Journal of Pediatric Sciences

SPECIAL ISSUE

"Treatment of Severe Epileptic Syndromes"

Editor

Alberto Verrotti

Department of Pediatrics, University of Chieti, Italy

'Relationships between continuous spike-waves during sleep (CSWS) and antiepileptic drug resistance'

Antonia Parmeggiani, Annio Posar

How to cite this article:

Parmeggiani A., Posar A. *Relationships between continuous spike-waves during sleep (CSWS) and antiepileptic drug resistance'*. Journal of Pediatric Sciences 2009:1:e15

CASE REPORTS

Relationships between continuous spike-waves during sleep (CSWS) and antiepileptic drug resistance

Antonia Parmeggiani[1], Annio Posar[1]

Abstract: Background and aims: The spectrum of neuropsychiatric disorders associated with continuous spike-waves during slow wave sleep (CSWS) syndromes is widely debated. Although seizures and CSWS disappear within puberty, heterogeneous neuropsychological and behavioural disorders can persist. This feature has increased the interest in etiopathogenesis and negative prognostic factors of these conditions. Delayed diagnosis and appropriate therapy, the high frequency, generalization, early onset, prolonged duration and drug resistance of EEG paroxysmal abnormalities are all unfavourable prognostic factors for neuropsychological and behavioural evolution. Pre-existing cerebral lesions, in some cases, may aggravate the prognosis. Case reports: We describe five patients with drug resistant CSWS presenting different clinical-EEG features. One of them had a typical picture of CSWS with paroxysmal abnormalities occupying more than 85% of N-REM sleep EEG recording (case 4); another had a classical Landau Kleffner Syndrome (LKS) (case 5). All cases presented CSWS resistant to several antiepileptic drugs; the localization of prevailing EEG paroxysmal abnormalities showed a good relation with neuropsychological findings, irrespective of IQ. All patients except case 1 presented IQ regression, with a significant gap between VIQ and PIQ to the detriment of the PIQ for cases 2, 3 and 4 and of VIQ for case 5 with LKS. IQ improved in cases 2 and 4 even if a gap remained to the detriment of PIQ in case 2. Cases 3 and 5 improved after CSWS disappearance even though both had a borderline FIQ at the last observation. Behavioural problems were present in all cases except the first, improving after CSWS fragmentation. Seizures occurred in all patients except case 3 representing the first symptom, but they generally disappeared before CSWS fragmentation. Cerebral lesions were present in cases 2 and 4 but did not seem to be responsible for CSWS evolution. Conclusion: It is necessary to be aware that CSWS can develop and that early diagnosis is very important to start an antiepileptic treatment. Further studies with a large sample and homogeneous EEG criteria are required to better characterize the enigma of CSWS.

Key words: CSWS, antiepileptic drug resistance
Received: 24/11/2009; Accepted: 25/11/2009

Introduction

Continuous spike-waves during sleep were first described in 1942 by Kennedy and Hill, who defined the clinical picture "Dementia dysrhythmica infantum" [1]. Subsequently, Landau and Kleffner described the acquired epileptic aphasia in 1957 [2] followed by Patry and collaborators' 1971 report on subclinical electrical status epilepticus induced by sleep in children [3], later defined by Tassinari and collaborators as electrical status epilepticus during slow sleep (ESES) [4,5]. EEG recordings and clinical pictures are characterized by subcontinuous /continuous EEG paroxysmal abnormalities during sleep, cognitive/behaviour impairment and seizures. The 1989 classification of epileptic syndromes described ESES using the term "epilepsy with

[1] Child Neurology and Psychiatry Unit, Department of Neurological Sciences, University of Bologna, Italy

Corresponding: Antonia Parmeggiani, MD
Child Neurology and Psychiatry Unit, Department of Neurological Sciences, University of Bologna, Via Ugo Foscolo 7- 40123, Bologna, Italy.
Tel: +390512092950
Fax: +390512092769
e- mail: antonia.parmeggiani@unibo.it

continuous spike-waves during slow wave sleep" (CSWS) [6]. The current new proposal for the classification of epilepsies includes CSWS and Landau Kleffner Syndrome (LKS) in the group of epileptic encephalopathies [7]. As already described, both CSWS and LKS may pass from one to the other [8]. The main problems for these syndromes are the continuous EEG paroxysmal abnormalities during sleep and cognitive and behavioural stagnation or regression, whereas epileptic seizures may be not so common. After a period of possible drug resistance, the EEG picture generally improves during puberty. Unfortunately neuropsychological problems persist in a half of cases giving a poor prognosis during adulthood. Antiepileptic drug resistance is common in these epileptic encephalopathies even though seizures are less important than EEG paroxysmal abnormalities for the poor prognosis. Seizures may precede or coincide with the appearance of EEG continuous paroxysmal abnormalities but they can disappear earlier; anyway they do not seem an important prognostic factor; instead, the long lasting and early onset of continuous EEG paroxysmal abnormalities influences the prognosis [8, 9, Parmeggiani and Posar in press]. Thus, delayed diagnosis and treatment may worsen the prognosis. Unfortunately, antiepileptic treatments may be ineffective. No controlled studies have been done on antiepileptic treatments in CSWS. It is already known that is better to avoid CBZ, PHT, PB, and a polytherapy, while VPA, ESM, LEV, BZD, STM, and corticosteroid treatment are indicated [9, Parmeggiani and Posar in press]. CSWS may be associated with cerebral lesions [10, 11] that may compromise the clinical picture before the appearance of CSWS or in addition to the effect of CSWS [Parmeggiani and Posar in press]. The aim of our paper is to describe 5 patients with drug-resistant CSWS presenting different clinical-EEG features.

Case reports

Case # 1: Male, referred to us at the age of 9 years 7 months for drug-resistant seizures. There was a family history of febrile convulsions and epilepsy. His parents were macrosomic, the father had a macrocrania. He was born at term following an uncomplicated pregnancy and normal delivery. Psychomotor development was normal. He was macrosomic. Onset of epilepsy occurred at 6 years of age. Initially, seizures were mild and rare, later more intense and frequent (several times a day). Seizures were brief, characterized by hemifacial and ipsilateral upper limb twitching mainly on the left side, anarthria, drooling, sometimes with secondary generalization, terminating with dysarthria and postictal sleep. When he was 8 years 5 months old, EEG showed CSWS with parieto-temporal paroxysmal abnormalities prevailing on the right. Since 9 years 7 months he has also had seizures with sensory disturbances and hyposthenia involving the left hemisoma. Seizures and CSWS were drug resistant (CBZ; VGB + CBZ; VPA + CBZ; VPA + CBZ + CLB; VPA + LTG; VPA + CLB; CLB; CLB+ESM).

Neurological examination showed: macrocrania, macrosomia, articular laxity, bilateral impairment of graphesthesia. Plasma amino acids, search for FRAXA and FRAXE, karyotype were normal.

At our first observation EEG showed multifocal spikes and spike-waves, clearly prevailing in right centro-parieto-temporal regions, and diffuse, fragmented by tongue movements; tapping was positive. The abnormalities were increased by N-REM sleep, when they became continuous on the right side. Brain MRI was normal.

Neuropsychological evaluation showed: full IQ (FIQ) = 112; verbal IQ (VIQ) = 114 and

performance IQ (PIQ) = 106; deficit of executive functions; learning disorders in reading, writing and arithmetic.

At the last observation, when he was 10 years and 2 months, seizures, CSWS and neuropsychological disorders persisted (CLB + ESM).

Case # 2: Female, referred to us for the first time at the age of 7 years for seizures and frequent EEG paroxysmal abnormalities. There was a family history of myasthenia and mood disorder. She was born at term following an uncomplicated pregnancy, presenting mild perinatal suffering. Psychomotor development was normal.

At 18 months she had an uncomplicated febrile convulsion. At 5 years 11 months she had the first seizure without fever in wakefulness characterized by left hemisoma brachiofacial twitching, with secondary generalization lasting 5 minutes. EEG showed bilateral paroxysmal abnormalities prevailing on the right. CBZ was started. A second similar seizure occurred 3 months later. When she was 6 years 6 months, EEG showed drug resistant CSWS (CBZ + CLB, CBZ + LTG, LTG, CLB, CLB + ESM, DZP, VPA + DZP, VPA, VPA + AZM, VPA + CZP). She had another 3 seizures, the last one at the age of 8 years 3 months characterized by right hemifacial twitching with secondary generalization and anarthria. Neurological examination showed bilateral strabismus and stuttering. Brain MRI displayed a periventricular leukomalacia.

When the patient came to our observation EEG showed multifocal and diffuse spike-waves enhanced by eye closure and hyperpnea prevailing on bilateral anterior regions, subcontinuous / continuous in N-REM sleep (Figure 1).

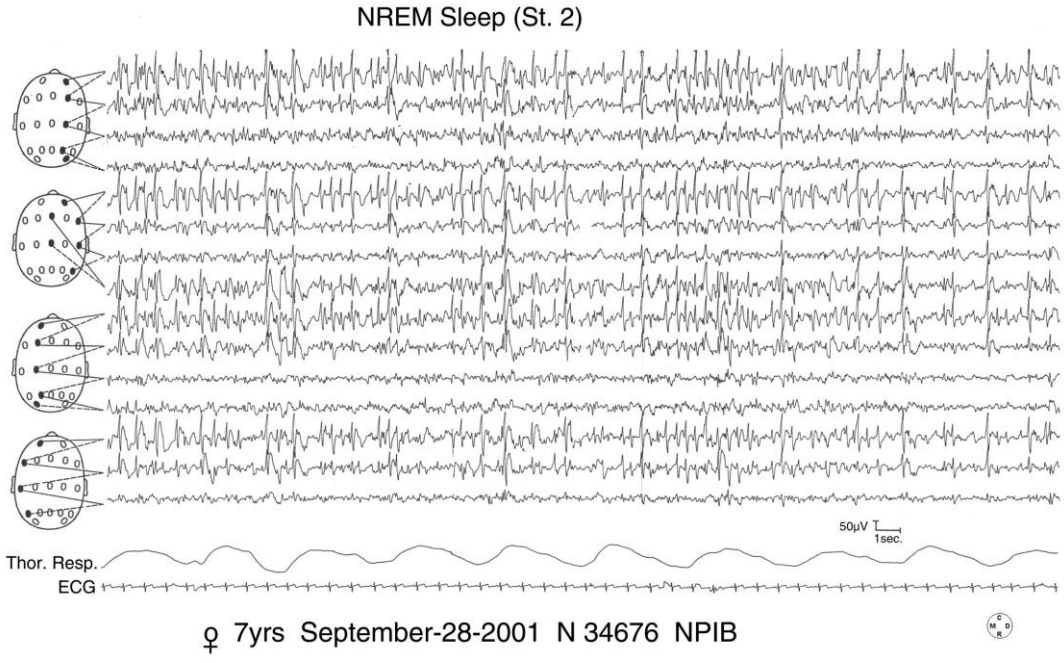

Figure 1: Case 2- EEG recording showing during N-REM sleep subcontinuous diffuse spike-waves prevailing over bilateral anterior regions.

Neuropsychological evaluation at the first observation showed FIQ = 126, VIQ = 120, PIQ = 126. In the following years IQ gradually decreased: when she was 9 years 9 months, FIQ = 88; VIQ = 101 and PIQ = 77. Deficits of attention and working memory were present, in addition to perseverations, poor flexibility of thought, deficit of executive functions, learning disorders prevailing in mathematical logic. Behaviour was characterized by hyperkinesia, disinhibition, lack of criticism; anxiety and depression symptoms were present. From the age of 10 years, CSWS fragmented with a gradual improvement in the clinical picture.
At the last observation (VPA + sertraline), at the age of 14 years 9 months, there was an evident recovery of IQ: FIQ = 117; VIQ = 128 and PIQ = 100. A learning disorder prevailing in arithmetic persisted, while behaviour had improved.

Case # 3: Female, referred to us at the age of 7 years 5 months for learning disorder and frequent EEG abnormalities. Family history was negative. Threatened abortion and threatened preterm labour had occurred during pregnancy; at the 40th week mild foetal suffering was noted. Psychomotor development was normal. She had always severe difficulties in reading, writing, and arithmetic. At the age of 6 years 6 months a therapy with VPA started due to referred absence seizures, never observed by the clinicians, and for frequent multifocal EEG abnormalities.

At our first observation, EEG showed spikes and spike-waves prevailing on the posterior regions, synchronous and asynchronous, more frequent on the right, with a tendency to diffusion, increased in wake by eye closure and hyperpnea, subcontinuous/continuous during N-REM sleep (Figure 2). Neurological examination was negative. Brain MRI was normal. Search for FRAXA and FRAXE was negative.

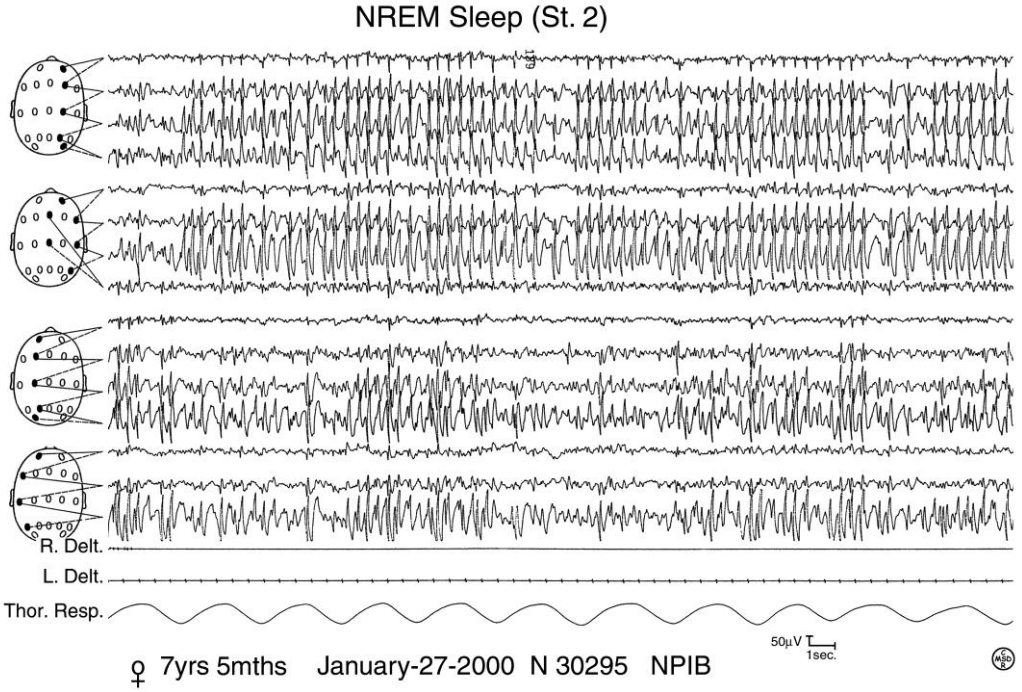

Figure 2: Case 3 - EEG recording showing during N-REM sleep subcontinuous diffuse spike and spike-waves prevailing over posterior regions and on the right side.

At the age of 7 years and 5 months neuropsychological evaluation showed FIQ =89; VIQ = 103 and PIQ = 75; visuo-perceptual and visuo-graphic abilities were clearly impaired. A severe learning disorder was present in reading, writing and arithmetic.

CSWS was drug resistant (VPA, BZD, LTG, ACTH, OXC, AZM, ESM, LEV). Subsequently, when EEG paroxysmal abnormalities became more frequent and diffuse, a cognitive decline occurred: when she was 9 years 6 months, FIQ = 65 (VIQ = 70, PIQ = 64). Moreover behaviour worsened with restlessness, disinhibition and verbal aggressiveness.

Since the age of 10 years, EEG paroxysmal abnormalities have progressively decreased, cognitive abilities and behaviour improved. At the last observation (LEV), when she was 17 years, FIQ = 79; VIQ = 80 and PIQ = 83; visuo-graphic and particularly visuo-perceptual abilities had improved as had reading speed.

Case # 4: Female, referred to us for the first time when she was 5 years 10 months for drug resistant seizures and cognitive regression. There was a family history of febrile convulsions, epilepsy, autism and mild language retardation. She was born at term following an uncomplicated pregnancy and normal delivery. Psychomotor development was normal.

At the age of 3 months she suffered biventricular obstructive hydrocephalus due to a choroid plexus papilloma of the third ventricle. The tumor was removed and a ventriculo-peritoneal shunt inserted. EEG showed sporadic spikes on centro-temporal regions, prevailing on the right. After surgery, periodic brain MRI showed only a mild dilatation of frontal horns of lateral ventricles.

At the age of 3 years 6 months, the first seizure occurred during sleep, arising from the occipital lobe and lasting 30-40 minutes. Awake EEG showed bilateral posterior paroxysmal abnormalities. VPA treatment started with remission of seizures that resumed at 4 years 5 months, when EEG showed CSWS. At this time diffuse and generalized spike-waves occupied more than 85% of N-REM sleep EEG recording. From the age of 5 years 1 month a gradual, progressive cognitive and behavioural decline occurred: after a few months the girl presented an autistic-like clinical picture and had suspected hallucinations. At 5 years 4 months frequent brief seizures with version of the head and eye deviation to the left occurred. LTG, TPM, CLB, ESM were ineffective on seizures and CSWS. The girl came to our observation when she was 5 years 10 months. Neurological examination was normal. EEG showed multifocal spike-waves, prevailing over posterior regions, diffuse and generalized, continuous during N-REM sleep. Neuro-psychological evaluation was impossible due to girl's mental deterioration. We tried CZP and AZM, without effect. One month later, a treatment with ACTH was administered and a progressive improvement of EEG during sleep was noted: since 6 years 2 months only infrequent focal and diffuse paroxysmal abnormalities have been recorded. At 5 years 11 months seizures stopped. When CSWS disappeared, cognitive, linguistic and behavioural recovery occurred, even if some deficits in attention, visuo-graphic abilities, spatial orientation and emotional lability persisted. At the age of 7 years 5 months (VPA + CZP) she had FIQ = 96; VIQ = 107 and PIQ = 85. At the last observation, when she was 10 years, the EEG showed an increase in paroxysmal abnormalities (VPA + CZP) and neuro-psychological evaluation showed: FIQ = 105, VIQ = 108 and PIQ = 101.

There were deficits of attention, working memory, visuo-perceptual and visuo-graphic abilities; a learning disorder in arithmetic was present; she had emotional lability and low self-esteem.

Case # 5: Female, referred to us at the age of 9 years for drug resistant seizures and language disorder. There was a family history of only one febrile seizure in the sister. Poor foetal growth was noted during pregnancy; birth weight was 2.6 Kg. She had a mild psychomotor development delay and primary nocturnal enuresis. At the age of 2 years frequent partial seizures were noted with psychomotor arrest, eyelid myoclonia and automatisms, lasting some minutes. EEG showed multifocal and diffuse paroxysmal abnormalities. VPA and CBZ were not tolerated; CLB, PRM and CZP were ineffective in controlling seizures. At the age of 5 years 8 months a dramatic language regression occurred, evolving over the course of 20 days into an expressive-receptive aphasia. Aggressive, oppositional behaviour and disturbed wake-sleep cycle were noted. EEG showed paroxysmal abnormalities on right temporal region, subcontinuous during sleep, sometimes diffuse. A treatment with ACTH was administered and a gradual improvement of language and behaviour occurred. She had another 4 episodes of aphasia lasting 30-60 days while taking CBZ + PRM + CZP. During the fifth episode of aphasia, ACTH treatment was given again. Brain MRI showed periventricular leukomalacia.

When she came to our observation at the age of 9 years seizures persisted (CBZ + PRM + CZP). Neurological examination was normal, aside from language and behaviour disorder. EEG showed multifocal spike-waves, prevailing over posterior regions, subcontinuous in N-REM sleep and persisting during REM sleep; diffuse and generalized spike-waves were also recorded. A complete standardized neuropsychological evaluation was impossible due to the girl's oppositional behaviour. On the basis of Draw-A-Man Test, mental age was 6 years. Receptive language was more impaired than expressive language. ESM was added and PRM stopped. Seizure frequency decreased, but the sixth (and last) episode of aphasia occurred at the age of 9 years 4 months. VGB was added: language and behaviour improved as did EEG recording. At the age of 10 years 2 months a WISC-R was for the first time available and the results were: FIQ = 59; VIQ = 55 and PIQ = 70; a severe impairment of learning abilities was present. In addition, the skill to compare rhythms in memory was poor. In the following years seizures gradually stopped and antiepileptic therapy was suspended.

At the last observation, when she was 17 years 10 months, EEG showed only rare focal and diffuse paroxysmal abnormalities. Language was still dysphasic. The patient was no longer on antiepileptic drugs. Neuropsychological evaluation showed: FIQ = 71; VIQ = 68 and PIQ = 83. The skill to compare rhythms in memory was normal. Deficits in reading, writing and arithmetic persisted.

Discussion

We described 5 patients two of whom have typical CSWS and LKS (cases 4 and 5) [2, 3, 8]. The other 3 cases differ because they never presented EEG criteria with diffuse and frequent paroxysmal abnormalities (more than 85% during N-REM sleep) as in CSWS or localized in temporal regions associated with acquired aphasia as in LKS [8]. Our cases had different seizure types before CSWS, only case 3 probably had no seizures or they had never been recorded. However, with or without seizures, all cases presented CSWS resistant to several antiepileptic drugs. Only ACTH gave an EEG improvement in case 4, transitory in

case 5 in whom CSWS was finally stopped by VGB. Unfortunately, there are no controlled studies on antiepileptic treatments in patients with CSWS.

Focal EEG paroxysmal abnormalities had different localizations over the centro-parietal, occipital, frontal or temporal regions. In our cases, the localization of prevailing EEG paroxysmal abnormalities showed a good relation with neuropsychological findings irrespective of IQ value [12]. For example, case 2 with frontal EEG abnormalities had perseverations, poor flexibility of thought, deficit of executive functions, learning disorders prevailing in mathematical logic. Instead, case 3 with posterior EEG abnormalities had clearly impaired visuo-perceptual and visuo-graphic abilities. Cases 4 and 5 with CSWS and LKS respectively [8] had typical EEG paroxysmal abnormalities in terms of localization and diffusion, frequently arising in N-REM sleep (more than 85%), to determine a cognitive deterioration with a major behavioural problem (case 4) or, in the case of LKS (case 5), recurrent aphasia. It is well known that localization and diffusion of EEG paroxysmal abnormalities may influence neuropsychological evolution [13, 14].

Except for the first case that had a normal FIQ but a learning disorder in reading, writing and arithmetic, all the other patients presented IQ regression, with a significant gap between VIQ and PIQ to the detriment of PIQ in cases 2, 3 and 4 and of VIQ in case 5 with LKS. IQ improved in cases 2 and 4, even if a gap remained to the detriment of PIQ in case 2. Cases 3 and 5 improved after CSWS disappearance even if both presented a borderline FIQ at the last observation. The impression was that with the increase in EEG paroxysmal abnormalities the neuropsychological abilities decreased sometimes very rapidly. In our cases, CSWS appeared at different ages and lasted for different periods from less than 1 up to 12 years. Behavioural problems were present in all cases except for the first, improving after CSWS fragmentation.

Epileptic seizures were present in all patients except case 3 and they represented the first symptom as reported elsewhere [15], but they generally disappear before CSWS fragmentation [16]. Sometimes seizure resistance to antiepileptic drugs correspond to subcontinuous/continuous EEG paroxysmal abnormalities as in our case 5. Seizure absence may delay the diagnosis of CSWS as occurred in our case 3 [17].

Cerebral lesions were present in cases 2 and 4 and did not seem responsible for CSWS evolution as reported in the literature [14].

Recently, Scheltens-de Boer reviewed literature reports on the clinical features, EEG, treatment and evolution of CSWS. Findings were inconclusive data, because of the lack of uniform clinical and EEG criteria [18]. We conclude that it is necessary to be aware how CSWS can develop and that early diagnosis is very important to start treatment. Hence, prolonged EEG recordings during sleep are recommended at onset and during the evolution to monitor cognitive and behavioural functions at onset, during the status and after CSWS disappearance when the patients become adult. This information will allow a prompt change in ineffective pharmacological treatment. However, to perform a brain MRI is recommended. Further studies with a large sample and homogeneous EEG criteria are required to better characterize the enigma of CSWS.

Acknowledgements: we thank Ms Massimo Armaroli for technical assistance and Ms Anne Collins for English revision.

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