Review article

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EEG features in Encephalopathy related to Status Epilepticus during slow Sleep

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ABSTRACT – Encephalopathy related to Status Epilepticus during slow Sleep (ESES) is a peculiar electro-clinical condition, with variable etiologies, characterized by an age-dependent phenomenon of extreme activation of epileptic activity during sleep, i.e. "status epilepticus during sleep", that is strictly associated with the appearance of cognitive and behavioral disturbances. Even though the peculiar EEG picture is fundamental for the diagnosis of ESES, clear-cut and shared diagnostic criteria for defining the EEG boundaries of this syndrome are still lacking. The diagnosis of ESES can be further complicated by the variability of the EEG findings, that during the course of the disease can change from diffuse to more or less focal and viceversa, depending both on the spontaneous clinical evolution of this condition and/or on the effects of medications. Given the complexity and the heterogeneity of EEG parameters during the ESES course, it is important to correlate the EEG findings with the concomitant cognitive and behavioral status, possibly taking into account not only the spike-wave index, but also other parameters, such as for instance the topography of the epileptic abnormalities, their patterns of spread, and their fluctuations over time. Moreover, the epileptiform activity not only during sleep, but also during wakefulness, the presence of focal slowing, the organization of the EEG background and a derangement of the sleep architecture may play a role in determining the clinical picture.

Key words: encephalopathy related to status epilepticus during slow sleep, ESES, CSWS, EEG features

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Since the first description in 1971 (Patry *et al.*), the peculiar EEG pattern during sleep of ESES represents, by definition, one of the main features and at the same time a key element for its diagnosis. The alternative term "Continuous Spikes and Waves during slow Sleep" (CSWS), accepted in 1989 also by the Commission on Classification and

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Terminology of the International League against Epilepsy (ILAE) further emphasizes the EEG picture as a cardinal element of this syndrome.

Even if the first "E" in the acronym "ESES" was initially meant to indicate "Electrical" SES (Patry *et al*., 1971), a few years later Tassinari and colleagues (1977) suggested the use of "E" for "Encephalopathy" with SES after noting that "the condition of a protracted SES can be the factor leading to severe mental deterioration and psychic disturbances". This early communication introduced *in nuce* the concept of Epileptic Encephalopathy, later on proposed by the International League Against Epilepsy (ILAE) Classification Task Force (1989).

Currently, ESES is defined as an age-related and self-limiting disorder (Tassinari *et al*, 2012; ILAE Commission, 1989), characterized by:

– a typical EEG pattern, consisting of a striking exaggeration of epileptic discharges during NREM sleep for a protracted period of time (months or years);

– a clinical picture based on global or selective cognitive regression/stagnation, behavioral disorders, motor deficits, with or without overt epileptic seizures.

EEG features

The most typical and easily recognizable pattern of ESES consists of the sudden appearance at drowsiness of (sub-)continuous diffuse epileptic activity represented by synchronous and rhythmic high-amplitude spikes and waves (SW), persisting during all NREM-sleep stages (*figure 1A*). In this condition, the sleep physiological graphoelements, particularly sleep spindles, can be difficult to detect. The SW may become slower and more rhythmic during slow sleep (*figure 1B*), sometimes producing a fragmented EEG pattern (Veggiotti *et al*., 2001) (*figure 2*).

Focal epileptiform abnormalities during wakefulness can be inconstantly seen also during sleep as focal spikes intermixed with the diffuse SW. In some cases, a focal slow activity is also present, reflecting the localization of the main epileptic focus, and probably contributing to the symptoms as well (Massa *et al*., 2000; Tassinari *et al*., 2000; Aeby *et al*., 2005; Dalla Bernardina *et al*., 2005) (*figure 3*).

During REM sleep, the diffuse discharges are replaced by more focal SW, resembling those observed during wakefulness (*figure 1*). Sometimes, brief bursts of diffuse SW can appear also during REM sleep, but this is usually in concomitance with an arousal.

The continuous and diffuse EEG pattern during NREM sleep results from a secondary bilateral synchronization of the focal/multifocal SW observed during wakefulness (*figure 1*). In other cases, the spreading of the discharges is unilateral, leading to a hemispheric ESES (Hirsch *et al*., 1995; Galanopoulou *et al*., 2000) (*figure 4*).

In some patients, the ESES pattern can be strictly focal (*figure 5A*) (Aeby *et al*., 2005; Tassinari *et al*., 2012; Caraballo *et al*., 2015) or unilateral, eventually spreading to the homologous contralateral regions, giving the false impression of multi-focality (*figure 3*). A bilateral ESES EEG pattern can result from a striking activation of focal paroxysms, independently on the two hemispheres. Often multifocal paroxysms show an independent and alternating increase in frequency on the two hemispheres. In these focal/multifocal cases, the spike frequency can be relatively high during REM sleep as well. Moreover, the activation of multiple independent foci can vary in the different stages of sleep. In cases of multiple foci, it might be relevant to compute the contribution of each single focus to the total spike-wave-index (SWI) separately (*figure 6*) (see also Peltola *et al*., 2014), which is the percentage of time occupied by SW discharges (Patry *et al*., 1971; see also below).

The unilateral, focal or multifocal ESES patterns can be interpreted as the result of an abnormal activation of SW abnormalities during NREM sleep, without secondary bilateral synchronization (which can appear eventually, later on, during ESES evolution). An early recognition of these patterns at ESES onset might help to clarify whether they have different etiological, physio-pathological and prognostic significance. During ESES evolution, a transition between diffuse, hemispheric and focal patterns can be observed in a given patient, possibly depending on the spontaneous fluctuations of the disease and on the ongoing therapy (*figure 5*) (Gordon, 2000; Holmes and Lenck-Santini, 2006).

Often, the introduction of a medical treatment tends to render the EEG pattern more focal (*figure 7*), however, the opposite is also possible (for instance, with carbamazepine and oxcarbazepine) (Dalla Bernardina *et al*., 2005; Pavlidis *et al*., 2015).

The morphology and amplitude of the epileptiform activity has been infrequently reported as a relevant parameter. In most patients, the epileptiform abnormalities during ESES are an exaggeration of the epileptiform activities before ESES onset, and their morphology ultimately depends on the epilepsy type. Consequently, the analysis of the morphology of the EEG abnormalities during both wakefulness and sleep might be a valuable parameter for a syndromic and/or etiological assessment of ESES (Dalla Bernardina *et al*., 2005).

The *topography of the epileptiform activity* can be extremely variable among different patients with ESES, in the same patients at different recordings, and even at different times during the same EEG recording.

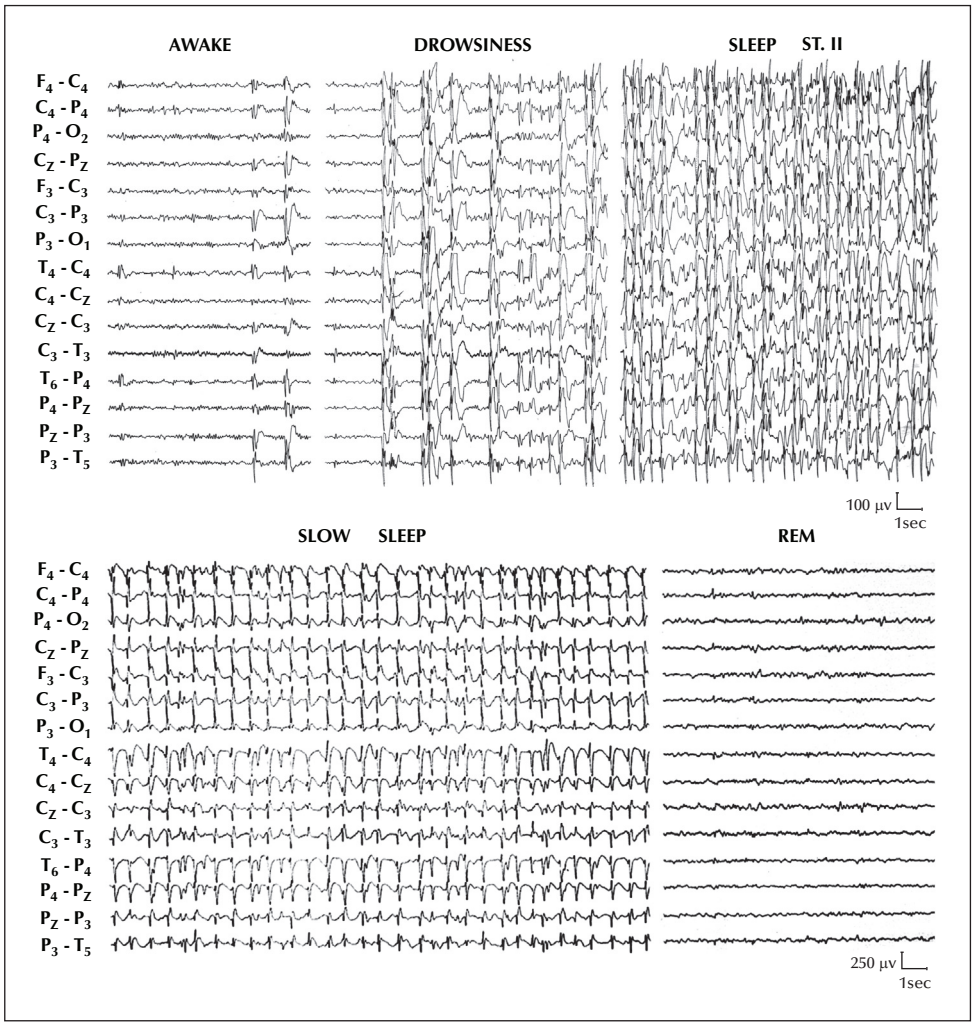

Figure 1. Male, 11 years and three months old. (A) Upper panel. The EEG during wakefulness is characterized by spike-and-waves in the right and left centro-parietal regions, with sudden exaggeration and diffuse spreading during drowsiness. During NREM Stage 2 sleep, the EEG shows continuous, diffuse and rhythmic spikes and waves with high amplitude. (B) Lower panel. The spike-and-waves become slower and more rhythmic during slow sleep and more focal during REM sleep, resembling the EEG activity during wakefulness.

The EEG of patients with epilepsy before ESES onset can show focal or multifocal epileptiform abnormalities, with the primary focus in the fronto-central, centro-temporal, temporal, parietal, occipital regions as well as in the vertex, depending on the type of epilepsy syndrome. Independent of the pre-ESES EEG topography, an EEG feature that can indicate evolution into ESES is the migration of the SW bilaterally to the frontal regions, moving back to their original topography at the time of ESES offset (either spontaneous or due to treatment) (Dalla Bernardina *et al*., 1978, 1984, 1989, 2005).

Therefore, the topography as well as the sleep-wake distribution of the epileptiform abnormalities during the evolution of ESES can vary significantly. In addition, the characteristics of the EEG pattern can be also influenced by the developmental stage and, as already mentioned, by ongoing therapy. Finally, some authors emphasize the importance of the localization and orientation of the spike-related EEG dipoles in the definition of the EEG pattern (Morrell *et al*., 1995; Galanopoulou *et al*., 2000).

At variance with the diagnostic importance of a high SWI during NREM sleep in ESES, relatively little attention has been paid to the features and clinical correlation of the EEG epileptic activity *during wakefulness*. Actually, this aspect can bear diagnostic and prognostic relevance (Dalla Bernardina *et al*., 1989). In patients with a typical ESES pattern during sleep, the EEG activity during wakefulness can consist of: (a) fairly focal SW (*figure 1*); (b) a frequent burst of diffuse SW, often with impairment of consciousness (atypical absences); (c) diffuse SW, often

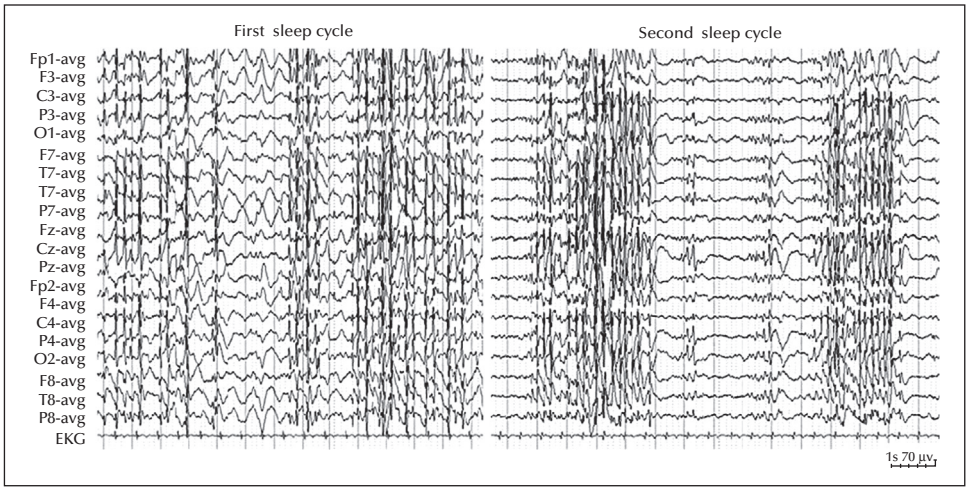

Figure 2. Fluctuations of EEG pattern during the night**.** Male, 11 years old. Symptomatic ESES on therapy with levetiracetam, valproic acid, and baclofen. The SW distribution changes from a continuous pattern during the first cycle of sleep (left panel) to a more fragmented pattern during the second sleep cycle (right panel). The global SWI during NREM sleep was 83%.

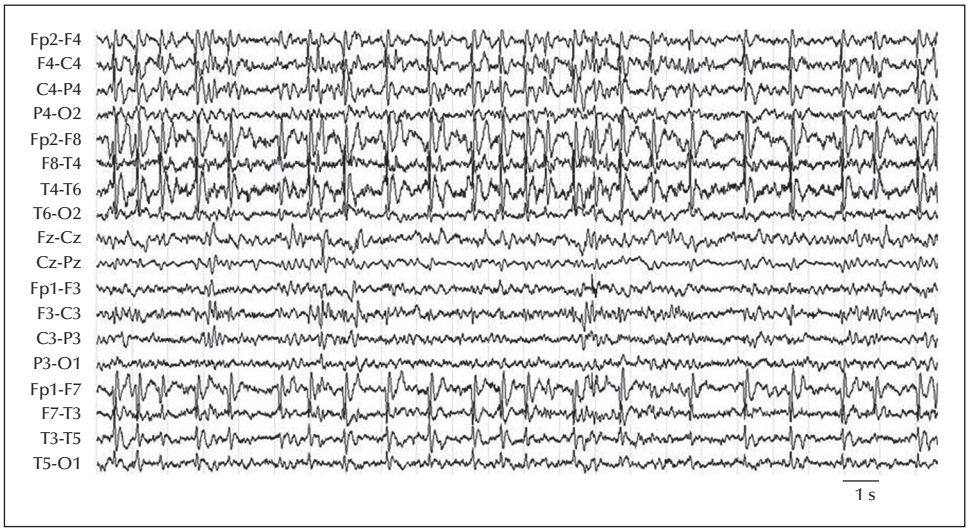

Figure 3. Focal slow components and "false multifocality". Female, eight years old, with idiopathic ESES. Subcontinuous rhythmical SW in the right centro-temporal regions rapidly spreading to homologous regions of the contralateral hemisphere (producing a bilateral focal status); the leading hemisphere is the right, in which we observe a predominance in amplitude, a constant anticipation of the right discharges over the left ones, and continuous delta activity intermingled with SW.

associated with absences with negative motor (atonic) or myoclonic component (*figure 8*). In these latter cases, the abrupt appearance of seizures during wakefulness can allow a timely diagnosis and a prompt therapeutic intervention (Dalla Bernardina *et al.*, 1989). However, in some cases the medical treatment can significantly improve the EEG picture during wakefulness, without modifying the ESES pattern. Therefore, even in the case of a dramatic EEG improvement during wakefulness, a sleep EEG should be performed.

The organization of the EEG background is also a relevant parameter. Sleep/wake architecture, as well as the sleep macrostructure are usually well preserved during ESES (Hirsch *et al.*, 1995), whereas, sleep microstructure (Nobili *et al.*, 2001) and slow wave activity during sleep (Bölsterli *et al.*, 2011; 2017) may be impaired.

Measures in ESES

EEG recording techniques in ESES

Various approaches have been adopted to record the EEG epileptiform activity related to ESES, ranging from

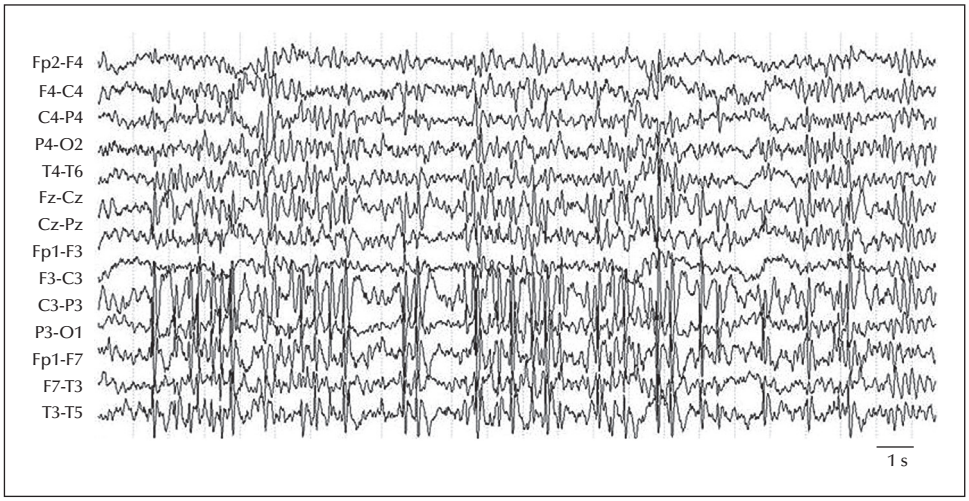

Figure 4. Hemispheric ESES (Hemi-ESES). Female, three years old. Cryptogenic ESES with epileptiform abnormalities involving the entire left hemisphere with occasional spreading to a Rolandic area of the right hemisphere.

a 24-hour EEG, sleep EEG (whole night or afternoon sleep) or polysomnography with or without video registration and with or without sleep medication (for a review, see Scheltens-de Boer, 2009).

The first NREM sleep cycle is a period of particular activation of epileptiform abnormalities; usually this activation decreases in the subsequent nocturnal sleep cycles. Therefore, an afternoon sleep EEG, including wakefulness and drowsiness, may be sufficient as a first screening, but for a correct diagnosis a full-night EEG recording is recommended (Gardella *et al.*, 2016).

The *percentage of epileptiform activity during sleep* can be expressed as SWI, defined as the percentage of NREM sleep occupied by spikes and waves (Tassinari *et al*, 2000; see also Cantalupo *et al.*, p. S31-S40). Different cut-off values have been adopted, ranging from 85% to 90% (Tassinari *et al.*, 2000) to 25% (Van Hirtum-Das *et al.*, 2006). These inconsistencies depend mainly on the lack of accepted criteria for the diagnosis of ESES. Moreover, as mentioned before, the different methodologies that have been used to measure the SWI and the evidence of SWI fluctuations in the same patient during the course of ESES may have further hampered the identification of a shared SWI threshold, and how and when it should be assessed. Even though it is quite exceptional that a SWI $\geq$80% is

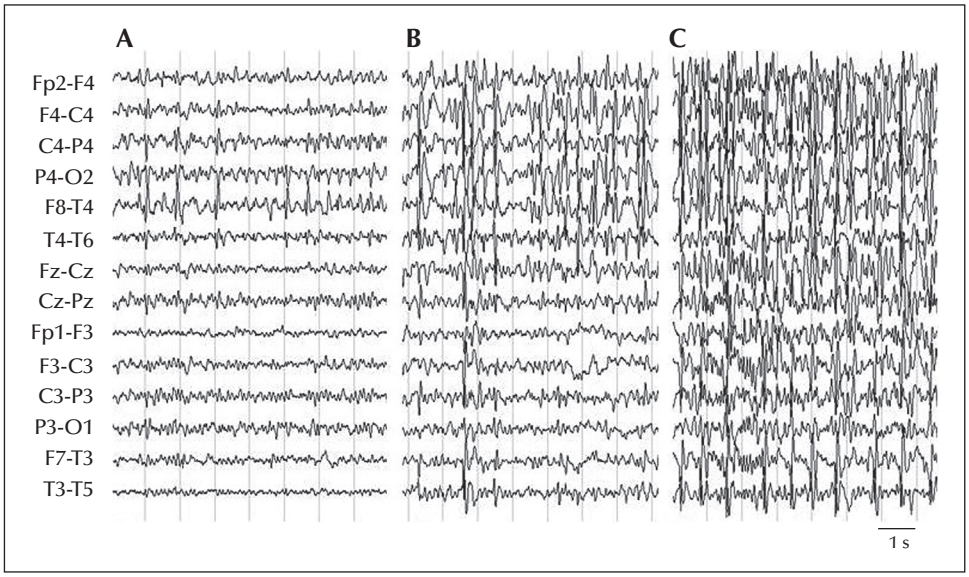

Figure 5. EEG topography evolution during the ESES course in the same patient. Three different sleep recordings in the same little girl with symptomatic ESES due to a right parietal polymicrogyria. The EEG pattern changes from focal (A: age six years, eight months) to hemispheric (B: age six years, 11 months) and diffuse (C: age seven years).

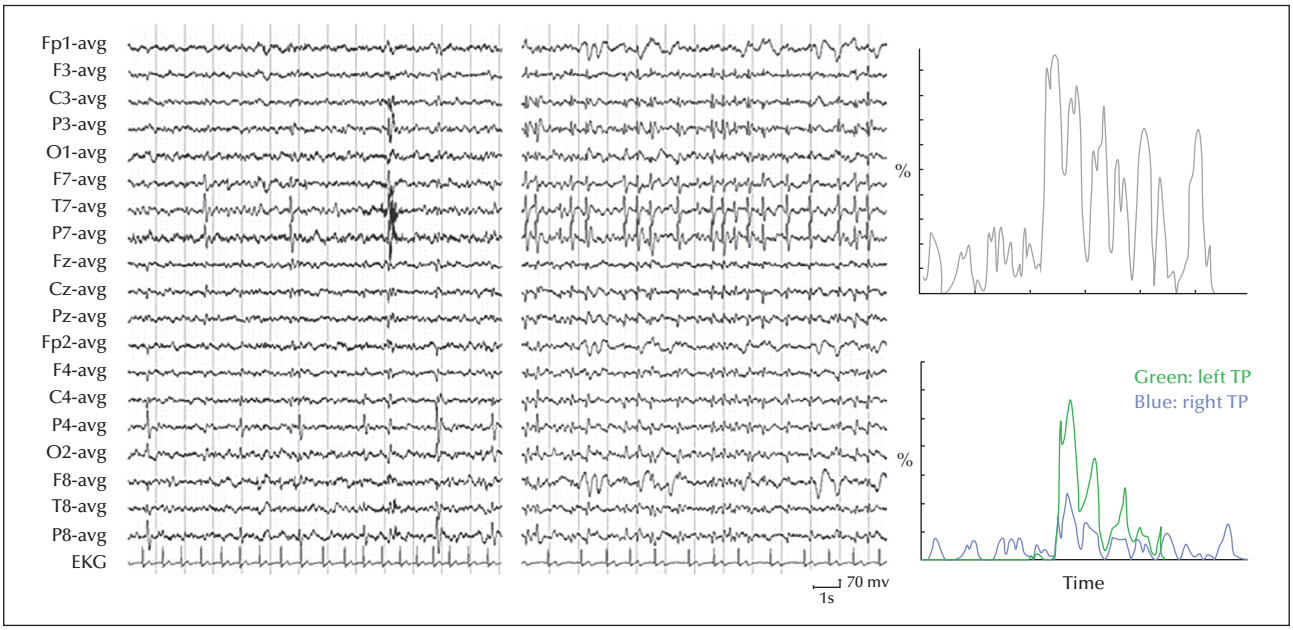

Figure 6. Two independent foci. A girl, eleven years and seven months old, affected by early developmental dysphasia; she had never had seizures. The ongoing therapy was sulthiame 250 mg/die. The EEG during wakefulness shows two independent foci in the right and left rolandic regions. Note the change in side prevalence from wakefulness (right parieto-occipital regions; left panel) to NREM sleep (left temporo-parietal regions; middle panel). Right panels: The SWI during NREM sleep is 66% (max. activation 96%). The NREM sleep/wakefulness SWI ratio is 5.9. The upper panel shows the fluctuations of the cumulative SWI (both foci) during the 24-hour EEG and the lower panel shows the SWI for each single focus, shoving a prevalent activation of the right epileptic focus during wakefulness and a significant predominant activation of the left focus (the side of speech dominance) during NREM sleep.

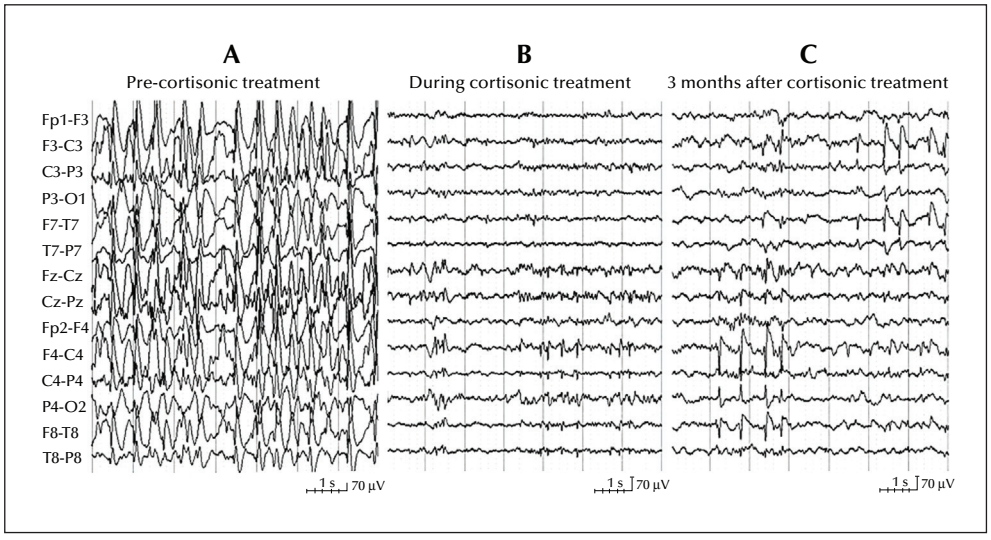

Figure 7. Effects of medical treatment. A nine-year-old boy with atypical benign partial epilepsy evolving to ESES and ADHD. In July 2010 (A), the patient's clinical picture worsened, (B) during steroid therapy - for 4 weeks with gradual withdrawal until November 2010. On February 2011 (C), the patient's condition was stable. The good clinical as well as EEG effects of steroid therapy partially continued.

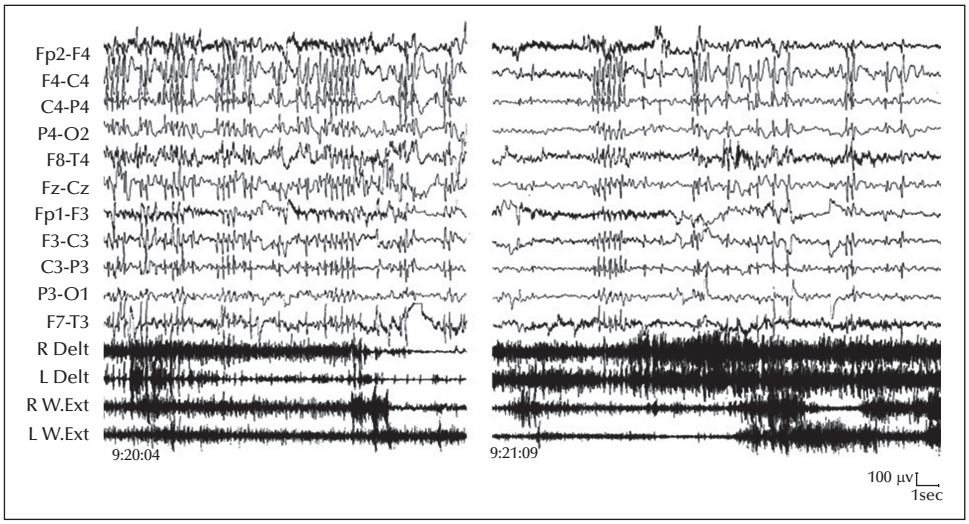

Figure 8. EEG and clinical features during wakefulness. A child, three years and five months old, with ESES. The EEG during wakefulness shows trains of irregular SW complexes, associated with atypical absences with myoclonic and atonic phenomena.

not associated with any cognitive, behavioral and/or motor disorder, the diagnosis of ESES cannot be based only on the measurement of the SWI. Indeed, ESES can be diagnosed only when there is evidence of an appearance or worsening of a neuropsychological impairment, associated with a striking increase of the epileptic activity during sleep.

Quantitative variation of the epileptiform activity during the night is sporadically mentioned (Tassinari *et al*., 2000; Galanopoulou *et al*., 2000; Larsson *et al*., 2010), most often reporting an increase of the epileptic activity during the first part of the night. An accentuation of the epileptic discharges can be observed in the period preceding the sleep onset (*figure 9*). Some data have also shown that the computation of the SWI during a short sleep period, e.g. an afternoon EEG, might be in some cases misleading with a lower diagnostic yield as compared to overnight EEG recording (Gardella *et al*., 2016; Cantalupo *et al*., p. S31-S40).

Some clinical considerations

ESES can occur as a single episode of variable duration and can recur as several episodes with more or less prolonged intervals. During follow-up, during the course of ESES, the epileptic discharges in sleep tend to become more focal and the SWI tend to decrease. In addition, in the active phase of ESES, fluctuations in the clinical picture (cognitive/behavioral impairment or seizure frequency) may not be paralleled by changes of the EEG features (such as SWI, topography, morphology, amplitude and sleep-wakefulness distribution of the discharges) (Morikawa *et al*., 1985; Hommet *et al*., 2000; Sánchez Fernández *et al*., 2012). For these reasons, the diagnosis and the monitoring of ESES requires both repeated EEG and neuropsychological investigations.

Receptive aphasia has been shown to be related to epileptic activity during sleep in the temporal regions, whereas a global cognitive decline with behavioral problems has been associated with frontal or diffuse spike topography (Beaumanoir, 1995; Tassinari *et al*., 2000). Therefore, the neuropsychological assessment should also take into account the topography of the EEG epileptic discharges, in particular in those cases with focal ESES that might cause very selective cognitive deficits (Kuki *et al*., 2015).

Additional parameters such as overt or subclinical seizure frequency, the age at ESES onset, and ESES duration could also be involved and require further studies to investigate their possible role in determining the ESES clinical features.

Conclusions

ESES is a peculiar electro-clinical entity whose main EEG characteristic is an extreme activation of paroxysmal activity during sleep, probably subtended by an age-dependent mechanism. Secondary bilateral synchrony contributes to the spread of focal epileptic discharges during sleep. The main EEG parameter, that has been assessed since the first description of ESES, is the SWI. However, establishing a minimum SWI for the diagnosis of ESES is somewhat arbitrary, mainly because of the lack of shared criteria and because of the diversity of measurement methods used in the different studies. Additional aspects that have to be taken into account in the evaluation of the EEG during ESES are the heterogeneity of the EEG features (such

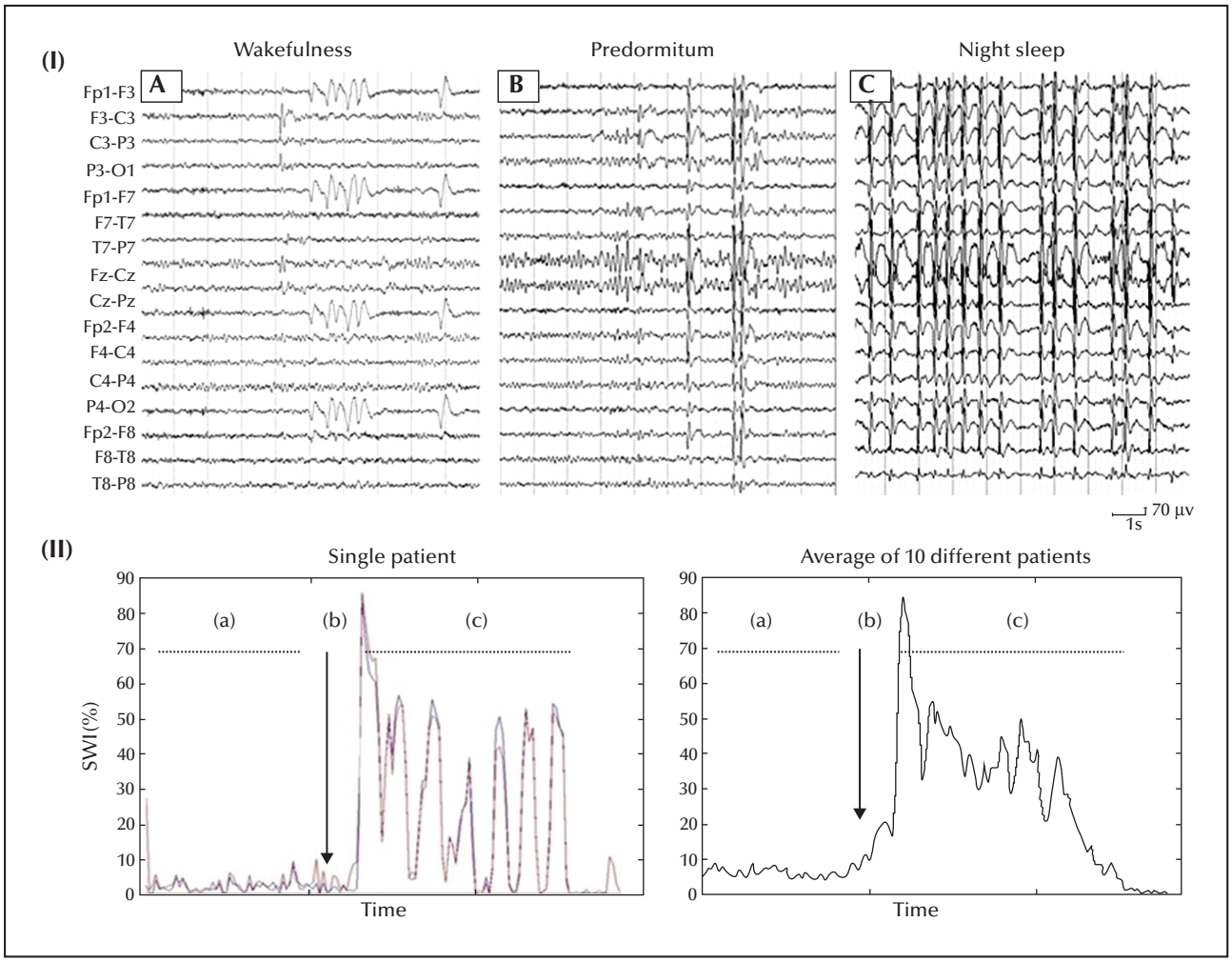

Figure 9. Distribution of epileptiform abnormalities during a 24-hour EEG. Lower panels: fluctuation of the SWI during 24-hour EEG recordings in a single patient (left) - shown in *Figure 1* - and fluctuation of average SWI of 10 different patients (right). For the computation of the SWI average, the EEG recordings of the 10 patients have been aligned to the onset of the nocturnal sleep. The graphs show low values of SWI during wakefulness (A), gradual, slight increase of the SWI in the period preceding the night sleep (B), and a sudden increase of the SWI at sleep onset, persisting during NREM night sleep, and decreasing during the REM phases, reflecting the physiological sleep macrostructure.

as, for instance, topography of the epileptic abnormalities and pattern of spread) that may change in a given patient at different time points of the disease course, but sometimes even in the same recording, and/or may depend on the ongoing therapy. On the other hand, it must be emphasized that the diagnosis of ESES cannot rely solely on the assessment of the SWI and/or other EEG features but requires demonstration of a neuropsychological/behavioral derangement associated with the appearance of the peculiar sleep EEG pattern. □

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