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A commentary on Encephalopathy related to Status Epilepticus during slow Sleep: from concepts to terminology

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The "debate" among Edouard Hirsch, Roberto Caraballo, Bernardo Dalla Bernardina, Tobias Loddenkemper and Sameer Zuberi (Hirsch *et al*., p. S5-12) highlights effectively some shared concepts that define Encephalopathy related to Status Epilepticus during slow Sleep (ESES). There is a large consensus among the five experts that the cardinal features that characterize ESES are: a) childhood onset; b) self-limited focal or generalized enhancement of EEG abnormalities during NREM sleep; c) acquired impairment of cognitive, behavioral and sometimes motor functions related to the appearance of the peculiar sleep EEG pattern; epileptic seizures are almost always present but their occurrence is not mandatory for the diagnosis of ESES.

We and most of the experts that participated in the debate believe that the three main features listed above can indeed define ESES as a separate syndrome with its nosographic place within the group of epileptic encephalopathies (see also Tassinari and Rubboli, p. S82-7).

This opinion is supported by the evidence of children, neurologically and cognitively normal before ESES onset (*i.e*., with idiopathic etiology), who start to present with cognitive and behavioral deterioration in concomitance with a striking exaggeration of EEG epileptic activity during NREM sleep (*i.e*. "status epilepticus during sleep (SES)"), without evidence of other factors that can derange neuropsychological development and regardless of the presence of diurnal or nocturnal epileptic seizures.

We believe that **idiopathic ESES** is a specific condition, which in some cases represents the evolution of an idiopathic rolandic epilepsy, but in other cases represents a condition in its own right from onset (patients presenting with seizures other than rolandic seizures, or even no seizures at all), and it illustrates the "core" concept of ESES itself, that is the deleterious, sometimes permanent, effects on cognitive/behavioral functions associated with exaggerated epileptic activity during NREM sleep in the developmental age.

From this perspective, LKS (which by definition does not have a symptomatic etiology) indeed appears to be a variant of idiopathic ESES, with a well defined neuropsychological deficit (auditory agnosia and language impairment). Once more, we wish to point out that the concept of the harmful effect of epileptic activity "*per se*" is incorporated into the definition of epileptic encephalopathy by the International League Against Epilepsy (ILAE) Classification Task Force (Berg *et al*., 2010), which includes not only conditions with frequent seizures but also those with a large amount of "interictal" epileptiform activity. In addition, in agreement with the recent ILAE proposals on the definition of "syndrome" (Berg *et al*., 2010; Scheffer *et al*., 2017), we believe that ESES is a syndrome defined by specific electro-clinical features, independent of etiology and indeed, can be associated with different etiologies.

It can be hypothesized that the striking enhancement of epileptic activity during NREM sleep (due to a structural etiology, antiepileptic drugs, or other factors?), that can occur in etiologically heterogeneous

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conditions, may disrupt sleep-related consolidation and maturation of cognitive processes, resulting in or aggravating an encephalopathy, involving pathogenetic mechanisms similar to those underlying "idiopathic" ESES.

We consider "status epilepticus during sleep" in ESES as a clinical condition characterized by sustained and protracted epileptic activity. As in other types of status epilepticus in which it is not necessary to quantify the amount of epileptic spikes to diagnose the status itself, but it is the electro-clinical picture that orients the diagnosis, we wish to tone down the relevance that has been given to the spike-wave index (SWI) in the diagnosis of ESES since its first description (Patry *et al*., 1971). The SWI threshold to diagnose ESES can be flexible, and can be <85%, provided that the main feature of ESES, *i.e*. occurrence of cognitive and behavioral deterioration associated with a striking enhancement of epileptic activity during NREM sleep, is demonstrated. These latter considerations raise the issue of other sleep-related parameters, besides SWI, that can play a pathogenetic role in ESES. We and all the experts agree that a derangement of sleep homeostasis caused by the exaggerated epileptic discharges during NREM sleep might play a crucial role in ESES. In recent years, a wealth of experimental and clinical research on sleep physiology has shown the important role of sleep homeostasis in memory consolidation and in learning processes (Tononi and Cirelli, 2014). Recently, some studies have shown that an impairment of sleep homeostasis caused by sleep-related epileptic activity could play a role in the cognitive derangement of ESES (Bolsterli *et al*., 2011, 2014, 2017; Rubboli *et al*., p. S62-S70; Tassinari and Rubboli, p. S82-7). We wish to emphasize the relevance of these findings to better understand ESES pathophysiology, but also because of the possible implications in the management of other epileptic conditions with a striking increment of epileptic activity during sleep in the developmental age.

In conclusion, in our opinion, what qualifies ESES as a unique and identifiable condition, *i.e*. a syndrome, is not just the peculiar EEG picture of the striking exaggeration of epileptic discharges during sleep, which can be subtended by different etiologies, but the dramatic, and often irreversible effects that this sleep-related epileptic activity can produce in developmental age on cognition and behavior. Several recent data suggest that sleep-related derangement of sleep homeostasis caused by protracted epileptic activity during sleep might be responsible for the encephalopathic picture. In this respect, ESES is a privileged model for the investigation of the reciprocal interactions between epilepsy, sleep and cognition. □

Disclosures.
None of the authors have any conflict of interest to declare.

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