Review article

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Encephalopathy related to Status Epilepticus during slow Sleep: current concepts and future directions

Carlo Alberto Tassinari [1], Guido Rubboli [2]

[1] University of Bologna, Bologna, Italy
[2] Danish Epilepsy Center, Filadelfia / University of Copenhagen, Dianalund, Denmark

ABSTRACT – We present some aspects relevant to the definition and diagnosis of Encephalopathy related to Status Epilepticus during slow Sleep (ESES) to further understand the pathophysiological mechanisms in the light of current knowledge and some recent research. Future lines of research in ESES that include investigation of impairment of sleep homeostasis and disruption of age-related plasticity processes in the developmental age are also discussed.

Key words: encephalopathy related to status epilepticus during slow sleep (ESES), CSWS, sleep homestasis, cortical plasticity, developmental age, critical period

Encephalopathy related to Status Epilepticus during slow Sleep (ESES), otherwise labelled as "continuous spike and waves during sleep (CSWS)" was first reported more than 45 years ago. Since then, a considerable wealth of clinical observations and neurophysiological, neuroimaging, and genetic findings have been accumulated. However, in spite of this abundance of information, several issues related to ESES, not least the very definition of this condition, are still debated. In this paper, we discuss, in the light of current knowledge and some recent research, some aspects relevant to the delineation and identification of this condition to further understand pathophysiological mechanisms; we will also outline possible lines for future research.

The definition of ESES

There is a large consensus that the cardinal feature of ESES, *i.e.* Encephalopathy related to Status Epilepticus during slow Sleep, is the appearance of, or worsening of previously present cognitive disorders and behavioural disturbances in association with the occurrence of a striking activation of EEG epileptic abnormalities during REM sleep (see also Hirsch *et al.*, p.S5-S12, and Tassinari and Rubboli, p.S13-S14). This central concept for the diagnosis of ESES, that has been proposed since 1977 (Tassinari *et al.*, 1977) and that is incorporated in the 2010 ILAE definition of epileptic encephalopathy (Berg *et al.*, 2010), needs to be reaffirmed. Indeed, as shown by a recent survey

Correspondence:
Guido Rubboli
Danish Epilepsy Center,
Filadelfia/University of Copenhagen,
Kolonivej 1 - 4293 Dianalund, Denmark
<guru@filadelfia.dk>

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(Sanchez Fernandez *et al*., 2013), about 60% of American pediatric neurologists and epileptologists consider the demonstration of cognitive and/or language regression not mandatory, and a further 6-13% not relevant, for the diagnosis of ESES/CSWS. We believe that ESES can be diagnosed only when there is evidence of a deterioration of the cognitive and behavioural status in concomitance with the occurrence of extremely abundant epileptic discharges during NREM sleep. In our opinion, the observation of an exaggeration of epileptic activity during NREM sleep, without any demonstration of a clinical effect, *i.e.* appearance or worsening of an encephalopathy, does not allow the diagnosis of ESES. This clinical-EEG correlation can be a complex task due to:

– a) the heterogeneity of neuropsychological disorders, such as attention deficit, decreased IQ, language disorders, disturbances in spatial and temporal orientation, and memory impairment, as well as motor disorders (see review by Tassinari *et al*., 2012);

– b) a preexisting cognitive and behavioural derangement, that in most severe cases, can render a clinical/neuropsychological assessment challenging even before the appearance of ESES;

– c) an extremely selective cognitive impairment which can occur in cases with very focal ESES (Kuki *et al*., 2014).

These difficulties demand the development of appropriate neuropsychological testing, individually tailored to specific deficits and possibly complemented by adequate neurophysiological and neuroimaging data (Filippini *et al*., 2013; Tassinari *et al*., 2015).

The proteiform clinical features of the encephalopathies have been extensively described (Panayiotopoulos, 1999; Galanoupoulos *et al*., 2000; Hughes 2010). Three main groups can be retained:

– a) a " pervasive" group with patients with concomitant impairment of language, memory, spatial orientation and with ADHD and autistic-like behaviors;

– b) a "combined" group with patients with multiple concomitant dysfunctions, with one domain most clinically impaired, *e.g.* language as in LKS, or mainly a "frontal", "occipital ", or "parietal" dysfunction, with spatio-temporal or motor disturbances such as negative myoclonus, dyspraxias, and gait disorders (Billard *et al*., 1982; Roulet Peretz 1993; Neville *et al*., 1998);

– c) a selective group with patients with a unique (as documented so far) specific impairment, as " a visual agnosia", as reported by Eriksson *et al*. (2003), or " a selective dysgraphia" as reported by Kuki *et al*. (2014). The dysfunction of a very restricted patch of cortex, or even of a limited number of cortical columns, could thus result in such a selective impairment which could be easily overlooked, challenging a precise and correct clinical assessment (Tassinari *et al*., 2015).

Obviously, the "pervasive", "combined" and "selective" groups are static "frames" of an evolutive multifactorial age-related condition. The same patient could possibly evolve from an initial selective impairment to a combined or pervasive condition and eventually reverse, not necessarily in that order, to a previous stage, when partial remissions and relapses occur during the evolution.

During ESES, epileptic seizures are reported in the majority of cases, however, it is accepted that some cases have no history of clinical seizures at all. Therefore, the presence of epilepsy cannot be considered a mandatory feature for the diagnosis of ESES.

Atypical evolution from benign childhood epilepsy with centro-temporal spikes (BCECTS) to ESES or LKS has been reported (Saltik *et al*., 2005; Kramer *et al*., 2009; Tovia *et al*., 2011; see also Caraballo *et al*., p. S15-S21). Some studies that have identified possible prognostic factors predicting an atypical evolution from BCECTS to ESES or LKS (Fejerman *et al*., 2000; Massa *et al*., 2001; Saltik *et al*., 2005) need to be confirmed by further data in larger populations. Actually, BCECTS and ESES have been suggested to represent the more benign and the more severe end of a spectrum encompassing childhood focal epilepies respectively, in which the positioning along this spectrum might be influenced by a complex interplay between brain development, maturation processes and susceptibility genes (Rudolf *et al*., 2009; Carvill, 2013; Lemke *et al*., 2013; Lesca *et al*., 2013; Lesca *et al*., p. S41-S47). These concepts introduce the role of genetic factors in the etiology of ESES. However, this latter point further emphasizes the need for a shared and accepted definition of ESES and of its diagnostic criteria that allows precise genotype-phenotype associations.

ESES, or CSWS, or....?

In its original description, Tassinari's group referred to the condition now labelled as ESES/CSWS as "Subclinical electrical status epilepticus induced by sleep in children" (Patry *et al*., 1971). At that time, the strict link between the peculiar EEG pattern during sleep and the cognitive/behavioural disturbances was not immediately appreciated, therefore the term "subclinical" was used. The concept that this sleep-related exaggerated epileptic activity was not "subclinical" but was indeed "clinical", producing an encephalopathy, was proposed in 1977, when Tassinari *et al*. (1977) reported 11 additional patients and the term "encephalopathy related to status epilepticus during slow sleep" (*i.e.* ESES) was coined (see also Tassinari and Rubboli, p. S13-S14). Later on, the term "Epilepsy with continuous

spikes and waves during slow sleep (ECSWS)" was introduced to refer to the same group of patients (Tassinari *et al*., 1985; Panayiotopoulos, 2005). The International League Against Epilepsy (ILAE) adopted the term "Continuous spikes and waves during sleep (CSWS)", and accepted that a similar EEG pattern could be associated also with Landau-Kleffner syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Engel, 2006). More recently, the term "Epileptic encephalopathy with continuous spike and waves during sleep" has been used by the Commission on Classification and Terminology of the ILAE (Engel, 2006; Berg *et al*., 2010). Even though these different terms were not accompanied by any defining criteria of the syndrome, we can assume that these diverse and partially overlapping terms have been used to define the same or very similar conditions.

The assessment of the EEG during sleep

Since the first description by Patry *et al*. (1971), a spike-wave index (SWI) during NREM sleep, defined as the percentage of time occupied by spike and wave discharges, was used to provide an objective measure of the amount of epileptic activity during sleep. In the six patients reported originally by Tassinari's group (Patry *et al*., 1971), the lowest SWI was 85% and since then this value has been considered the threshold over which a diagnosis of ESES could be made. Over the years, many different studies have used considerably different SWI, whose threshold could vary from 25% to 90% (reviewed by Scheltens-de Boer, 2009; see also Cantalupo *et al*., p. S31-S40, and Gardella *et al*., p. S22-S30). However, rarely these studies report a clear description of the methods to measure the SWI, or which type (in terms of morphology and topography) of sleep-related epileptic discharges were assessed. Furthermore, recording setting (overnight EEG *versus* daytime sleep EEG) and length of the recording varies considerably in the different investigations.

Several pieces of evidence have shown that, in subjects in whom a striking activation of epileptic abnormalities occurs during sleep in comparison to wakefulness, a cognitive/behavioural derangement can occur with SWI lower than 85%. Therefore, the concept of a minimum SWI necessary for the diagnosis of ESES can be flexible, and not rigidly delimited by a SWI threshold >85%, once the main feature of ESES, *i.e*. occurrence of cognitive deterioration associated with sleep-enhanced epileptic activity, is demonstrated. This implies that the diagnosis of ESES cannot depend solely on the assessment of the SWI but it requires a precise correlation with the clinical picture. These concepts in some respect apply also to the spike topography, in particular in focal ESES, once there is evidence that a more or less selective neuropsychological deficit can be related to an enhanced focal-multifocal epileptic EEG activity during sleep in the cortical area involved in the performance of that neuropsychological task (Kuki *et al*., 2014; Tassinari *et al*., 2015). This conforms to the concept underlying the definition of ESES, *i.e*. disruption of cognitive functions in relation to increased epileptic activity during sleep in the cortical areas involved in the disrupted cognitive processes.

Is ESES a model of cognitive deterioration caused by impaired NREM sleep homeostasis ?

Following the concepts just mentioned above, the evidence that in ESES a cognitive/behavioural derangement can be observed with very different SWIs, and sometimes without a linear correlation between the severity of the encephalopathic picture and the SWI value, suggest that other parameters besides SWI might be relevant to further understand the relationships between the peculiar sleep EEG pattern and the clinical, *i.e*. encephalopathic, picture. Recent data suggest that the negative effects of ESES may depend on the impairment of synaptic homeostasis processes occurring during normal sleep which are particularly important in the developmental age. The synaptic homeostasis hypothesis (SHY) proposes that synaptic strength increases within neuronal networks during wakefulness (*e.g*. due to learning processes) and is renormalized or downscaled during sleep through synaptic weakening/elimination (Tononi and Cirelli, 2014). Changes in synaptic strength are reflected in the EEG by changes of sleep slow wave activity. In ESES, an impairment of synaptic downscaling has been demonstrated by Bolsterli and Huber (2011, 2014) (see also Rubboli *et al*., p. S62-S70). In addition, they have shown that an altered overnight decrease of slow wave slope - a sign of altered slow wave homeostasis -during ESES improves with remission of ESES (Bolsterli *et al*., 2017). Indeed, this study suggests that the SWI may not be the only parameter that should be investigated in ESES, and a derangement of homeostatic sleep processes, as measured by the decline of the slope of sleep slow waves, might better reflect the severity of the cognitive derangement. These findings suggest a fascinating as well as likely pathogenic mechanism: the prolonged paroxysmal activity (during around eight hours of sleep per day for several months up to a number of years) could interfere with the changes in sleep slow wave activity that normally occur in the course of sleep and this may be causally related to impairment in

cognitive functions and behavior associated with ESES (Tassinari and Rubboli, 2006; Rubboli *et al*., p. S62-S70). Other physiological graphoelements of sleep have been recently shown to play a role in the consolidation of memory and maintenance of cognitive function. In particular, sleep spindle activity has been demonstrated to be associated with different aspects of cognitive performance in children, and variation in spindle activity in adult sleep may shed light on the role of this sleep signature in the developmental age (Chatburn *et al*., 2013; Reynolds *et al*., 2018; Vermeulen *et al*., 2018). In ESES, lack or decrement of physiological sleep features, such as spindles, might be an additional factor impairing the remodelling of neuronal networks subserving cognitive processes, that normally occur during sleep.

This evidence introduces new methodological perspectives for the analysis of the electro-clinical correlations in ESES and opens new avenues to investigate and further understand this syndrome, providing a novel approach to elucidate the relevance of sleep-related paroxysmal activities, not only for ESES, but for a large population of children with significant activation of epileptic activity during sleep.

Critical periods and plasticity as relevant age-related variables in the pathophysiology of ESES

As thoughtfully discussed by Issa (2014), the model of critical periods (as proposed by Hubel and Wiesel, 1970) can further contribute to the understanding of the neurobiology of ESES. According to Issa (2014):

– *"there are in childhood critical-sensitive periods allowing the cortex to adapt to the idiosyncrasies of individuals and their environment;... Although the exact age range that covers the language critical periods... is often debated,... the age at which Landau-Kleffner patients have electrographic seizures falls within the commonly agreed critical periods* [...];

– *"In ESES, the organisation of cortex is driven into an abnormal structure by state-dependent (sleep) epileptiform activity during the critical period, but the abnormal electrical activity stops, once the critical period is over* [...].

Since the cognitive and behavioral disorders start and end at nearly the same time as the start and end of the critical periods, these disturbances appear to be strongly linked to these periods, that are crucial for normal development. According to Issa's hypothesis, the "electrical status epilepticus" would drive maladaptive plasticity during these critical periods; the termination of these periods would cement those adaptive changes, thus explaining the long-lasting effects of ESES on cortical functions (Issa, 2014). In addition, during these periods, the role of NREM sleep is extremely relevant for brain plasticity, and this can explain why sleep disruption does not just prevent new acquisitions but would actually degrade previously developed cortical structures (Frank *et al*., 2001). In ESES, this could hinder the physiological switch from one hemisphere to another or it could result in a redistribution of functions across different cortical areas at an early age (Issa, 2014).

The complexity and variability that characterize the ESES syndrome, as we have underlined above, render the diagnosis hazardous based on a single semiological component. The amount of paroxysmal activity during sleep, "the spike and wave index", within the appropriate clinical context could be misleading. Further parameters are needed in order to elucidate the natural history of ESES. The contribution of new neuroimaging techniques, such as diffusion tensor imaging tractography, to explore age-dependent differences and heritability of the perisylvian language network (Budisavlievic *et al*., 2015), altered white matter connectivity (Ameis and Catani, 2015; Catani *et al*., 2016) or networks related to behavior, cognitive and motor tasks (Catani *et al*., 2013; Parlatini *et al*., 2017) might add new perspectives in the study of ESES. Moving from hodology to function (Catani, 2007) could be a rewarding route towards further understanding of this fascinating condition. □

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

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