Review article

Epileptic Disord 2019; 21 (Suppl. 1): S71-S75

Cognitive impairment and behavioral disorders in Encephalopathy related to Status Epilepticus during slow Sleep: diagnostic assessment and outcome

Alexis Arzimanoglou [1,2], Helen J. Cross [3]

[1] Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon (HCL), Member of the European Reference Network EpiCARE, Lyon, France
[2] Epilepsy Unit Hospital San Juan de Dios, Member of the ERN EpiCARE and Universitat de Barcelona, Barcelona, Spain
[3] UCL-Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children NHS Trust, Member of the European Reference Network EpiCARE, London, UK

ABSTRACT – Encephalopathy related to Status Epilepticus during slow Sleep (ESES) is an age-dependent phenomenon, with usual spontaneous resolution during teenage years. However, cognitive outcome is often more disappointing, with permanent cognitive deficits in the large majority of children seen in later life. Presuming this to be an epileptic encephalopathy, current treatment practices are almost exclusively guided by the effect of the AEDs used on the degree of EEG abnormality in sleep. However, the major goal of therapy in ESES syndrome should in fact be to prevent or reduce associated cognitive and neurodevelopmental deficits. Whether or not the EEG pattern of ESES should be completely suppressed to improve cognition is unknown. Discussions on both diagnostic assessment and outcome of cognitive impairment and behavioral disorders should systematically take into account the complexity of the disorder; not only in terms of the evolution or fluctuations of the EEG patterns but also in relation to the underlying etiologies (at least lesional *versus* non-lesional) and age at diagnosis. We present a common basic assessment protocol, including the minimum technical requirements for polygraphic recording, and a treatment practice protocol that could both be applied in all centres dealing with this rare form of epilepsy. Such an approach would also allow a comprehensive collection of data prospectively, for a better understanding of the natural evolution of the disorder and an evidence-based evaluation of our practices.

Key words: encephalopathy related to status epilepticus during sleep, ESES treatment, continuous spike and waves during sleep, CSWS, EEG technical requirements

Correspondence:
Alexis Arzimanoglou
Department of Paediatric Clinical Epileptology,
Sleep Disorders and Functional Neurology,
University Hospitals of Lyon,
59 Boulevard Pinel, 69500 Lyon, France
<aarzimanoglou@orange.fr>

doi:10.1684/epd.2019.1060

Studies describing quantitative aspects of epileptiform abnormalities on EEG are overrepresented in the literature, whereas those evaluating evolution of cognition and behavior are undervalued. The large variation in the design of the studies, the tests used, the age ranges evaluated and the variability in outcome measures preclude any reasonable comparison. Consequently, studies attributing improvement exclusively to epileptiform discharges should be interpreted with caution (Sanchez Fernandez *et al*., 2015). Probably the only relatively strong data available suggests that severity and duration of initial regression are the most important risk factors of cognitive impairment in the long term (Van Bogaert, 2013).

Outcome and predictors of outcome

Electrical status epilepticus of slow sleep is by definition what could be classified as a true epileptic encephalopathy. It is believed that cognitive and behavioural difficulties are the direct result of the underlying epileptic activity and any targeted treatments. However, we need to review the evidence on outcome; specifically, the relationship with resolution of the epileptiform activity, the influence of aetiology and indeed the role of treatment. Further, do we have evidence that we can actually influence outcome?

Like other epilepsy syndromes, Encephalopathy related to Status Epilepticus during slow Sleep (ESES) is described on the basis of electroclinical features but may have many aetiologies - specifically lesional and non-lesional. Presentation of cognitive deficit has been suggested to be related to the geographical prominence of spike wave activity - in Landau-Kleffner, this is seen with temporal prominence, whereas more global problems are associated with a frontocentral focus. However, there does not appear to be any evidence of a predictor of outcome dependent on localisation of epileptiform discharges.

Many have demonstrated ESES to be an age-related phenomenon; illustrated by both lesional and non-lesional cases. It has been well demonstrated that children with *hemipolymicrogyria* may present with focal seizures but can subsequently evolve with development of atonic attacks associated with the finding of electrical status epilepticus of slow sleep. In longitudinal studies, such attacks resolve along with the ESES (Guerrini *et al*., 1998; Caraballo *et al*., 2013) - however, there are no cognitive or behaviour measures included in the studies reported, so the overall impact on this aspect is unknown. It is now known that such phenomena occur in "acquired" cases or those with developmental pathology and may occur with unilateral or bilateral disease. In the case of unilateral structural abnormalities, surgery has been demonstrated to resolve the ESES but definitive improved cognitive outcome, although suspected as being likely, has not been proven (Loddenkemper *et al*., 2009).

There are many methodological problems with long-term studies reported to date within the literature. Not least, series often include both lesional and non-lesional cases, with very small numbers owing to the rarity of the condition. Further, there is significant heterogeneity in the treatment utilised even in a single centre with no structured protocols, which applies also to reporting of outcome and time period (van den Munckhof *et al*., 2015). The natural history is such that electrical status epilepticus has a good prognosis and resolves with age - it is difficult to know therefore the impact of any intervention over time. This is well illustrated by the surgical Landau Kleffner series of Morrell; the initial series of 14/54 children who underwent surgery (multiple subpial transection) after full assessment although 6 had normal speech postoperatively and five improved (Morrell *et al*., 1995; Grote *et al*., 1999); a later follow-up study demonstrated that the extent of improvement was related to time from surgery. Indeed, a recently reported study showed no difference in outcome as to whether surgery was undertaken or not (Downes *et al*., 2015).

Praline *et al*., (2003) reported on seven adults who had experienced CSWS or Landau Kleffner Syndrome in childhood. At the time of review, they were aged 16-26 years; five had CSWS syndrome and two Landau Kleffner. They confirmed the epilepsy to have a good prognosis in the long-term; only one had continuing active epilepsy. However, 3/5 who had CSWS in childhood remained significantly cognitively impaired (Praline *et al*., 2003).

Possible predictors of outcome include age at onset, duration of ESES, response to treatment, aetiology and predominant location of the interictal focus. An older age at onset and shorter duration of ESES are correlated with a better cognitive outcome although this does not appear to be absolute (Scholtes *et al*., 2005). This aside, in a further study of 10 patients with non-lesional ESES followed for 15.6 years, patients with prolonged global intellectual regression had the worst outcome whereas those with more specific and short-lived deficits showed the best recovery (Seegmuller *et al*., 2012). Further, there was no correlation between outcome an age at onset or age at cessation of ESES, but the three most severely affected individuals had the longest duration of ESES. Kramer *et al*. reported on 30 patients from four clinics who had been determined to have ESES; 20 had an associated intellectual regression, having previously been normal, 3 of whom

Table 1. Minimum technical requirements for polygraphic recordings of ESES/CSWS*.

1. For the diagnosis at least one overnight polygraphic recording is required.
2. For follow-up an overnight sleep recording is recommended, however a nap polygraphy can be sufficient.
3. In both cases (overnight and nap polygraphy), it is mandatory: • to acquire both wakefulness and sleep in the same recording; • to assess sleep stages, thus it is essential to acquire both EEG and polygraphic signals (see below).
4. All signals should be digitized and stored with sampling rates at least of 250 Hz (higher sampling rates – 512, 1024 Hz or superior – are strongly encouraged).
5. EEG: • at least 19 electrodes should be used, based on the 10-20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). The use of higher number of electrodes (i.e. 10-10 system) or supernumerary electrodes is encouraged; • digital recording reference should be an additional electrode (or combination of electrodes), and not one of those in the 10-10 or 10-20 system. Additional electrodes at POz and Fpz are frequently used as 'common reference' and 'subject ground', respectively.
6. Electroculogram (EOG): • at least two bipolar EOG channels should be included. The recommended procedure is to place one electrode approximately 1 cm above and slightly lateral to the outer canthus of right eye (right-EOG or ROC) and another electrode 1 cm below and slightly lateral to the outer canthus of the left eye (left-EOG or LOC), both referred to the same (right) ear or mastoid electrode (alternatively each ROC and LOC could be referred to the respective contralateral mastoid).
7. Electromyograms (EMG): • one antigravitary muscle (either mylohyoideus or submentalis or mentalis muscle); • one limb muscle (either leg – i.e. tibialis anterior – or arm – i.e. extensor digitorum – muscle).
8. Pneumogram (PNG): • at least one belt – equipped with piezoelectric or inductance-plethysmography sensors – placed around the thoracic or abdominal compartments to measure the tension changes as a surrogate for measuring respiratory effort.
9. Electrocardiogram

(*) Prepared in collaboration with G. Rubboli and G. Cantalupo.

did not respond to treatment. They found a significant correlation between residual cognitive deficits and the total ESES period (Kramer *et al*., 2009). However, careful longitudinal review has illustrated that although such correlations are evident, prognosis of an individual is highly variable.

Pera *et al*. (2013) reviewed 25 children with a mean follow-up of 13.5 years; they suggested five patterns of clinical course within this otherwise small series with not necessarily a clear correlation between clinical course and EEG response to treatment. Group 1 demonstrated the classical regression with EEG abnormality, and improvement with EEG response to treatment; Group 2 had predominantly motor deficit with minimal cognitive change; Group 3 had cognitive deficits that persisted despite improvement in the EEG; Group 4 had associated cerebral lesions, with little change in cognition over time; and Group 5 included two patients with progressive deterioration based on neuropsychological tests without temporal correlation with ESES duration (less than seven months), and no association with clinical and electroencephalographic relapses. In total, 44% of the whole group had permanent cognitive impairment in the long term (Pera *et al*., 2013).

Diagnostic assessment of cognition and behavior in ESES

Because ESES is a highly heterogeneous and a relatively rare entity (even when atypical forms are included), multicentric studies usually fail in reaching a statistically significant number of participants; long-term follow-up is usually not possible, often because of lack of funding. However, improving our knowledge on outcome requires a method to measure it. Lessons from the past should lead the epileptological

community to a more pragmatic approach and avoidance of circular statements; instead of indefinitely concluding that "*controlled multicentric studies are needed...*" we could agree upon a basic diagnostic assessment protocol to be followed by all major paediatric epilepsy centers.

A common-to-all, basic diagnostic assessment protocol

All children with ESES, independent of underlying etiology, should **from onset** be referred to a pediatric neurology center specialized in epilepsy. A commonly agreed, user-friendly software could be used to collect relevant data (that one day, if needed, could be merged into a common database) to include:
– main neurological and somatic examination findings at onset;
– family history, including familial cognitive and behavioral problems;
– a minimum 24-hour video-EEG, preferably before administration of any treatment or within the first 8 weeks; agreement could be made upon a set of minimum technical requirements for polygraphic recordings (*table 1*);
– the realization of a predefined, commonly agreed, core battery of neurocognitive tests and evaluation scales (see below) covering the most crucial parameters, sufficiently straightforward to be reproduced in different clinical settings;
– high-resolution MRI performed according to standard epilepsy protocols (Gaillard *et al*., 2009);
– genetic evaluation (to be enriched on the basis of progress made in the field).

Practices that may need a consensual attitude

– An agreement on the first three AEDs to be used, including dose per kg, duration of each trial and minimal efficacy criteria. Lack of results from controlled trials should oblige us all to follow a consensual approach, referring to existing open studies, rather than a dogmatic position based on personal beliefs and impressions;
– An agreement upon a core battery of neurocognitive tests, to be repeated at regular intervals (once a year?). Depending on the ages and abilities of the patients, tests should cover the major domains of cognition (intelligence, language, memory, attention, visuospatial functions, executive functions);
– An agreement upon a basic scale evaluating AED side effects (Morita *et al*., 2012) to be repeated at regular intervals, particularly after a change in AED therapy; This could be systematically coupled to a sensitive and time-efficient screening tool for attention and executive functions, such as EpiTrack Junior (Kadish *et al*., 2013).

Practices that probably can only be decided arbitrarily!

An agreement upon intervals for 24H VEEG. Variability in current practices complicates comparison of findings across various studies, and limits the possibility of generating evidence-based guidelines for patient follow-up (Jehi *et al*., 2015). The reason that such an agreement between centres is hard to obtain probably reflects a disagreement upon primary efficacy criteria. One, rather classical, approach would be the "percentage of amelioration of the sleep-EEG ESES pattern", reproducing what we are currently applying in the majority of centres.
However, another option, probably better serving our primary aim (see above) could be to use the results from core battery neuropsychological tests as an efficacy criterion. For example, at least for a period of 12 months, the AED prescribed would be replaced only in case of signs of cognitive deterioration (validated by a minimum of tests) or in case of clinically identifiable epileptic seizures. EEG variations would still be recorded without automatically leading to modifications of treatment.
If an agreement on the second option suggested above proves impossible to attend, we could at least agree that each individual centre would accept to systematically determine its treatment attitudes on the basis of the same criterion: either EEG variations or the results of the neuropsychological follow-up. Such an approach would at least allow the constitution of two comparable groups, in terms of global evolution in the long-run, of children treated for ESES.
In summary, the fluctuating clinical and EEG courses of ESES complicate the diagnostic process and evaluation of treatment. We need to validate a feasible screening method to be used by clinicians of all major paediatric epilepsy centres. It should be in accordance with the main lines of current clinical practices and preferably under the authority of a well-defined endorsed Task Force such as within the ILAE. The policy of publishing small series of patients per centre has clearly failed in reaching meaningful clinical conclusions. The natural course of the disorder(s) remains poorly known and multiple underlying mechanisms link the EEG patterns to developmental outcomes. A consensus on a homogeneous approach should be considered a priority. □

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

References

Caraballo RH, Cersosimo RO, Fortin PS, *et al*. Congenital hemiparesis, unilateral polymicrogyrai and epilepsy with or without status epilepticus during sleep: a study of 66 patients with long term followup. *Epileptic Disord* 2013; 15: 427.

Downes M, Greenaway R, Jolleff N, *et al*. Outcome following multiple subpial transection in Landau-Kleffner syndrome and related regression. *Epilepsia* 2015; 56(11): 1760-6.

Gaillard WD, Chiron C, Cross JH, *et al*. Guidelines for imaging infants and children with recent-onset epilepsy. *Epilepsia* 2009; 50: 2147-53.

Grote CL, Van Slyke P, Hoeppner JAB. Language outcome following multiple subpial transection. *Brain* 1999; 122: 561-6.

Guerrini R, Genton P, Bureau M, *et al*. Multilobar polymicrogyria, intractable drop attack seizures and sleep related electrical status epilepticus. *Neurology* 1998; 51: 504-12.

Jehi L, Wyllie E, Devinsky O. Epileptic encephalopathies: optimizing control and developmental outcome. *Epilepsia* 2015; 56: 1486-9.

Kadish NE, Baumann M, Pietz J, Schubert-Bast S, Reuner G. Validation of a screening tool for attention and executive functions (EpiTrack Junior) in children and adolescents with absence epilepsy. *Epilepsy Behav* 2013; 29: 96-102.

Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). *Epilepsia* 2009; 50: 1517-24.

Loddenkemper T, Cosmo G, Kotagal P, *et al*. Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 2009; 64: 328-37.

Morita DA, Glauser TA, Modi AC. Development and validation of the pediatric side effects questionnaire. *Neurology* 2012; 79: 1252-8.

Morrell F, Whisler WW, Smith MC, *et al*. Landau-Kleffner syndrome; treatment with subpial transection. *Brain* 1995; 118: 1529-46.

Pera M, Brazzo D, Altieri N, Balottin U, Veggiotti P. Long-term evolution of neuropsychological competences in encephalopathy with status epilepticus during sleep: A variable prognosis. *Epilepsia* 2013; 54: 77-85.

Praline J, Hommet C, Barthez MA, *et al*. Outcome at adulthood of the continuous spike-waves during slow sleep and Landau Kleffner syndromes. *Epilepsia* 2003; 44: 1434-40.

Sanchez Fernandez I, Loddenkemper T, Galanopoulou AS, Moshe SL. Should epileptiform discharges be treated? *Epilepsia* 2015; 56: 1492-504.

Scholtes FB, Hendriks MPH, Renier WO. Cognitive deterioration and electrical status epilepticus during slow sleep. *Epilepsy Behav* 2005; 6: 167-73.

Seegmuller C, Deonna T, Mayor Dubois C, *et al*. Long-term outcome after cognitive and behavioral regression in nonlesional epilepsy with continuous spike-waves during slow-wave sleep. *Epilepsia* 2012; 53: 1067-76.

van Bogaert P. Epileptic encephalopathy with continuous spike-waves during slow-wave sleep including Landau-Kleffner syndrome: what determines outcome? In: *Outcome of childhood epilepsies*. Arts WF, Arzimanoglou A, Brouwer OF, Camfield C, Camfield P. Paris: John Libbey Eurotext, 2013: 141-8.

van den Munckhof B, van Dee V, Sagi L, *et al*. Treatment of electrical status epilepticus in sleep: a pooled analysis of 575 cases. *Epilepsia* 2015; 56(11): 1738-46.