

## Electro-Clinical Aspects and Evolution of the Syndrome of Epilepsy with Continuous Spikes and Waves during Slow Sleep (CSWS)

Yavaş Uykuda Sürekli Diken Dalga ile Giden Epilepsi Sendromunun Elektro-Klinik Özellikleri ve Gelişimi

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**Objectives:** Electro-clinical data obtained from 38 patients were evaluated before, during, and after the end of continuous spikes and waves during slow sleep (CSWS).

**Patients and Methods:** At the Centre Saint Paul we observed 38 cases with epilepsy with CSWS between 1971 and 1998, of which 60% was males.

**Results:** Before the discovery of CSWS, awake EEG was normal in two cases or showed focal or multifocal abnormalities (n=12), focal and diffuse abnormalities (n=14), and diffuse abnormalities (n=10). Sleep EEG performed in 12 cases showed an increase in interictal abnormalities. An increase was noted in the number of seizure types during CSWS. One type was observed 12%, generally a focal motor seizure. In 42%, the initial seizure type was associated with atypical absences; in 46% with atypical absences, seizures with falls, and absence-status. Seizures disappeared in all cases regardless of the severity of epilepsy. Mean duration of epilepsy was 12 years (range 4 years and 4 months to 14 years and 11 months).

**Conclusion:** The syndrome of epilepsy with CSWS is an age-related syndrome in which seizures always disappear regardless of their intensity and severity during the evolution..

**Key Words:** Child; child behavior disorders/physiopathology; electroencephalography; epilepsy/physiopathology/drug therapy; epilepsy, absence; epilepsy, partial; epilepsy, generalized; sleep/physiology; sleep stages/physiology; status epilepticus.

**Amaç:** Yavaş uykuda sürekli diken dalga ile giden epilepsi sendromlu (CSWS) 38 hastanın elektro-klinik verileri, hastalık öncesinde, sırasında ve sonrasında değerlendirildi.

**Hastalar ve Yöntemler:** 1971-1998 yılları arasında 38 hastada CSWS gözlemlendi. Bunların %60'ı erkekti.

**Bulgular:** Hastalık saptanmasından önce uyanırken çekilen EEG iki olguda normaldi; 12 olguda fokal ya da multifokal anormallikler, 14 olguda fokal ve diffüz anormallikler, 10 olguda diffüz anormallikler gösterdi. On iki olguda elde edilebilen uyku EEG'sinde interiktal anormalliklerde artış saptandı. Hastalık gelişimi sırasında nöbet tiplerinde artış gözlemlendi. Olguların %12'sinde tek tip, fokal motor, nöbet gözlemlendi. Olguların %42'sinde başlangıçtaki nöbet tipine atipik absanslar, %46'sına atipik absanslar yanı sıra düşmeli nöbetler ve absans status eşlik etmekteydi. Hastalığın şiddetinden bağımsız olarak, nöbetler tüm olgularda ortadan kayboldu. Ortalama epilepsi süresi 12 yıl (dağılım 4 yıl 4 ay -14 yıl 11 ay) idi.

**Sonuç:** Yavaş uykuda sürekli diken dalga ile giden epilepsi sendromu, nöbetlerin, hangi yoğunluk ve şiddette olursa olsun, kaybolduğu, yaşla ilişkili bir sendromdur.

**Anahtar Sözcükler:** Çocuk; çocuk davranış bozuklukları/fizyopatoloji; elektroensefalografi; epilepsi/fizyopatoloji/ilaç tedavisi; epilepsi/absans; epilepsi, parsiyel; epilepsi, jeneralize; uyku/fizyoloji; uyku evreleri/fizyoloji; status epilepticus.

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The initial description of continuous spikes and waves during slow sleep (CSWS) was based on a strict EEG criterion, i. e. the presence of continuous spike-and-wave discharges during at least 85% of non-REM sleep. It was described for the first time in 1971 by Tassinari in collaboration with Patry and Lyagoubi<sup>[1]</sup> under the title of sub-clinical "electrical status epilepticus" induced by sleep in children. This condition had been observed at the Centre Saint-Paul in six patients. The clinical situation was heterogeneous: five children had epileptic seizures, five were mentally retarded and one child had no language. Later Tassinari et al.<sup>[2,3]</sup> used the term of "electrical status during sleep" in children or ESES. In 1983, during a workshop held in Marseille, this appellation was criticized because it was difficult to accept that CSWS can be considered as a status without clinical signs and because ESES can be observed in children who do not have seizures. Consequently, the term "continuous spikes and waves during sleep" was proposed<sup>[4]</sup> and it is under this denomination that it was included in the International Classification of Epilepsies and Epileptic Syndromes of the International League Against Epilepsy in 1989.<sup>[5]</sup>

The definition accepted by the ILAE was the following: "Epilepsy with CSWS results from the association of various seizure types, partial or generalized, occurring during sleep, and atypical absences when awake. Tonic seizures do not occur. The characteristic EEG pattern consists of continuous diffuse spike-waves during slow sleep, which is noted after onset of seizures. Duration varies from months to years. Despite the usually benign evolution of seizures, prognosis is guarded because of the appearance of neuropsychological disorders."

This syndrome is an age-related childhood syndrome. It is relatively rare. Individual series are generally small (from 2 to 5 cases). The most important is that of Morikawa et al.<sup>[6]</sup> with 31 cases, which account for approximately 0.5% of all childhood epilepsies in their center over 10 years. Kramer et al.<sup>[7]</sup> in a cohort of 440 consecutive paediatric patients with at least two seizures, found that epilepsy with CSWS and Landau-Kleffner Syndrome were extremely rare (0.2% each) as compared to rolandic seizures (8%) or benign childhood occipital seizures (2%). At the Centre Saint-Paul we observed 38 cases between 1971 and 1998 (about 1% of our children population). Because of the selection of severe cases, this prevalence is probably overestimated.<sup>[8,9]</sup> This report

will be based on these 38 cases followed at the Centre Saint-Paul and on data derived from the literature.<sup>[10-15]</sup> Of these 38 patients, eight were lost to follow-up, five are still in evolution and 25 are in recovery.

### GENERAL DATA

The sex ratio showed a male preponderance (60%). A personal history was obtained in 20 cases (more than 50%) including pre- or perinatal damage (n=14), neonatal convulsions (n=3), congenital hemiparesis (n=12), tetraparesis (n=2), prematurity (n=4), psychomotor retardation (n=15), delayed language (n=6), and consanguinity (n=3).

A familial history of epilepsy was noted in six cases (16%), which, in the literature, ranges from 10 to 16%. There are no genetic studies regarding sleep EEG in siblings and other relatives. However, we have two cases (not yet published) where one child has a CSWS syndrome and his sister a selective disorder in the apprenticeship of reading. Her EEG showed spikes and spike and wave discharges over the left occipital area, being sometimes subcontinuous with an extreme activation during slow sleep and diffusion of the abnormalities mimicking that of CSWS.

Neuroimaging was performed in all cases. It was abnormal in more than 60%. In the eldest cases (n=24) pneumoencephalography and/or CT scan were performed. They showed unilateral atrophy in nine cases, diffuse atrophy in two cases, localized frontal atrophy in one case, and a porencephaly in two cases. The most recent cases (n=14) had magnetic resonance imaging, which was normal in four cases. It showed a cortical migration disorder in four patients, including extensive frontoparietal polymicrogyria (n=2), bilateral perisylvian polymicrogyria (n=1), and left temporal focal dysplasia (n=1). It showed periventricular leucomalacia in three cases and unilateral atrophy in the remaining three patients. SPECT examination was performed by Gaggero et al.<sup>[16]</sup> in 10 patients, which revealed areas of low cerebral blood flow in four cases. Using a PET scan, Park et al.<sup>[17]</sup> reported a focal increase in metabolic activity.

### ELECTRO-CLINICAL FEATURES BEFORE THE DISCOVERY OF CSWS

The occurrence of the first seizure fell within the range of eight months to 12 years of age (mean 4 years 8 months; median 4 years 7 months). In 40%, it was unilateral. In 32%, it was described as a generalized clonic seizure. In the other cases, seizures were described as partial motor, general-

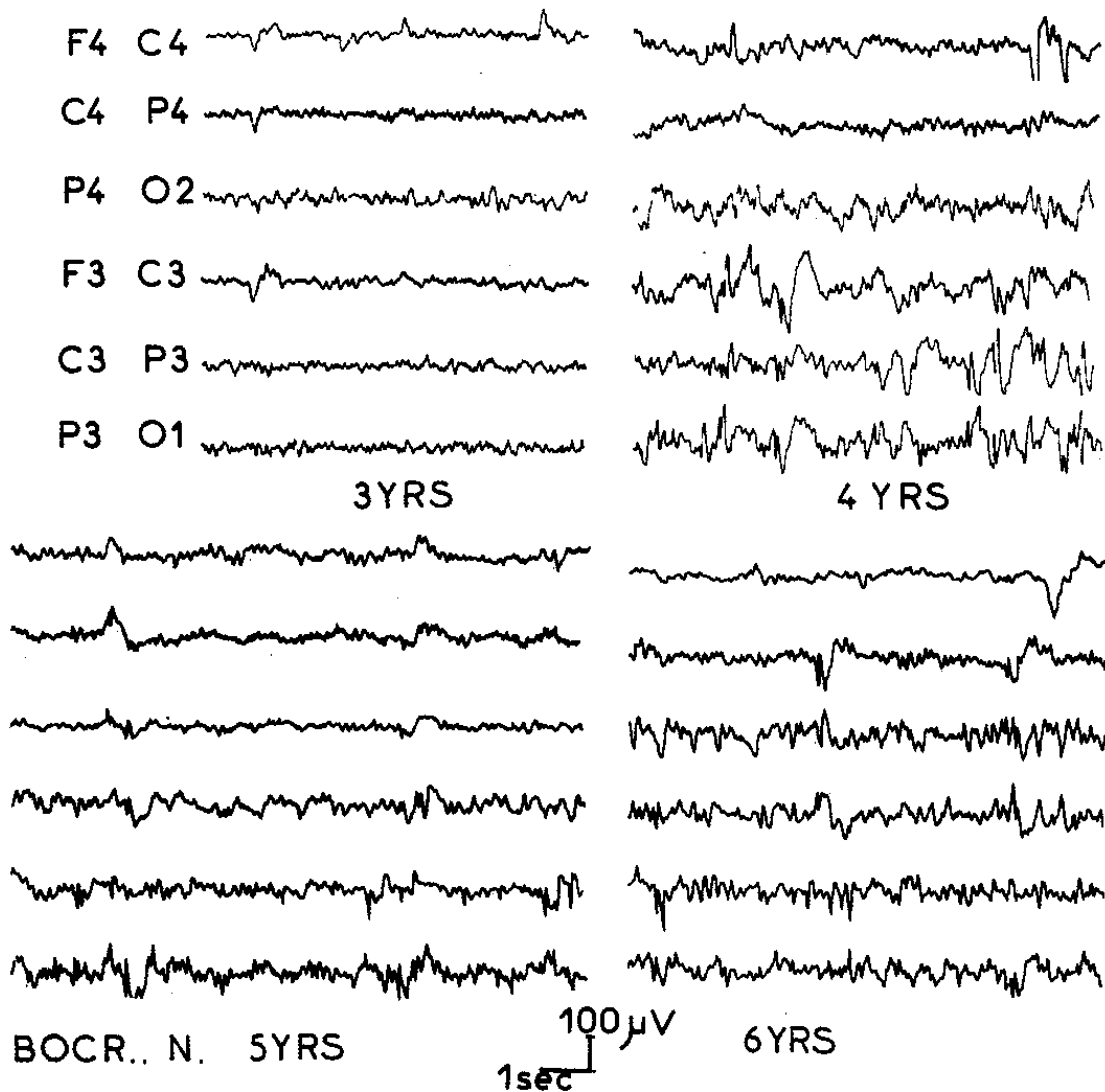


FIGURE 1

A girl with a right congenital hemiparesis. At 3 years before the first seizure, slight asymmetry between the two hemispheres, the background activity is undervolted on the left. At 4 and 5 years spikes and waves over the left hemisphere predominantly over the posterior area. At 6 years spikes occurring independently on both hemispheres.

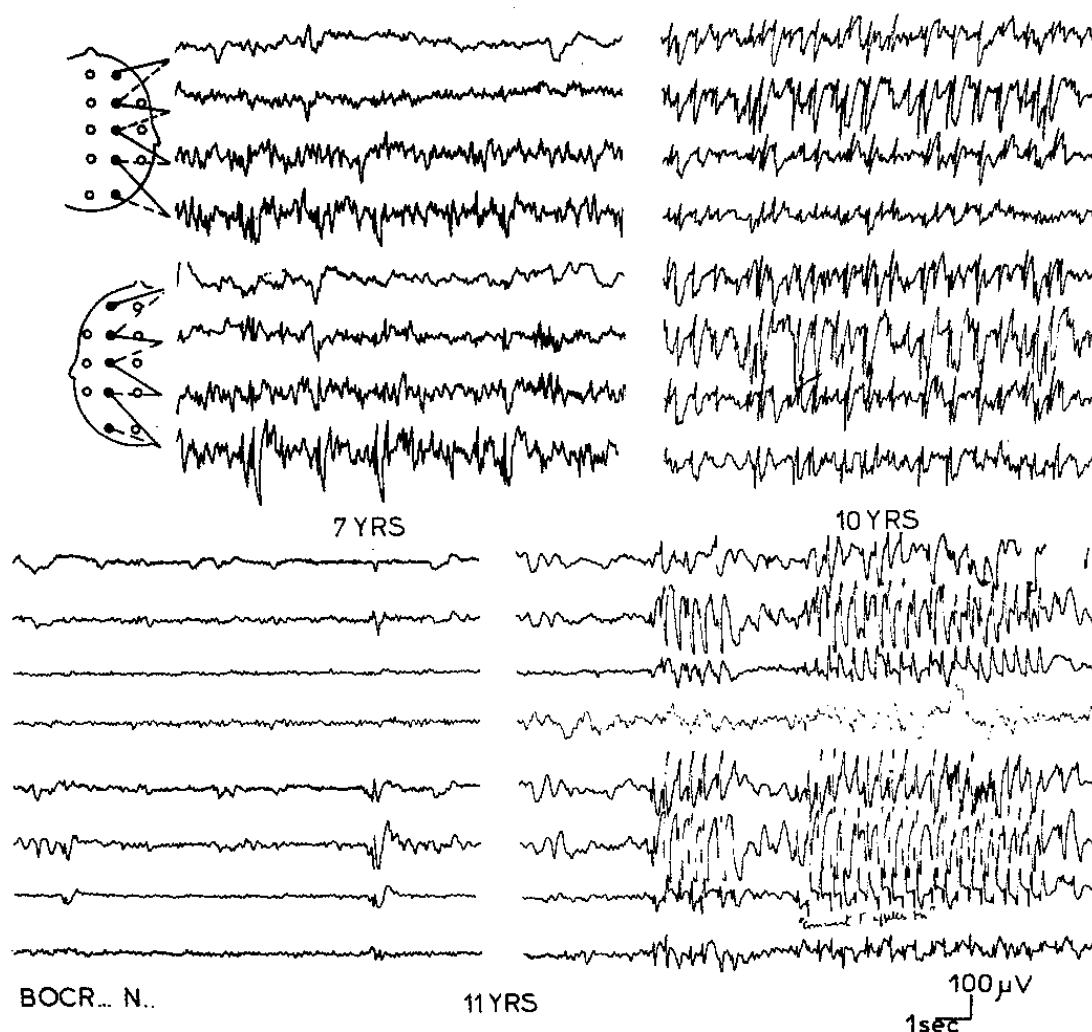
ized tonic-clonic, complex partial, absence or myoclonic absence. In four cases, we observed very particular seizures with loss of consciousness, atonia, and jaw contraction. In 45% of cases, the first seizure occurred during sleep.

Before the discovery of CSWS, an awake EEG was performed in all cases. It was normal in two cases and showed focal or multifocal abnormalities in 12 cases (Fig. 1), focal and diffuse abnormalities in 14 cases and diffuse abnormalities in 10 cases. Sleep EEG performed in 12 cases showed an increase in interictal abnormalities without alteration of sleep patterns and cyclic organization of sleep.

The psychomotor development was normal in 23 patients. The remaining cases had an isolated delay in language.

#### ELECTROCLINICAL FEATURES DURING CSWS

At the time of the discovery of CSWS or even before, new seizure types appear: atypical absences, falls and sometimes absence-status. However, no tonic seizures are seen. Before or during the occurrence of these new seizure types, dysfunctions of varying intensity arise, which are sometimes severe enough to justify an EEG recording during wake and sleep. During waking, we noted the appear-



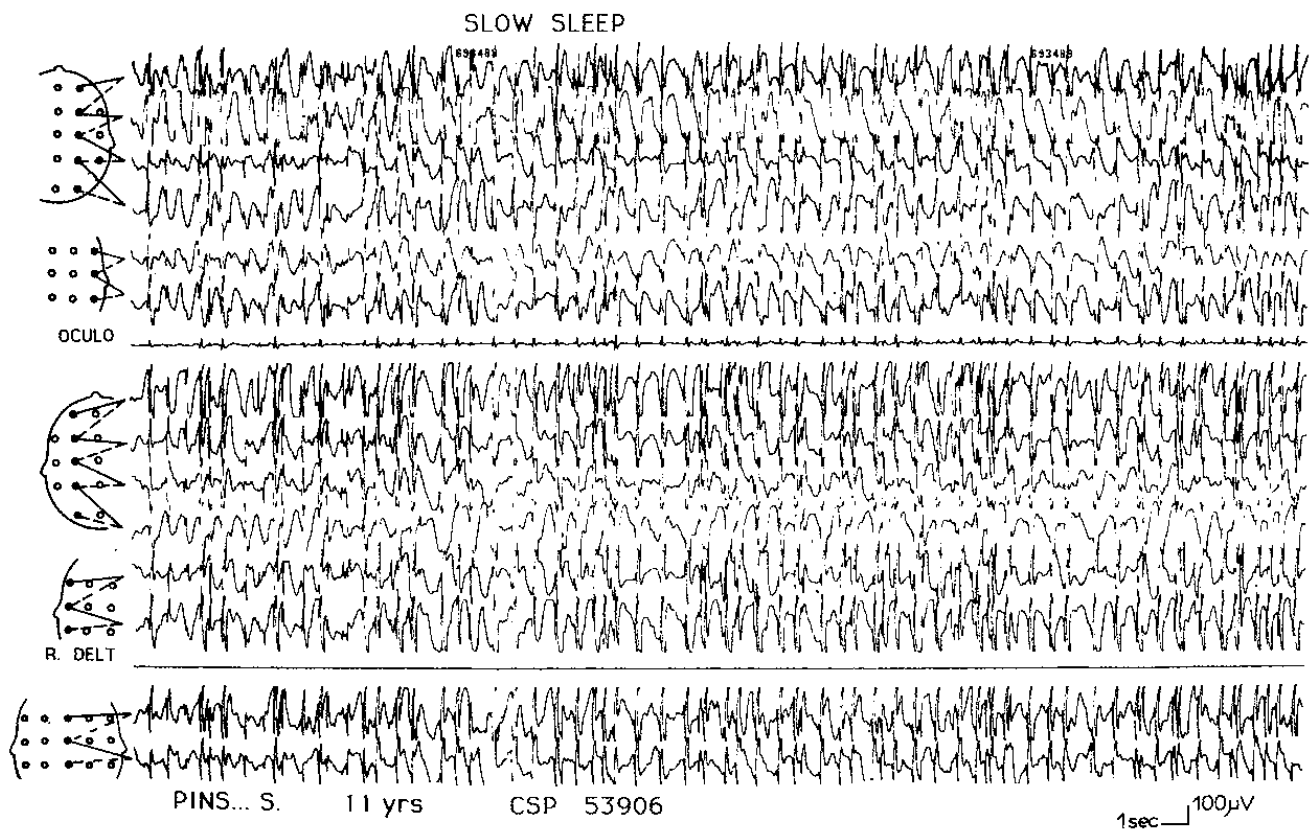
**FIGURE 2**

The same girl as in Fig. 1. Spikes and spikes and waves at 7 years become more diffuse at 10 years. At 11 years, focal abnormalities are less evident on the left, whereas on the right, during the hyperpernea, burst of diffuse spikes and waves seem to be accompanied by a slight loss of consciousness.

ance of, or an increase in, diffuse spikes and waves (SWs) at 2-3 Hz, organized in bursts (Fig. 2) with or without clinical manifestations (loss of consciousness, slight eyelids myoclonias). As soon as the child fell asleep, EEG showed continuous bilateral and diffuse slow SWs, persisting through all the slow sleep stages (Fig. 3). Initially, Tassinari stressed the fact that the SW index should be no less than 85 per cent of the total duration of slow sleep, although possible variants have been accepted nowadays. This problem was discussed in a symposium held in Venice in 1993.<sup>[14]</sup>

In the definition of the ILAE,<sup>[5]</sup> some aspects have not been mentioned, i.e., the morphology, frequency and periodicity of the SW discharges. Neither have the possible existence of an asymmetry of the SWs or of a focus during the periods of fragmentation of CSWS. Concerning their morphology, the dis-

charges are represented by a more or less slow wave with a more or less fast spike. Polyspike waves or bursts of fast rhythms never occur. The frequency is variable, being slow, around 1.5 to 2 Hz, or faster around 3 to 5 Hz. The discharges appear as soon as the child falls asleep and persist during all the slow sleep periods. Each time the child falls asleep, this state of continuous SWs can be long-lasting and can appear on several recordings over months or years. The index percentage of SW is higher during the first cycle and decreases during subsequent sleep cycles. The SWs are generally bilateral and symmetrical; however, they can be asymmetrical in some lesional cases, as in cases with polymicrogyria.<sup>[16]</sup> In the periods of fragmentation of continuous SWs, focal or multifocal abnormalities can be observed, generally over the frontal or parieto-occipital areas (Fig. 4). During



**FIGURE 3**

A boy with left frontal atrophy. Bilateral diffuse continuous spikes and waves during slow sleep. Note the high voltage and the slow frequency, at 1-2 Hz, of the SW discharges.

REM sleep, the CSWS disappears and the focal abnormalities become more evident. It is also possible to observe diffuse SWs similar to those recorded in the waking state. In six cases, subclinical focal discharges were recorded during REM sleep, generally involving the frontal area. Although in most cases the physiological patterns of sleep are absent, it is possible, in some cases, to observe them in the last cycle. However, the slow sleep stages with CSWS and the REM periods without CSWS can be identified. The proportion of non-REM to REM sleep is approximately 80 to 20.

Both the age of discovery and duration of CSWS are often difficult to assess, as many children do not have sleep EEG recordings at the time of appearance of the first clinical symptoms. In our cases, the mean age of discovery was 7 years and 3 months (range 2 years 8 months to 14 years) and the mean duration was three years (range 8 months to 6 years and 7 months).

#### Seizures during CSWS

There was an increase in the number of seizure types. In only 12% of cases, one type was observed, generally a focal motor seizure. In 42%, the initial

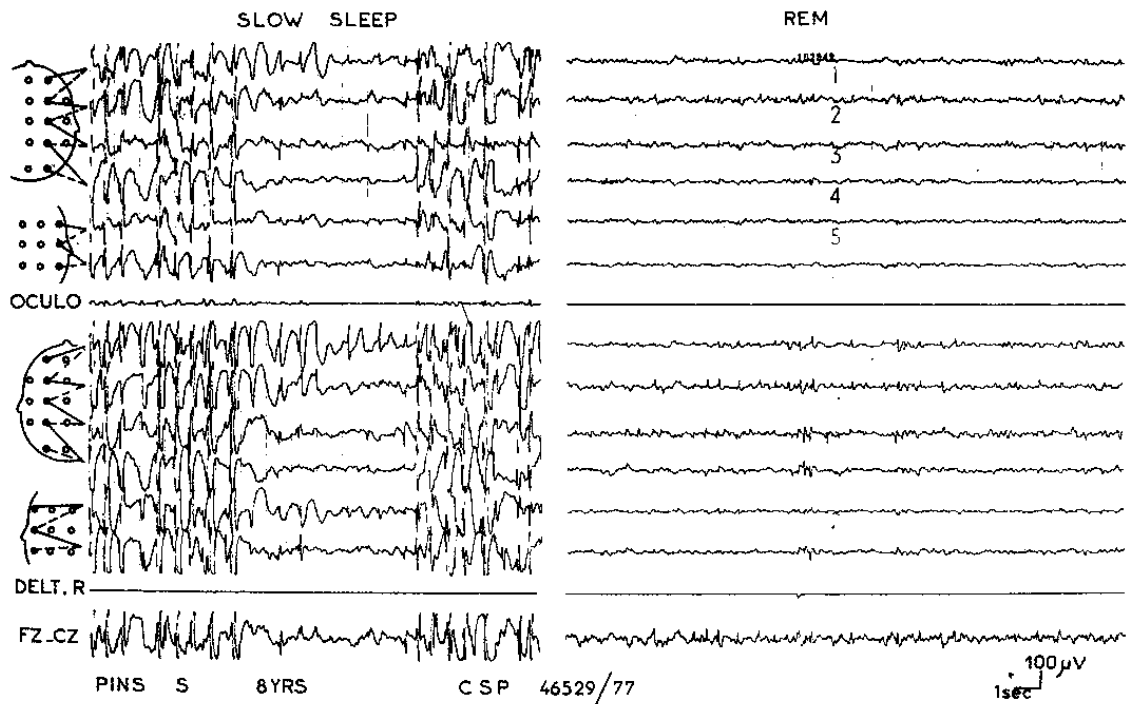
seizure type was associated with atypical absences; in 46% with atypical absences, seizures with falls, and absence-status. Similar findings were reported in the data sheets presented by the participants of the workshop held in Venice in 1993.<sup>[9]</sup>

#### Severity of Epilepsy

In 7% of patients, seizures were rare and occurred generally during sleep. In 50%, they occurred several times a week, being in the form of atypical absences, generalized convulsive seizures, and partial motor seizures. In 43%, they appeared several times a day with atypical absences, generalized tonic-clonic seizures, sudden falls, and absences status. Tonic seizures were never reported nor observed. Ninety-three percent of patients experienced severe epilepsy, compared with 70% in the literature.<sup>[9]</sup> Nevertheless, it is necessary to emphasize that tonic seizures were not observed at all both in this study and by other authors.

#### Psychomotor Development during CSWS

Concerning the impairment in psychomotor development, our data are insufficient due to the lack of precise evaluations during CSWS. In 23 patients the psychomotor development was nor-



**FIGURE 4**

The same boy as in Fig. 3. On the left, during non-REM sleep, a short period of fragmentation of diffuse spike-wave discharges with left frontal spikes and spikes and waves. On the right, during REM sleep diffuse continuous SW discharge disappears, and only localized spike bursts are seen, predominating over the left hemisphere.

mal prior to CSWS. However, in all patients, we observed severe decreases in IQ ranging from 45 to 78 points, a significant impairment in temporospatial orientation and memory, behavioural disturbances with reduced attention span, hyperkinesia, aggressivity, difficulties in social contacts, and sometimes manifestations of behavioural inhibition. In some cases, clinical features were considered "psychotic." Two-thirds of patients exhibited a very marked reduction in language skills, with an expressive dysphasia in some. In fifteen patients in whom abnormal development was observed prior to the occurrence of CSWS, a massive regression was noted in all fields, with three patients exhibiting severe aggressivity.

#### ELECTROCLINICAL FEATURES AFTER THE END OF CSWS

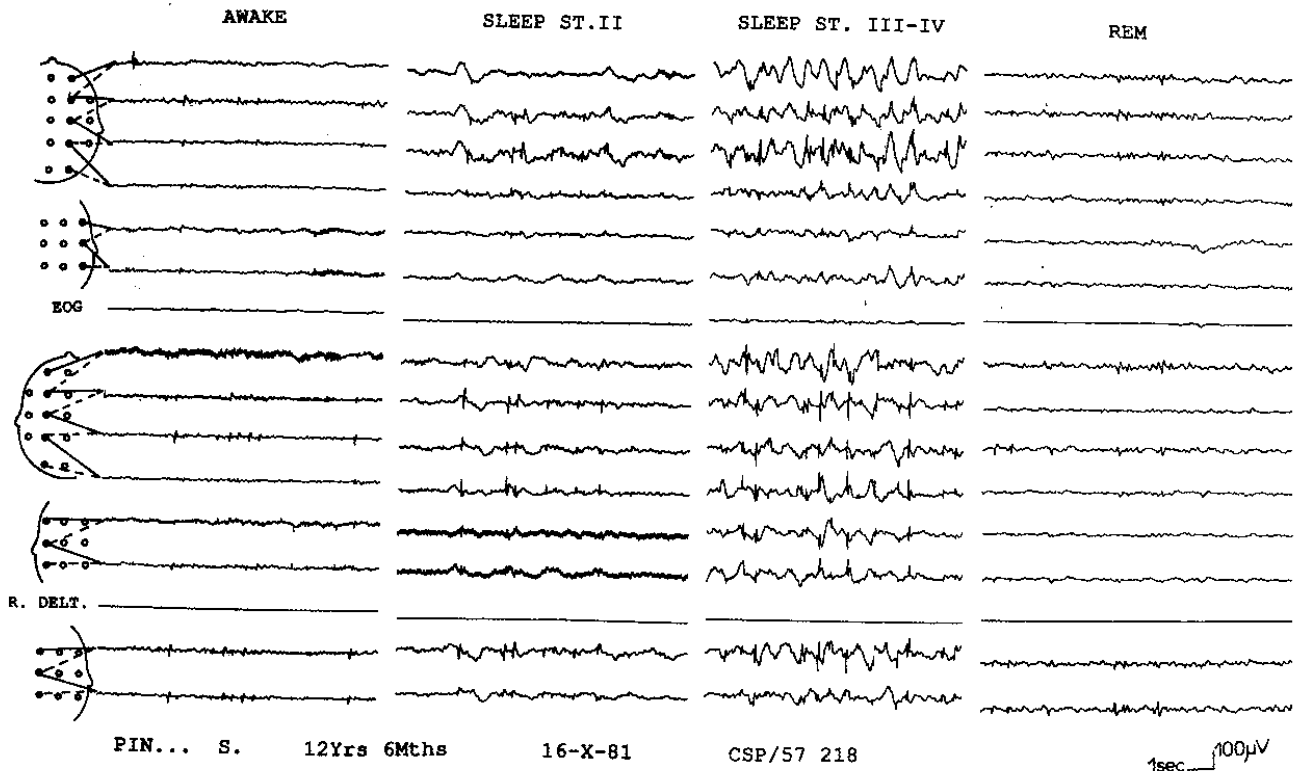
##### Epilepsy

Seizures disappeared in all cases, whether lesional or non-lesional, whether epilepsy had been severe or not. Similar observations have been reported.<sup>112,191</sup> Mean duration of epilepsy was about 12 years in our series, ranging from 4 years and 4 months to 14 years and 11 months. In 31%, the disappear-

ance was simultaneous with the offset of CSWS. In 44%, seizures disappeared before the end of CSWS, whereas, in 25%, they persisted after the end of CSWS, becoming rare and consisting of absences without falls, generalized clonic or tonic-clonic seizures.

##### EEG after the End of CSWS

This study encompasses data on only 25 patients, as eight patients were out of follow-up and five patients are still exhibiting an evolving course. EEG was normal at awake and sleep in eight cases, with normalization being progressive and taking a mean of three months after the end of CSWS. Repeated awake and sleep EEG recordings show that the normalization may continue for an average of 15 years after the end of CSWS. In five cases, it was normal at awake while showing focal abnormalities during sleep. In 12 cases, however, focal abnormalities existed during awake and sleep recordings. No diffuse abnormalities were recorded in any patients. In all cases, the cyclic organization of sleep was normal. All stages of sleep were present at a normal percentage, with normal sleep patterns in all patients (Fig. 5).



**FIGURE 5**

The same boy as in Fig. 3 and Fig. 4. At 12 years 6 months, the boy is seizure-free. The awake EEG shows left focal spikes activated by sleep which is well organized. Disappearance of the continuous SW discharges.

### Neuropsychological Development after CSWS

Of twenty-five patients, 16 patients were normal prior to CSWS. In all cases, albeit always slow and often only partial, a global improvement was noted in performance and/or behaviour after the end of CSWS. The impairment in the temporospatial orientation and memory as well as the disturbance in language skills disappeared in all subjects. However, compared to the former intelligence levels, IQ scores remained low in about 50% of cases. Behavioural disturbances persisted in 50%. This variable degree of improvement after the end of CSWS has been demonstrated by Billard et al.<sup>[11]</sup> and Morikawa et al.,<sup>[12]</sup> which corroborates the hypothesis that "CSWS is responsible for the intellectual, language and psychiatric disturbances."<sup>[8]</sup> Only 50% had normal lives, but none reached university education. Fifty percent had to live in sheltered living situations. The poor prognosis were not attributed to the age of discovery of CSWS, to the severity of epilepsy, or to the severity of the associated disturbances. Nor were the presence or absence of a cerebral lesion implicated. It may, however, be related to the duration of CSWS.

The following data can be summarized about the follow-up of our 25 patients who are seizure-free and no longer experience CSWS: (i) the mean duration of follow-up was 8 years and 6 months; (ii) the mean age at the last visit was 18 years; (iii) 15 patients have been leading their lives without treatment, five patients are under low-dose monotherapy while five patients still receiving a combination of two agents.

As far as the therapy is concerned, there is not yet a miraculous cure. In general, a good response can be achieved to seizures, but not to CSWS. In some cases clobazam, valproate in association with ethosuximide, or steroids can produce a favourable effect but often only of short duration. Moreover, it is absolutely certain that some drugs like carbamazepine, vigabatrin, as well as polytherapy lead to deterioration in the electro-clinical features.

### NOSOLOGICAL PROBLEMS

The EEG pattern in CSWS can be seen in different conditions. It is an age-dependent phenomenon with a tendency to secondary bilateral synchrony.<sup>[19,20]</sup>

Continuous spikes and waves during slow sleep can be observed in children without epilepsy but having neuropsychological disturbances.

In contrast, CSWS without neuropsychological deficits but with epilepsy were observed in some cases by Aicardi and Chevrie in 1982.<sup>[21]</sup> They reported the condition as "atypical benign childhood partial epilepsy." The clinical picture closely resembled CSWS. The onset was between two and six years of age in children with normal development and no neurological signs. All patients exhibited at least two seizure types: typically atonic and nocturnal partial motor. Atonic seizures occurred in clusters lasting one to several weeks, generally interspersed with free intervals of weeks. They involved the whole axial musculature leading to sudden falls on the ground or were localized in the head or the arm or the hand.<sup>[22,23]</sup> The awake EEG showed centro-temporal spikes and diffuse abnormalities. Sleep EEGs showed an important activation with the appearance of CSWS, although the duration of CSWS was not mentioned (was it weeks, months, or years?). The electroclinical course showed an apparently complete remission. In fact, the main difference between our cases and those of Aicardi is relevant to the intellectual sphere. In patients with atypical benign partial epilepsy, there was no intellectual deterioration. However, no information was provided concerning the possible existence of minor behavioural disturbances. A more extensive neuropsychological investigation would perhaps reveal the presence of a slight deterioration.

Deonna et al.<sup>[24]</sup> reported six similar cases in 1986. They emphasized that, deterioration observed in EEGs coincided with the appearance of neuropsychological dysfunctions.

The situation in some cases were worsened by polytherapy, which ameliorated after tapering or withdrawal of the treatment. Ultimately, all the children recovered a normal neuropsychological state.

Another problem is that of benign epilepsy with centro-temporal spikes (BECT). In some very rare cases with CSWS, the clinical symptomatology and the evolution of epilepsy are very similar to those observed in BECT. In few cases of BECT, more or less typical absences can be observed with diffuse spikes and waves on EEG.<sup>[19,25]</sup> In BECT, interictal abnormalities are generally in the centro-temporal regions, while in epilepsy with CSWS, they are rather frontal or parieto-occipital. In BECT a very important activation of the discharges

can be seen; however, the typical EEG pattern of CSWS is rarely found. We reviewed in 1995 our 70 cases<sup>[9]</sup> then in 1999 our 98 cases of BECT<sup>[26]</sup> and never observed CSWS in all cases. True CSWS had been observed in some cases of BECT after the introduction of carbamazepine, with worsening of the seizures and appearance of atypical absences, seizures with falls, and negative myoclonus.<sup>[27,28]</sup> However, this clinical picture was transitory and disappeared after the withdrawal of the drug. Mental deterioration is constantly observed in CSWS, while in the majority of cases of BECT, neuropsychological functions are fully preserved, or a slight impairment may appear only to regress.

Finally two points need to be emphasized: in BECT, a history of familial epilepsy is very important (40% of cases) and encephalopathy, which is present in about 50% of CSWS patients, is absent.

Finally, Landau-Kleffner syndrome is above all a clinical diagnosis as in some cases, an EEG picture of CSWS can appear during the evolution.

## CONCLUSION

The syndrome of epilepsy with CSWS is an age-related syndrome in which seizures always disappear regardless of their intensity and severity during the evolution, but the prognosis is reserved because of the existence of neuropsychological disorders. Two diverse situations can be identified: the syndrome of epilepsy with CSWS, and the occurrence of CSWS during a limited period of time in some patients with or without epilepsy.

Many questions remain open. Why is it that, in the epilepsy with CSWS, CSWS leads to an irreversible encephalopathy with permanent neuropsychological deficits, while in other cases it does not trigger a definite encephalopathy? Why is the same lesion, such as bilateral perisylvian microgyria, associated with a full recovery of seizures in the epilepsy with CSWS and with the appearance of a Lennox-Gastaut syndrome with intractable seizures in others? Why do some children at the same age, with the same epileptic seizures develop CSWS and others do not?

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