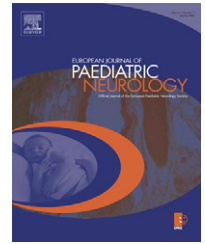




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Case study

Epileptic encephalopathy with bilateral continuous spike-waves during slow sleep in a child with vacuolating megalencephalic leukoencephalopathy[☆]

Bosanka Jovic-Jakubi^{a,*}, Žarko Martinović^b, Duško Kozić^c

^aClinic of Mental Health and Child Neuropsychiatry, Medical School, University of Niš, Serbia

^bInstitute of Mental Health, Department of Epilepsy and Clinical Neurophysiology, Belgrade, Serbia

^cInstitute of Oncology—Diagnostic Imaging Center, Sremska Kamenica, Novi Sad, Serbia

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ABSTRACT

This case report describes the clinical evolution of a symptomatic epileptic encephalopathy with bilateral continuous spike-waves during slow wave sleep (BCSWS) in a 3-year-old girl. Her epilepsy with focal motor seizures during sleep was later complicated by myoclonic, atonic and clonic seizures culminating in BCSWS. The clinical picture, clinical course and magnetic resonance imaging findings were characteristic of primary white matter disease, probably, vacuolated megalencephalic leukoencephalopathy with subcortical cysts (MLC). To the best of our knowledge, this is the first reported case of BCSWS in a patient with leukodystrophies or MLC. This case report indicates that epileptic encephalopathy with BCSWS may be a cause of neurological or neuropsychological deterioration in MLC.

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1. Case report

We report a 4 years-old girl born at term, from the normal pregnancy and uneventful delivery. Her psychomotor development was normal until 8th month, when the parents noted that the baby had truncal instability. At the age of 12 months, the neurological examination revealed a left-sided hemiparesis and bilateral ataxia.

At the age of 2 1/2 years, her first nocturnal seizures manifested as eye blinking and left-hand twitchings lasting several minutes. Valproate therapy in total dose of 300 mg/day was started. However, seizure frequency further increased from 1 to 2 per months reaching to 10–15 seizures, in

November 2003. At the time, she was hospitalized at the Clinic for Developmental Neuropsychiatry where seizures of severe intensity with head nodding and occasional falls to the ground were frequently observed. Neurological examination disclosed a spastic dihemiparesis, predominantly left-sided, adyadochokinesis, truncal ataxia, and signs of pseudobulbar paralysis, hypersalivation. The speech was nasal, non-articulated and incomprehensible. The gait was hardly possible even with support. The head circumference was increased more than 2 SD for the age.

Sodium valproate (900 mg/day giving a blood level of 103.4 μg/ml) was ineffective. Clonazepam in maintenance dose of 2 mg/day resulted in significant clinical improvement.

[☆]The research was carried out at Clinical Centre Niš, Clinic of Mental Health and Child Neuropsychiatry, 18000 Niš.

*Corresponding author. Tel./fax: +381 18 533 032.

E-mail address: bosajj@yahoo.com (B. Jovic-Jakubi).

EEG findings: EEG at onset of epilepsy recorded irregular background activity and diffuse epileptiform abnormalities with a tendency toward generalization. Next month, EEG during valproate treatment showed a delta dysfunction of the right fronto-central region as well as secondarily generalized epileptiform paroxysms. In this period of neuropsychological worsening, EEG during sleep disclosed the electrical status epilepticus (ESES), since bilateral paroxysms of irregular and

slow spike-waves (BSCWS) were continuous (Fig. 2a) and occupied 96% of sleep recording. Sleep spindles and K-complexes were not present. After the awakening, the ESES ceased and only sporadic low amplitude spikes or spike-waves were recorded in the right fronto-temporal region. The uncovering of focal discharges proved that the mechanism generating BSCWS was a secondary bilateral synchrony.¹ The same was proven in EEG recorded in October 2003 when a right hemispheric lateralization of paroxysms after the progressive suppression of BSCWS with rectal application of diazepam (5 mg) (Fig. 2b). EEG recordings during 2004 showed the cessation of BSCWS and slow background activity was masked by diffuse benzodiazepine fast activity.

Neuropsychological exploration before seizure onset (in March 2003) showed a developmental quotient on Brinet-Lezine scale was 65. During the persistence of the BSCWS in EEG, Neuropsychological re-test disclosed a severe mental deterioration for 23 points to 42. Considerable recovery occurred in next several months with high dose benzodiazepines treatment. More than 85% seizures reduction was achieved and no further cognitive decline has been noted. One year later psychological retesting showed no remarkable cognitive deterioration (total IQ score 41).

Cranial magnetic resonance imaging (MRI) (performed on 03.03.2003) showed multiple, irregular, partly coalescent lesions of periventricular white matter on relaxation times T1W (Fig. 1a), which on relaxation times T2W they appeared as areas of hypersignal. Multiple cystic enlargements in subcortical white matter were present, maximal in temporal lobe (Fig. 1b). Brain computerized tomography showed signs of brain atrophy without any calcification.

Neuroophthalmological examination, laboratory analyses, lactate and piruvate in the blood, CSF analysis and nerve conductivity study showed normal findings. Virusological analyses were negative for cytomegalovirus (both blood IgG and IgM), Epstein-Barr virus (IgG and IgM), and herpes simplex virus: IgG-17, IgM negative. Screening for inborn errors of metabolism was negative. The molecular genetical analysis is planned.

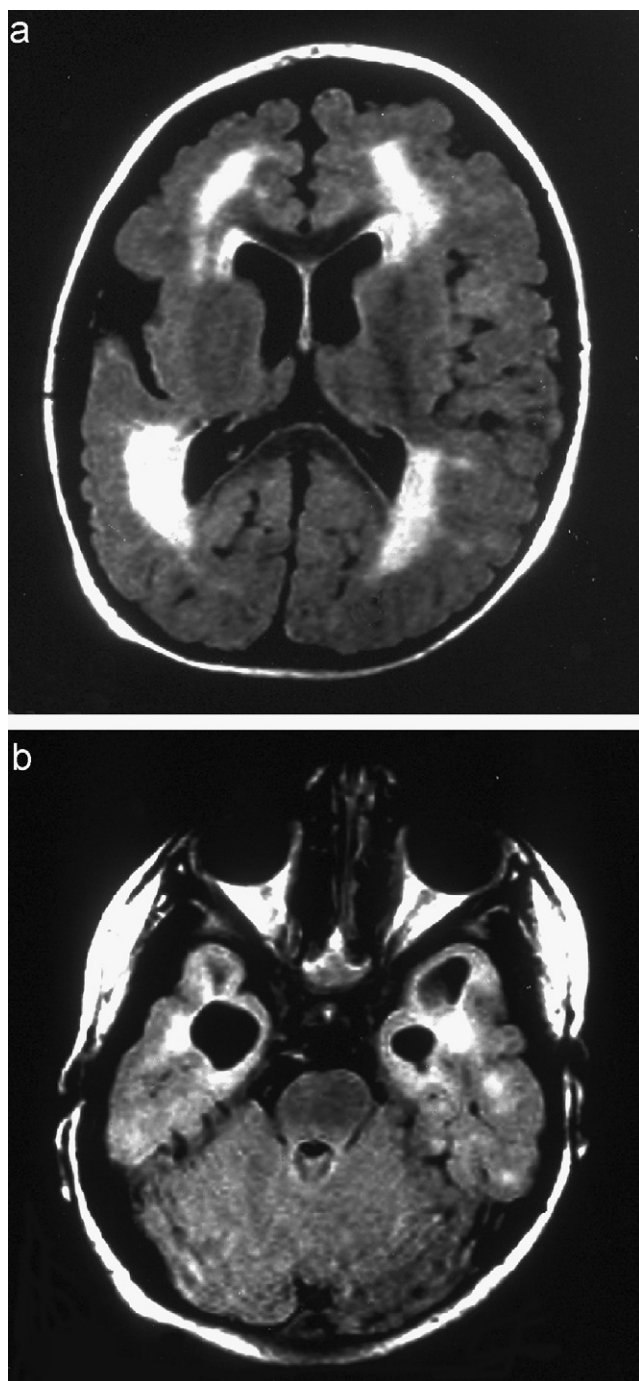


Fig. 1 – Diffuse dysmyelination of supratentorial white matter (a) and bilateral temporal cysts (b) on FLAIR axial image, in 4-year-old child with vacuolating megalencephalic leukoencephalopathy.

2. Discussion

Clinical and MRI findings in our patient are highly suggestive of a white matter disorder, most probably vacuolated megalencephalic leukoencephalopathy with subcortical cysts (MLC),¹ a rare disease characterized by acquired macrocephaly during the first year of life, developmental delay of varying degrees, slowly progressive ataxia and spasticity, and initially preserved intellectual function. MLC was recently localized on chromosome 22q.³ Characteristic diffuse abnormalities of the cerebral hemispheric white matter on MRI are particularly evident on fluid-attenuated inversion recovery images.² Other etiologies of leukoencephalopathy were excluded in our patient. Cytomegalovirus was excluded with virusological analysis and the absence of calcification on brain computerized tomography.

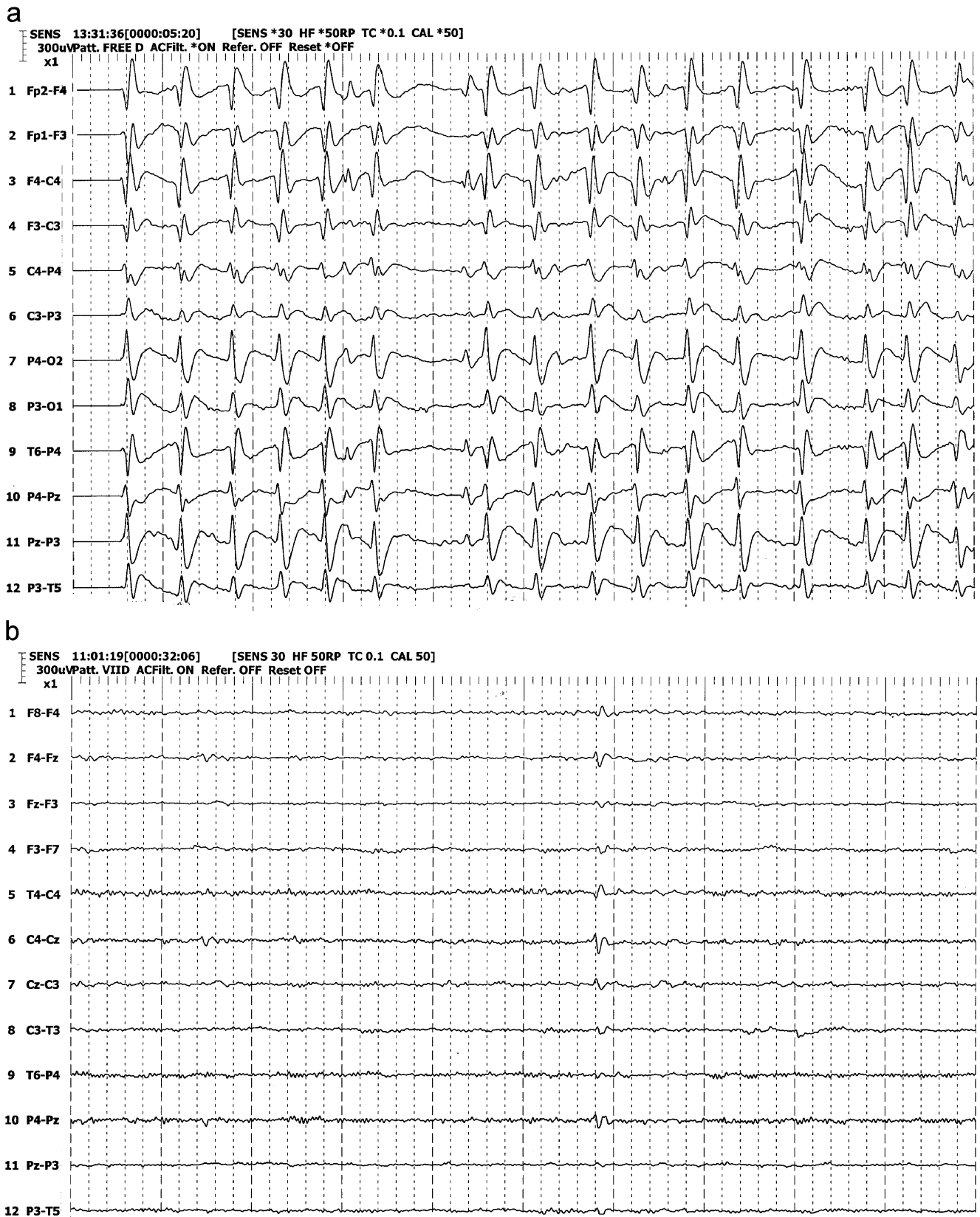


Fig. 2 – (a) EEG recording during sleep, on May 20, 2004. Bilateral, continuous 2 Hz spike-waves of high amplitude. Sleep spindles or K-complexes have not been recorded. Calibration mark in Figs. 2a and 2b: horizontal 1 s, vertical 50 μ V, and **(b)** EEG after rectal diazepam and waking up the patient. Complete suppression of bilateral spike-waves leaving diazepam induced fast, low amplitude background activity with only some sharpish elements.

Other leukodystrophies have different clinical picture with exceptional occurrence of seizures and an unremarkable EEG or various slow waves, non-epileptiform abnormalities.⁴ In contrast, MLC is characterized by a common and early occurrence of epileptiform EEG abnormalities and epilepsy usually manifesting as partial, atonic and myoclonic seizures, mostly with a low frequency (1–10 per year) (5). On the contrary, our patient had a much higher seizure frequency and presented with the BSCWS, an epileptic encephalopathy presenting with various focal or generalized seizure types. Its only constant diagnostic criterion is BCSWS discharges occupying at least 85% of slow wave sleep (in our patient it amounted to 96% of total sleep time). The time period with BSCWS in our patient was associated with severe clinical, and in particular neuropsychological deterioration, which is also characteristic for this rare epileptic encephalopathy.¹ Since the patients with MLC usually have a mild clinical course with gradual worsening of neurological disability,² the BSCWS in present patient may be regarded as the cause of considerable deterioration of neuropsychological functions and/or motor functions, as is often reported in this type of epileptic encephalopathy.¹ The involvement of both white and gray matter in our patient with MLC may explain the appearance of epileptic seizures and severe epileptiform EEG abnormalities including BSCWS.

Several antiepileptic drugs (carbamazepine, tiagabine, vigabatrin) may aggravate the epilepsy in MLC while benzodiazepines usually have a favorable effect. Valproate has a low potential for pharmacodynamic aggravation of seizure except in the presence of encephalopathy as in our patient.⁶ Abolition of BSCWS with clonazepam in our patient is in accordance with long-lasting effect of chronic oral treatment with benzodiazepines in ESES.⁵

3. Conclusion

Pre-existing encephalopathy in present patient with BSCW satisfied clinical and MRI criteria for diagnosis of MLC defined by clinical picture and the typical findings on MRI. Her symptomatic epilepsy was complicated by BCSWS, an epileptic encephalopathy that caused significant clinical and neuropsychological deterioration and improved with clonazepam. This is the first reported case of the BCSWS in a patient with MLC or leukodystrophy.

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