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Refractory nonconvulsive status epilepticus in Creutzfeldt-Jakob disease

Maria Aiguabella[1], Mercè Falip[1], Misericordia Veciana[1], Jordi Bruna[1], Antoni Palasí[1], Luisa Corral[2], Jose-Ignacio Herrero[2], Susana Boluda[3], Jaume Mora[4], Alex Iranzo[5], Carme Serrano[6]

[1] Neurology Department, Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona
[2] Intensive Care Unit, Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona
[3] Anatomical Pathology Department, Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona
[4] Nuclear Medicine Department, Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona
[5] Neurology Department, Hospital Clinic, Barcelona
[6] Neurology Department, Hospital de Sant Joan de Deu de Martorell, Martorell, Barcelona, Spain

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ABSTRACT – Creutzfeldt-Jakob disease (CJD) is a rare human transmissible spongiform subacute encephalopathy. The most common clinical manifestations of CJD include rapidly progressive dementia, behavioural changes, cerebellar dysfunction and myoclonus. Other seizure types are rare and nonconvulsive status epilepticus (SE) is exceptional. We report a case of a 44-year-old man who presented a psychotic episode followed by akinetic mutism and refractory nonconvulsive SE. The final diagnosis was CJD. Continuous video-EEG monitoring revealed the ictal pattern of nonconvulsive SE to be periodic sharp wave complexes characteristic of CJD. *[Published with video sequences]*

Key words: electroencephalography, status epilepticus, nonconvulsive, Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD) is a rare transmissible spongiform encephalopathy, caused by prions. The initial symptoms can be confusion, short-term memory loss, behavioural changes or neurological focal deficits such as ataxia. Subsequently, the disease evolves with rapidly progressive dementia and cortical myoclonus and finally akinetic mutism (Johnson and Gibbs, 1998). Seizures and status epilepticus (SE) are not reported to be frequent in patients with CJD (Wieser *et al.*, 2006; Fernández-Torre *et al.*, 2004).

EEG monitoring is a fundamental approach in the diagnosis of CJD, and the typical hallmark is the presence of periodic sharp wave complexes (PSWC) consisting of a generalised or lateralized complex with a duration of 100-600 ms and an intercomplex interval of 500-2000 ms. The electrical pattern is often confusing, making it very difficult to differentiate CJD from nonconvulsive SE (Fernández-Torre *et al.*, 2003, Rees *et al.*, 1999).

We report a patient with CJD who developed nonconvulsive SE. Continuous video-EEG monitoring was performed and revealed an EEG ictal pattern of PSWC.

Correspondence:
M. Aiguabella Macau
Hospital Universitari de Bellvitge,
Servei de Neurologia,
Feixa Llarga s/n,
Hospitalet de Llobregat,
08907 Barcelona,
Spain
<37785mam@comb.cat>

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Case study

The patient was a right-handed 44-year-old man, without personal pathological antecedents but with a family history (first and second degree) of schizophrenia and epilepsy.

Four months before being referred to our centre he suffered vertigo, gait abnormalities, bradykinesia, and tremor of the upper extremities. Two months later he presented a psychotic episode with paranoid delusions and was admitted to a monographic psychiatric hospital where brain CT scan and lumbar puncture were performed without abnormal findings. Subsequently, neuroleptic treatment was started. During the following month his clinical condition worsened, developing mutism, inability to walk, erratic involuntary movements in the upper extremities, somnolence leading to stupor, and was referred to our hospital.

Upon admission (day 1) the patient was stuporous only responding to pain stimuli and presented frequent spontaneous myocloni in the upper limbs. The continuous EEG showed almost continuous generalised periodic epileptiform discharges (GPEDs) with a frequency of 1.5 Hz *(figure 1A)*, and brief periods of generalised slow activity without interictal epileptiform discharges. There was no relationship between EEG and myoclonus. The initial diagnosis was nonconvulsive SE *versus* encephalopathy with triphasic waves. Antiepileptic drug treatment (clonazepam and phenytoin) was started. Initially, the EEG pattern changed (GPEDs disappeared) but no clinical improvement was observed. The patient was continuously EEG monitored, and four or six hours later brief complex partial seizures were observed, suggesting a cyclic form of complex partial SE. Clinically, seizures included right oculocephalic version and clonic movements of the face and right arm, and sometimes oromandibular automatisms. The ictal EEG pattern consisted of flattening of the background activity [electrodecremental pattern (EDP)] followed by GPEDs (1 Hz) terminating in generalised theta activity without GPEDs. The mean duration of the ictal episodes was 30-60 seconds *(figure 1B; see video sequence)*. Intravenous levetiracetam was added without clinical improvement and the patient was referred to the intensive care unit in order to start pharmacological anaesthesia. Under anaesthetic treatment (midazolam) a burst-suppression pattern was obtained (1 burst/10 seconds).

Brain MRI showed areas of hyperintensity (in FLAIR and diffusion sequences) in both caudate and lenticular nucleus and different cortical areas *(figure 2A)*. Both tumoural (carcinoembryonic antigen, alpha fetoprotein, prostatic specific antigen and human chorionic gonadotrophin antigen) and autoimmunity markers (anti-nuclear, anti-DNA, anti-thyroid, anti-GAD, anti-Hu, anti-Ta and anti-Ma2 antibodies) were negative. Toracoabdominal CT scan was normal, a lumbar puncture was repeated (0 cells, normal glucose and proteins) and a 14.3.3 protein test was requested.

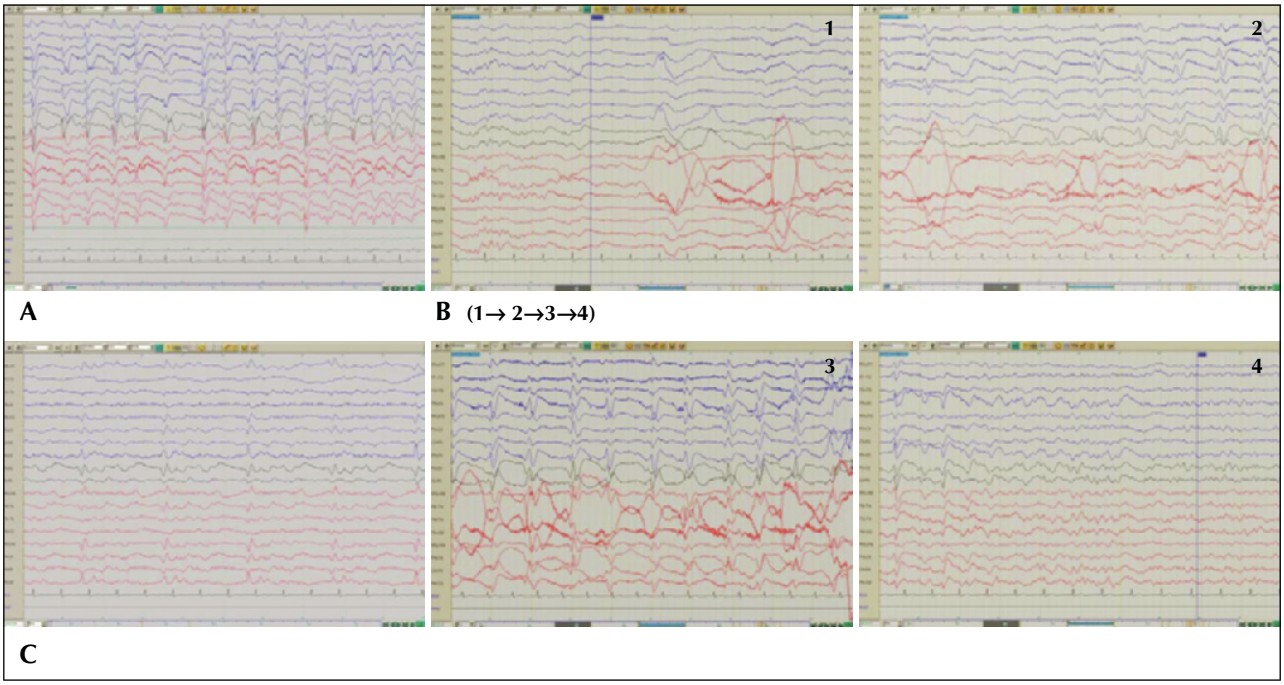

Figure 1. A) EEG day 1: generalised PSWC at high frequency.
B) Electroclinical seizure *(see video sequence)*: electrodecremental pattern followed by generalised PSWC.
C) EEG day 16: generalised PSWC at low frequency.

During pharmacological anaesthesia no more partial seizures were observed and when the anaesthesia was lowered, GPEDs appeared with a frequency of 0.5 Hz, although the patient never regained consciousness. During the following days, the frequency of the GPEDs decreased *(figure 1C)* and the patient presented erratic movements of both upper and lower extremities which did not correspond clinically to myoclonus or even partial seizures. Moreover, no correlation with the EEG pattern was observed. At day 18 an HMPAO-SPECT was performed *(figure 2B)* when the patient presented movements of both extremities. A severe hypoperfusion of cerebral and cerebellar cortex and basal ganglia was observed.

At day 20, a diagnosis of CJD was highly suspected. All the supportive treatment was terminated and the patient died on day 25. The protein 14.3.3 test result, which arrived several days later, was positive. The pathological study confirmed the diagnosis of sporadic CJD with an atypical PrP pattern.

Discussion

The typical EEG pattern of CJD consists of PSWC, which may be observed in all variants with the exception of the new variant, in which this pattern does not appear. In some cases, the PSWC can appear lateralized to one hemisphere, similar in appearance to periodic lateralized epileptiform discharges (PLEDs). This lateralized pattern could be related to an earlier stage of the disease (Wieser *et al.*, 2006). In our case, the pattern observed in the first EEG was characterized by PSWC at 1.5 Hz, but later the PSWC acquired a discontinuous pattern in relation to seizures.

Epileptic seizures are infrequent in CJD, being observed in only 15% of cases (Johnson and Gibbs, 1998) and usually appear in the final stages of the disease. SE in CJD patients is extremely rare and only a few cases of SE in CJD have been reported previously in the literature, some of which are convulsive (Parry *et al.*, 2001; Neufeld *et al.*, 2003) and others nonconvulsive (Rees *et al.*, 1999; Cohen *et al.*, 2004; Fernández-Torre *et al.*, 2004; Rossetti and Dunand, 2007). Our patient was referred to our hospital due to prolonged stupor where he presented continuous episodes of stereotyped right oculocephalic version and clonic movements of the right hemibody, without regaining consciousness between episodes, highly suggestive of partial SE.

The differential diagnosis between CJD and nonconvulsive SE may be complex (Fernández-Torre *et al.*, 2003; Rees *et al.*, 1999) because it is dependant on EEG features. In these patients, a continuous video-EEG monitoring is useful in order to look for electroclinical seizures and changes in the periodic pattern. Moreover, the administration of benzodiazepines usually improves the ictal pattern

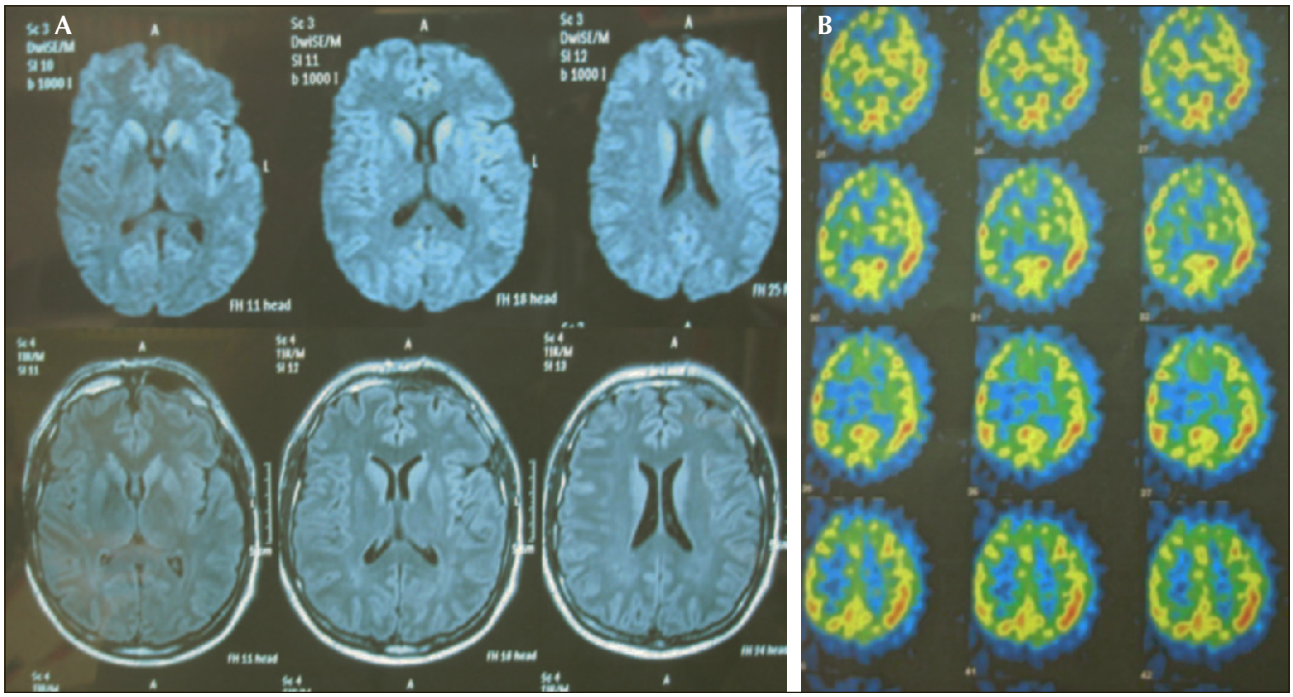

Figure 2. A) MRI (diffusion and FLAIR, axial section): hyperintensity areas in both caudate, lenticular nucleus and cortical areas.
B) SPECT (axial section) day 18: severe cortical and cerebellar hypoperfusion.

of nonconvulsive SE but does not modify the encephalopathic pattern. However, in some cases the periodic pattern of CJD and other encephalopathies can disappear after administration of a benzodiazepine, but without any associated clinical improvement (Elliott *et al.*, 1974). Unfortunately, in some patients the EEG pattern is not sufficient to differentiate between the two entities (nonconvulsive SE *vs* encephalopathy). In our patient benzodiazepines and phenytoin changed the basal EEG. The continuous PSWC were substituted by a discontinuous pattern in which PSWC were observed at the same time as clinical seizures, suggesting that the antiepileptic drugs probably caused the transition from a continuous to a cyclic form of complex partial SE.

The significant EEG patterns recorded during SE in CJD patients include: continuous epileptiform activity (Rees *et al.*, 1999; Fernández-Torre *et al.*, 2004), critical patterns (Cohen *et al.*, 2004), PLEDs (Neufeld *et al.*, 2003) and stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) (Rossetti and Dunand, 2007). In more advanced phases of the disease the seizures disappear and the typical PSWC appear along with clinical myoclonus. PSWC observed in cases of CJD are usually generalised but they can be focal or lateralized, correlating with focal FLAIR MRI cortical abnormalities. The critical EEG pattern of our patient showed generalised EDP followed by discontinuous episodes of PSWC with an abrupt end; PSWC were generalised although clinical signs were focal indicating a seizure origin in the left hemisphere.

The mechanism by which neuron populations burst in synchrony to produce PSWC are not known, but cortico-subcortical and thalamo-cortical networks could be involved. In our patient PSWC were observed until the end of the disease, when SPECT showed severe hypoperfusion of both cortical and subcortical regions. We also noticed a progressive decrease of PSWC frequency during the evolution of the disease, possibly reflecting the progressive death of both cortical and subcortical neurons. This synchrony could be also modified at the beginning of the disease by seizures, which in our patient always began with a generalised EDP, followed by the PSWC.

In summary we conclude that CJD may be associated with refractory SE in adult patients. However, differential diagnosis between CJD and nonconvulsive SE is difficult because the respective EEG patterns may be similar. In our case, the significant ictal pattern of nonconvulsive SE in a patient with CJD consisted of PSWC. □

Legend for video sequence

The seizure starts with an electrodecremental pattern for seven seconds, followed by periodic sharp waves complexes at 1 Hz, initially at low amplitude, but growing in amplitude; finally the PSWC ends abruptly. Clinically, the seizure starts with a tonic flexion of the right arm followed by clonic movements of the same arm together with oromandibular automatisms, which end at the same time as the PSWC.

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

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