries: Study in a large series (60 cases)

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Summary
Objective: The study aims at a better definition of continuous spike—waves during sleep (CSWS) with an early thalamic lesion, focusing on various grades of sleep-potentiated epileptiform activity (SPEA). Their possible relationship with different clinical features was studied to try to define prognostic factors of the epileptic disorder, especially relating to behavior/cognitive outcome, in order to improve prevention and treatment strategies.
Methods: Sixty patients with early thalamic injury were followed since the first registration of SPEA with serial neurological, long term EEG monitoring and neuropsychological examinations, as well as neuroimaging and a detailed clinical history. They were classified in three different groups according to the sleep spike—waves (SW) quantification: electrical status epilepticus during sleep (ESES), more than 85% of slow sleep; overactivation between 50% and 85% and simple activation between 10 and 50%). Results were then examined also with a statistical analysis.
Results: In our series of CSWS occurring in early brain injured children with unilateral thalamic involvement there is a common neuropathologic origin but with various grades of SPEA severity. Statistical analysis showed that patients evolving toward ESES presented more commonly

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the involvement of the mediodorsal part of thalamus nuclei and a bilateral cortico-subcortical brain injury, epilepsy was more severe with a delayed onset; moreover, in the acute stage .ESES patients presented the worst behavior/cognitive performances. As to cognitive and behavior outcome, longer SPEA duration as well as bilateral brain injury and cognitive/behavior impairment in acute phase appear linked to a poor outcome; some particular neuropathology (ischemic stroke and haemorrhagic infarction) as well as hydrocephalus shunting are associated with behavior disorders.

Conclusions: Discrete features seem to support different underlying mechanisms in ESES patients in comparison with less severe SPEA; they represent negative prognostic factors. Longer SPEA duration as well as bilateral brain injury and cognitive/behavior impairment in acute phase seem predictive of a worse cognitive/behavior outcome.

Introduction

An EEG paroxysmal activation during sleep may occur in children with early thalamic injuries as reported in sporadic cases (Incorpora et al., 1999; Kelemen et al., 2006; Monteiro et al., 2001) and in large series of early brain lesions involving thalamus, especially vascular in origin (Guzzetta et al., 2005; Sánchez Fernández et al., 2012a). The clinical syndrome (epilepsy with continuous spike—waves during slow wave sleep: CSWS*)[1] is an age-related epileptic encephalopathy acknowledged by the Commission on Classification and Terminology of the International League Against Epilepsy (1989) and is characterized by a combination of focal epilepsy, neurocognitive regression and an electroencephalographic pattern of electrical status epilepticus during sleep (ESES*). It may classically be affirmed when paroxysmal activity occurs in >85% of slow sleep (Tassinari et al., 2000), even though some authors uses different cut-off rates (Buzatu et al., 2009; Caraballo et al., 2013; Sánchez Fernández et al., 2012b; Scheltens-de Boer, 2009; Van Hirtum-Das et al., 2006). In few studies on patients with CSWS collected in tertiary hospitals (Buzatu et al., 2009; Sánchez Fernández et al., 2012b; Van Hirtum-Das et al., 2006), early neurodevelopmental lesions concern 41 to 49% of cases and the only large series of brain injured children with CSWS focusing on early thalamic lesions showed a higher frequency of CSWS when thalami were involved (Sánchez Fernández et al., 2012a). So, thalamus early injuries seem to play a role in determining age-related sleep EEG paroxysmal activation.

Our study aims at a better definition of CSWS with an early thalamic lesion in a sample of 60 children. Various grades of sleep-potentiated epileptiform activity (SPEA) were considered as proposed by Sánchez Fernández et al. (2012b), and their possible relationship with different clinical features was studied in order to try to define prognostic factors of the epileptic disorder, especially relating to behavioral and cognitive outcome; that would be useful to highlight mechanisms underlying clinical features in CSWS with an early thalamic injury and to improve prevention and treatment strategies.

[1] We used the acronym ESES to indicate the EEG abnormality and CSWS to refer to the disease with continuous spike—waves during sleep.

Patients and methods

Sixty children (30 boys and 30 girls) with CSWS associated with early thalamic lesions consecutively admitted to the Child Neurology Unit of the Catholic University since 1999 were enrolled in the study. Twenty nine of these patients had been included in an old study (Guzzetta et al., 2005), but were now studied again after a further 8 year follow-up. Our study was retrospective as to information regarding the period preceding the first SPEA registration; thereafter it was prospective and the patients were followed up according to a planned protocol. The follow-up protocol consisted of serial EEG monitoring, neurological, behavioral and neuropsychological assessments, at least twice a year, as well as neuroimaging (MRI) if necessary and a detailed clinical history.

Usually, EEG registration included about two hours of sleep EEG, without administration of any sleep-inducing drug. In cases of doubt, an overnight sleep recording was also performed. Patients belong to three different groups according to the sleep spike—waves (SW) quantification based on visual inspection: (i) 28 cases with continuous and diffuse SW in more than 85% of slow sleep (according to the ESES classical definition of Tassinari et al. (2000); (ii) 26 cases with an overactivation consisting of SW between 50% and 85% of slow sleep; (iii) 6 cases with a simple activation (between 10 and 50% of slow sleep). We divided the evolution of the disease into four stages according to the slightly modified proposal of Sánchez Fernández et al. (2012b): *dormant* from birth till age of seizure onset, *prodromal* from seizure onset to the first registration of paroxysmal activation during sleep, *acute* stage that lasts until the stable disappearance of paroxysmal activation during sleep and finally the *residual* stage. We preferred on one hand (onset of acute stage) the reference to the more objective sleep EEG findings rather than to the cognitive and behavior disorder (considered by Sánchez Fernández et al. (2012b), less exactly identifiable; on the other hand, we considered the beginning of residual stage at the time of stable disappearance of sleep paroxysmal activation rather than of seizures that in symptomatic cases like ours may continue independently of SPEA. The onset and the end of SPEA in ESES cases included the possible initial and final transition consisting of overactivation. The stable disappearance of SPEA however was recognized after two consecutive sleep EEG without paroxysmal activation in at least six months.