

The epileptic syndromes with continuous spikes and waves during slow sleep : definition and management guidelines

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Abstract

The authors propose to define the epileptic syndromes with continuous spikes and waves during slow sleep (CSWS) as a cognitive or behavioral impairment acquired during childhood, associated with a strong activation of the interictal epileptiform discharges during NREM sleep – whatever focal or generalized – and not related to another factor than the presence of CSWS. The type of syndrome will be defined according to the neurological and neuropsychological deficit. These syndromes have to be classified among the localization-related epileptic syndromes. Some cases are idiopathic and others are symptomatic. Guidelines for work-up and treatment are proposed.

Key words : Epilepsy ; sleep ; childhood ; cognitive impairment ; continuous spike-waves.

Introduction

In 1957, Landau and Kleffner reported six children with normal early language development who became aphasic after the onset of minor seizures (1). Electroencephalogram (EEG) showed bilateral epileptiform discharges which were prominent in the temporal regions, and the authors suspected that persistent convulsive discharges resulted in the functional ablation of brain areas concerned with linguistic communication. The language disturbance was further characterized as auditory verbal agnosia, i.e. the impossibility to give a semantic meaning to the phonemes, leading to a severe expressive and receptive verbal deficit (2). Additional observations showed that the type of aphasia may be less severe than auditory verbal agnosia, and that language regression together with sleep activated epileptiform discharges may occur without any clinical seizure (3-6). Longitudinal follow-up of these children showed that the seizures as well as the EEG abnormalities remit before mid-teens (3-5). The Landau-

Kleffner syndrome (LKS) was recognized by the International League Against Epilepsy (ILAE) as a synonymous of acquired epileptic aphasia to be classified among the epilepsies and syndromes of childhood undetermined whether focal or generalized (7).

The notion of electrical status epilepticus during slow sleep (ESES) was proposed by Tassinari and coworkers for a particular EEG pattern characterized by diffuse spike-waves occurring during at least 85% of slow sleep and persisting on 3 or more records over a period of at least 1 month (5, 8, 9). The children with ESES had clinical seizures (partial or generalized seizures during sleep or atypical absences when awake), and most of them had global cognitive regression leading to severe mental retardation. However, some of these children had more selective language-related impairment identical to that observed in LKS. Moreover, the evolution of the epilepsy showed remission before adolescence even if most patients had persistent and sometimes severe neuropsychological sequels. Despite the clear overlap with ESES and LKS, the ILAE proposed to classify this syndrome separately under the name “epilepsy with continuous spike-waves during slow-wave sleep (CSWS)” (7).

Subsequently, observations of children presenting types of acquired cognitive impairment other than aphasia or dementia in association with CSWS were reported. These included autism and more selective cognitive impairments like frontal lobe dysfunction (attention deficit disorder with impulsiveness, mood swings and perseveration) (10, 11), non-dominant hemisphere impairment (apraxia and hemineglect) (12), opercular dysfunction (severe oral motor dysfunction, drooling, dysarthria and decreased speech output) (13-15), visual agnosia (16), and learning arrest (17).

Strong activation of epileptiform discharges during sleep leading to a CSWS pattern was already described more than 20 years ago by Jean Aicardi in children suffering from an epileptic syndrome

resembling benign epilepsy with central temporal spikes (BECTS) but with atypical features like frequent brief seizures (atypical absences, focal positive or negative myoclonia) or cognitive impairment (18). This atypical form of BECTS was further characterized in the literature under the name “pseudo Lennox syndrome” to display the fact that sleep EEG showed diffusion of the epileptiform discharges over whole scalp (19). This led to the assumption that some cases of epilepsy with CSWS were to be classified among the idiopathic partial epileptic syndromes. On the other hand, CSWS was reported in children with cerebral palsy showing brain lesions like porencephalic cysts, polymicrogyria, congenital hydrocephalus or thalamic perinatal ischemic lesions (20-24). This evidenced that some cases of epilepsy with CSWS belong to the group of symptomatic partial epileptic syndromes.

These observations prompted authors to propose that all these syndromes are parts of a spectrum of acquired neuropsychological disturbances that have in common the presence of CSWS, which should be considered as an EEG pattern encountered in idiopathic as well as in symptomatic epileptic syndromes (5, 23, 25, 26). However, there is no consensus on the EEG criteria needed to define these syndromes as cases of LKS or BECTS with acquired cognitive impairment have been reported without the presence of spike-waves during at least 85% of NREM sleep (25, 27-33). This article will attempt to define epileptic syndromes with CSWS, to delineate its limits, to approach its physiopathology, and to propose guidelines for its management.

Tentative definition : the spectrum of epilepsies with CSWS and its limits

The concept underlying a tentative delineation of diagnostic criteria common for all types of epilepsies with CSWS – including LKS - is that the abundant epileptic activity activated during sleep plays a major role in the cognitive and behavioral deficits presented by these children. Clues supporting this concept are the followings : (1) a close temporal relationship between cognitive deterioration and enrichment and diffusion of the sleep discharges on EEG has been repeatedly reported ; (2) clinical remission is usually associated with EEG improvement ; (3) there is an association between the importance of cognitive sequels and the long duration of CSWS ; and (4) nearly all types of cognitive or behavioral disturbances (aphasia, apraxia, agnosia, dementia, autism, executive dysfunction,...) have been described in association with the CSWS pattern (3, 5, 17, 23, 25, 32, 34-37).

Therefore the authors propose to reserve the term of epilepsy with CSWS when there is a *con-*

junction of two features. The first is a cognitive or behavioral impairment acquired during childhood (between the ages of 1 and 10 years) and not related to another factor than the presence of CSWS, for instances a side effect of an anti-epileptic drug (AED), an underlying metabolic or heredo-degenerative disease, or a psycho-affective problem. The second is a strong activation of the interictal epileptiform discharges during sleep, which may be focal but tend to diffuse over the whole scalp. The threshold of at least 85 % of the NREM sleep time occupied by the epileptiform discharges is thus not an obligatory criteria.

According to this concept, another terminology than CSWS would be more appropriate, for instance “sleep spiking related cognitive impairment”. However, the authors propose to keep provisionally the terminology “CSWS” because it is the terminology recognized by the ILAE.

In proposing to decrease the threshold of sleep related epileptic activity, the authors are conscious that the prevalence of these syndromes will be much higher than that reported in the literature, and that the risk of overlap with other epileptic syndromes or developmental disorders is increased.

Overlap may concern symptomatic generalized epilepsies like the Lennox-Gastaut syndrome, as well as partial idiopathic epilepsies like BECTS.

The differential diagnosis with Lennox-Gastaut syndrome will usually be possible easily with a prolonged video-EEG recording. The presence of partial motor seizures will suggest epilepsy with CSWS, whereas tonic seizures when awake or asleep, and fast rhythms during sleep are the signature of Lennox-Gastaut syndrome (9, 25). Tonic seizures may occur subclinically and may be revealed only by a polygraphic sleep EEG tracing with simultaneous EMG.

The differential diagnosis with partial idiopathic epilepsy may be more puzzling. It is usually assumed that children with BECTS have infrequent and easily controlled seizures, and do not present cognitive deficits. However, when detailed neuropsychological investigations are performed, non specific verbal as well as non verbal deficits are found in up to 50% of the patients (29-31, 38, 39). An interesting point is that cognitive dysfunction is more prominent during the active phase of the disease and usually resolve with the resolution of the epilepsy. Moreover, atypical cases presenting with frequent and difficult-to-treat brief seizures like focal myoclonia or atypical absences are occasionally encountered (13, 18, 19, 40, 41) ; in those atypical cases, cognitive and behavioral deficits together with strong activation and diffusion of the interictal epileptiform discharges during sleep are usually found. Finally, evolution from an idiopathic partial epilepsy to an epilepsy with CSWS is not an infrequent finding, which may be precipitated by the use of some anti-epileptic drugs (9, 28). So

it is now largely admitted that an overlap exists between BECTS (and other types of idiopathic partial epilepsies) and epilepsies with CSWS, making the differential diagnosis between these epileptic conditions impossible and probably unnecessary in border cases (25, 42). Reports of BECTS and CSWS in members of the same families also support this view (43).

Differential diagnosis with developmental disorders of the immature brain like autism and specific language impairment can also happen. It is well recognized that the incidence of interictal epileptiform discharges is much higher in children suffering one of these disorders than in controls (44-48). It is generally assumed that these epileptiform discharges do not have significant impact on the cognitive or behavioral impairment, and have to be considered as either the marker of an underlying cerebral lesion or the genetic trait of an idiopathic epilepsy. However, the finding of a strong activation of the interictal epileptic activity during sleep in some cases raises the question of an overlap between epilepsies with CSWS and these behaviorally defined developmental disorders. The distinction with a CSWS associated disorder, and more specifically with LKS, should theoretically be easily made with an anamnesis oriented to the profile of evolution. LKS is by definition an acquired aphasia, meaning that language was normally developing before the occurrence of regression. On the contrary, impairment from early age with continuing progresses is the rule in specific language impairment, whatever impairment concerns expressive or receptive verbal abilities (49). Things are more complicated in autism, defined as impaired social interaction, language, communication, imaginative play, and range of interests and activities starting before the age of 3 years (48). Regression after early normal development is reported in about one third of autistic children (50). This suggests that children showing autistic regression are good candidates for sleep EEG studies. This assumption was however not confirmed in a recent study showing that the prevalence of epilepsy or abnormal spiking EEG was not higher in the subgroup of autistic children with regression than in the subgroup without any history of regression (51). So the significance of interictal epileptiform discharges in autism and specific language impairment is still unclear. Well designed pharmacological studies are warranted in order to clarify the role of epilepsy and interictal epileptiform discharges in cognitive and behavioral impairment of children with developmental brain disorders.

Physiopathology of the CSWS phenomenon and of the neuropsychological deterioration

It is now largely admitted that the diffusion of the epileptiform discharges during NREM sleep is

related to a mechanism of secondary bilateral synchrony from a focal cortical onset. It is probable that thalamic nuclei play an important role in this phenomenon, presumably through a development of the physiological slow-sleep oscillation into diffuse slow waves because of the lack of inhibitory constraint. This hypothesis is supported by experimental CSWS-like pattern obtained in cats following unilateral thalamic ablation (52). The role of the thalamus in the generation of the CSWS phenomenon was recently emphasized by reports of patients showing thalamic clastic lesions on MRI (22). Arguments in favor of a focal origin of the CSWS phenomenon are the following: (1) in some cases, the spike-wave complexes remain unilateral during NREM sleep (5); (2) even in patients showing diffuse spike-waves during sleep as well as generalized absence-type seizures, focal onset was suggested by careful neurophysiological study, i.e. measurement of interhemispheric peak differences using coherence and phase analyses (53); (3) unilateral intracarotid amobarbital injection performed in a presurgical context of refractory LKS cases have shown bilateral suppression of epileptiform activity (54, 55); (4) magnetoencephalographic (MEG) studies of LKS cases evaluated for surgery suggest that the perisylvian cortex is a likely pacemaker of epileptic discharges (56, 57); and (5) positron emission tomography (PET) frequently shows areas of cortical dysfunction of variable location (12, 13, 58-60). Therefore, epilepsies with CSWS should logically be classified among the localization-related epileptic syndromes, of idiopathic or symptomatic nature.

The initial hypothesis of a "functional ablation" of eloquent cortical areas by the "persistent convulsive discharge" to explain the neuropsychological impairment, as proposed half a century ago by Landau and Kleffner (1), remains the most largely accepted hypothesis. However, it must be emphasized that some observations are not fully explained with this theory. Firstly, the temporal association between CSWS on EEG and neurological regression is not always strict. This fact was already mentioned by Landau and Kleffner and was confirmed by other authors studying patients with LKS using longitudinal EEG and neuropsychological evaluations (2, 33, 61). Secondly, if some authors found a strict association between the pattern of neuropsychological derangement and the location of the interictal focus (5), others did not. In particular, patients showing clinical frontal dysfunction and parietal epileptic focus have been reported (58). Thirdly, PET studies using the tracer 18F-fluorodeoxyglucose (FDG) have shown that, contrary to patients with BECTS who usually show a normal pattern (62), abnormalities are frequently found in patients with CSWS investigated in the active phase of the disease. However, the type of PET abnormality is highly variable, ranging from

focal or multifocal cortical hypometabolism to focal hypermetabolism, or to the association of hypometabolism and hypermetabolism in different areas in the same patient (12, 13, 58-60). A tentative physiopathological hypothesis which has the advantage to reconcile these apparent discrepancies emerged from connectivity studies obtained from FDG-PET data (58). This hypothesis is based on the concept of surrounding and remote inhibition, which has been demonstrated in animal models of epilepsy (63, 64). It proposes that the foci of increased glucose metabolism are the epileptic foci (which may in some patients not be intense enough to be imaged by PET), and that these foci inhibit other cortical areas which may be either in the border of the hypermetabolic area (surrounding inhibition) or distant from it (remote inhibition). Therefore, it is the location of the inhibited cortical area which might determine the type of neuropsychological profile.

Guidelines for work-up of patients with suspected CSWS

The suspicion of CSWS will arise from cognitive or behavioral dysfunction in a child with or without known epilepsy. The first step will be to characterize the type and the evolution of the cognitive impairment. In particular, efforts to reconstitute the profile of evolution from the first months of life are mandatory in order to make the distinction between a developmental and an acquired process. This step is time-consuming and is not always easy to perform because case histories may be imprecise and evolution profiles complicated, with periods of progression, stagnation and regression in a limited period of time in the same patient. In most cases, the clinical evaluation will usefully be completed by a neuropsychological and linguistic evaluation, the tests administered depending on the age, collaboration and global level of the child. A behavioral questionnaire to be completed by parents or teachers is also very useful and should be encouraged in suspicion of behavioral troubles.

If the cognitive or behavioral profile suggests an epileptic syndrome with CSWS, the second step will be the realization of a long term video-EEG. Awake and sleep recording will be separately analyzed. The analysis of awake records will focus on the presence of interictal abnormalities (epileptiform discharges, slow dysrhythmia), but also on the presence of subtle seizures like absences or negative myoclonia. Myoclonia must be carefully researched using video and surface EMG electrodes, because the EEG correspondent does not differ from interictal focal epileptiform abnormalities (41). The sleep EEG must be analyzed qualitatively and quantitatively. The qualitative analysis will focus on global organization of the EEG, the diffusion of the epileptiform discharges, and asso-

ciated abnormalities like slow dysrhythmia. The goal of the quantitative analysis is to calculate a spike-wave index score during slow-wave sleep.

The third step will be the realization of a cerebral structural magnetic resonance imaging (MRI). Lesions are found on MRI in about 20% of the cases. These cases belong to the subgroup of symptomatic epilepsies with CSWS. Lesions usually consist in clastic cortical lesions (encephalomalacia, polymicrogyria), but subcortical abnormalities like ventricular enlargement or thalamic ischemic perinatal injuries are occasionally found (20-22, 65). It must be emphasized that the chances to find a structural lesion with MRI are very low if neurological examination does not show any sign of cerebral palsy.

Genetic complementary investigations are indicated in the presence of particular signs or symptoms, like profound mental retardation, microcephaly or dysmorphic features. Indeed, the CSWS pattern can be encountered in syndromes with known chromosomal deletions affecting for example the 15q region, or in Rett syndrome (66-68).

More sophisticated investigations like PET with FDG or MEG are indicated if specific questions are raised, for example in the context of presurgical evaluation or drug effect evaluation.

Treatment

In the absence of any published placebo controlled study on the use of AED in epilepsies with CSWS, treatment of these epileptic conditions relies upon expert-based consensus guidelines and uncontrolled published series. The evaluation of a drug effect is probably more difficult in epilepsies with CSWS than in any other epileptic condition because (1) clinical and EEG fluctuations with time without any change of treatment are frequently observed, and (2) the goals of the treatment is not only to abolish the seizures with minimal side effects, but also to obtain neuropsychological improvement in decreasing the interictal epileptiform activity during sleep. This is why protocols of treatment should include counts of seizures, neuropsychological evaluations and prolonged video-EEG sessions.

At the Venice colloquium in 1993 about CSWS and related conditions, valproate (VPA) was proposed as first choice drug, either in monotherapy or in association with a benzodiazepine (32). It is the opinion of the authors that VPA should no longer be considered the drug of first choice, at least to try to "clean up" the sleep EEG (VPA may be efficient to treat associated seizures like atypical absences). The positive effects of VPA relies on relatively old series including few patients (69, 70). Data concerning the effect of benzodiazepines on the EEG are more convincing. De Negri *et al.* reported a

remission of CSWS in 9 out of 15 patients with a one-month intra rectal diazepam treatment (71); among these 9 patients, 7 showed an improvement in their neuropsychological evaluation after 6 months. Other authors reported similar efficacy with clonazepam or clobazam (9, 26, 70).

Among the other old drugs, there is a consensus stating that carbamazepine, phenobarbital and diphenhydramine are usually inefficacious and may even aggravate the EEG and clinical condition of children with CSWS (5, 69). On the contrary, ethosuximide and sulthiame are old drugs which may be helpful in reducing CSWS (69, 72-74), but sulthiame is not available in Belgium.

Concerning the new AED, recent case studies and small series suggest that topiramate and levetiracetam in add-on treatment are useful in some patients (75-78), but further studies are needed to define the place of these drugs in the treatment of CSWS.

It must be emphasized that the response to conventional AED is often incomplete and/or transitory. Corticosteroids seem to have more long lasting effects. Four studies focusing on the effects of corticosteroids in epilepsies with CSWS were published, using variable regimens. In the first study, 3 patients received either prednisone or hydrocortisone during 4 to 12 months (69). In the second study, 4 patients received early and prolonged ACTH or corticosteroid therapy, with high initial doses (79). In the third study, 2 patients received high dose intravenous methylprednisolone pulses for 3 days followed by a one-month oral prednisolone cure (80). In the fourth study, 10 patients received prednisone for 6 months, at relatively low doses (1 mg/kg/day) (81). Improvement of language, cognition and behavior was reported in all but one patient of these 4 series. Clinical improvement was at time spectacular, especially in children treated relatively early in the course of the disease, and was usually accompanied by an improvement of the EEG, with complete disappearance of the epileptiform activity in some cases. Some patients relapsed during steroids withdrawal, the risk of relapse seeming to be related to brief duration of treatment. Thus relapse of CSWS during steroids tapering is not the rule, and a unique cure may arrest the disease. This potential benefit has to be balanced with the well-known side effects of a long term steroids therapy. Special concerns in children are weight gain with Cushingoid aspect, failure to thrive and increased risk of bone fracture. Concerning this last point, it must be emphasized that the risk of bone fracture related to osteoporosis is increased during the treatment, but disappears within one year of stopping therapy (82).

Amongst the other therapeutic modalities, authors have reported some benefits of intravenous immunoglobulins or vagus nerve stimulation (VNS) in limited series of patients (83-85).

Finally, surgery using multiple subpial transections has to be considered in refractory cases of LKS. This technique developed by Franck Morell as a surgical treatment of epileptic foci located in eloquent cortex has indeed shown benefits only in patients with a pure verbal auditive agnosia, and not in other phenotypes of CSWS epilepsy (55, 86-88). Good candidates are patients in whom a unilateral perisylvian epileptic origin is suggested on the basis of the non invasive presurgical evaluation. MEG might be particularly useful in this perspective (57). Improvement of language after surgery was reported in the majority of patients, but was most likely to be seen years, rather than months, after surgery, which raises the question of the natural evolution to recovery (87).

Long-term outcome

The CSWS phenomenon is age-related and will remit usually before the age of 15 years. Thus the long-term prognosis of the epilepsy is good, even for patients with symptomatic epilepsy with CSWS, for instance those presenting with cortical malformations (20). On the other hand, the prognosis of intellectual functioning and language abilities is much more variable. Improvement in language dysfunction, mental retardation, and psychiatric disturbances generally occurs but the majority of affected children never return to normal levels, particularly in the verbal area and attention (3, 10). Persistent impairment in verbal short-term memory was demonstrated in patients after recovery from LKS using functional imaging: when compared to controls, patients showed decrease activation for an immediate serial recall words task in those posterior superior temporal gyri that were involved in the epileptic focus during the active phase of the disease (89).

Outcome at adulthood has been recently reported in 7 young adults. This study confirmed the good prognosis of epilepsy, still one patient having active epilepsy. The neuropsychological disorders particular to each syndrome persisted. Only 2 patients had achieved normal schooling. Three patients remained globally mentally deficient. The intellectual functions of both patients with LKS were normal; however, their everyday lives were disturbed by severe, disabling language disturbances (90).

Guidelines for treatment of epileptic syndromes with CSWS

As pointed out in the previous sections of this paper, epileptic syndromes with CSWS are very heterogeneous not only for the clinical presentation

but also for the presumed etiology. Therefore, the treatment will be individualized in taking into account the following considerations : (1) What is the clinical phenotype ? Is it a true LKS or a less severe type of cognitive or behavioral dysfunction ? (2) How is the profile of evolution ? Is it a rapid and massive regression or a developmental delay with recent stagnation for the acquisition of new skills ? (3) What is the suspected etiology ? Is it an idiopathic epilepsy with probable complex genetic background or a symptomatic epilepsy related to a structural brain lesion ? (4) How is the EEG during slow sleep ? Is it a pattern of a continuous generalized high amplitude spike-waves activity with destructed background or an important enrichment in focal epileptiform discharges with preserved background ? (5) Are there clinical epileptic seizures ? If yes, are they infrequent nocturnal tonic-clonic seizures or thousands of daily brief seizures like atypical absences or focal myoclonia ?

In the opinion of the authors, the general rules for treatment are the followings :

- (1) Avoid carbamazepine, oxcarbazepine, phenobarbital and diphenhydramine, and begin to taper off these drugs if CSWS appeared in a patient treated for epilepsy by one of these drugs.
- (2) A benzodiazepine is the first line treatment, associated with VPA in the presence of clinical seizures.
- (3) If this failed, and if the clinical profile is a severe and rapid cognitive deterioration after normal development (in particular verbal auditory agnosia, i.e. LKS) in the absence of structural lesion on MRI, a corticosteroid cure has still to be considered, and should be prolonged for a period of at least 6 months in case of positive answer. In the other situations, therapeutic trials with ethosuximide, topiramate and levetiracetam are recommended before using steroids. It is important to be aware that the efficacy of each drug has to be monitored by combined clinical and EEG evaluations, that conclusions about efficacy of a drug may still be drawn after a trial of 2 months, and that relapse after initial positive answer is not infrequent. Monotherapy is rarely attained in these cases, but tritherapy or quadritherapy should be avoided considering the increasing risk of cumulative side effects, in particular in the domains of cognition and behavior.
- (4) Surgery by multiple subpial transections should be restricted to highly selected cases of LKS with electrophysiological evidence of unilateral epileptogenic zone.
- (5) Other therapeutic options like intravenous immunoglobulins and VNS should be considered after failure of the previously considered options.

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