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Epilepsia partialis continua as the presenting symptom in probable sporadic Creutzfeldt-Jakob disease

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ABSTRACT – Creutzfeldt-Jakob disease (CJD) is a rare form of rapidly progressive neurodegenerative disorder. Literature survey reveals only four reported cases of CJD with epilepsia partialis continua. Here, we present a review and a case study, with video-EEG sequences and characteristic MRI findings, of a fifth patient who presented with epilepsia partialis continua in the very early stage of the disease and followed a fatal course which was faster than expected. *[Published with video sequences]*

Key words: epilepsia partialis continua, EPC, Creutzfeldt-Jakob disease, CJD, PLEDs

Creutzfeldt-Jakob disease (CJD) is a rare form of rapidly progressive neurodegenerative disorder. Sporadic CJD (sCJD) is the most common form seen in humans. The clinical presentation of CJD is heterogeneous but most patients display similar clinical features including dementia, myoclonus, and cerebellar and pyramidal dysfunctions (Brown *et al*., 1986). The diagnosis is based on clinical features, as well as EEG and MRI findings, with the exclusion of other causes of dementia (World Health Organisation, 1998; Poser *et al*., 1999; Zerr *et al*., 2009).

Focal motor or generalised seizures have been reported in 15-21% of patients with CJD during the later stages of the disease (Johnson and Gibbs, 1998; Cokgor *et al*., 1999) and are known to be poorly responsive to antiepileptic treatment (Burger *et al*., 1972). However, seizures, as the presenting symptom of CJD, are uncommon and occur in only about 3% of cases (Aronyk *et al*., 1984). Rarely, EEG and clinical features may suggest partial status epilepticus including epilepsia partialis continua (EPC) (Lee *et al*., 2000; Parry *et al*., 2001; Donmez *et al*., 2005; Lowden *et al*., 2008). Here, we report another patient with CJD who presented with epilepsia partialis continua and periodic lateralized epileptiform discharges (PLEDs) on EEG in the early course of the disease.

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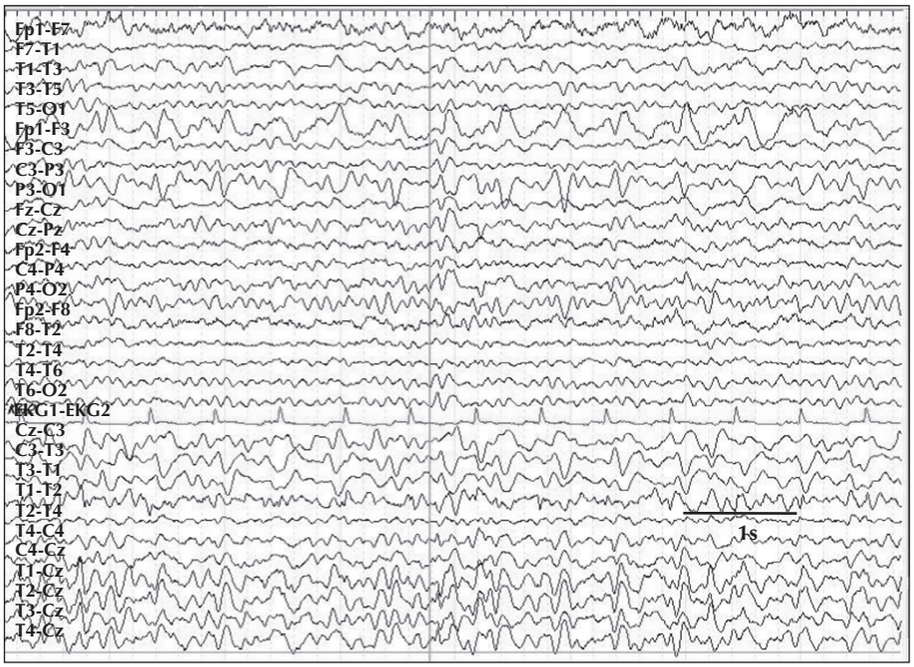

Figure 1. EEG recording revealed background slowing on the left hemisphere and the appearance of periodic sharp wave discharges on the left fronto-centro-temporal region with a frequency of 1-2 Hz (LF: 0.3Hz, HF: 70 Hz, sensitivity: 10 microV/mm).

Case study

A 70-year-old, right-handed farmer was admitted to the emergency room with difficulty in speech and inability to walk. His complaints started about three weeks previously and had progressed particularly in the last 10 days. The first disturbance he noticed was numbness in his right hand. Within a week, rigidity and sometimes jerks appeared in his right hand. Stuttering and dysarthria also developed. The jerks became more frequent and extensive, eventually involving his right lower limb and interfering with his gait. Within three weeks, he had become totally unable to walk. His family denied any change in his level of consciousness but noticed some deficits in remote memory. No other type of seizure was present. There was no history of an infection, fever, toxic exposure regarding herbicides or pesticides, corneal transplant or cadaveric growth hormone use. He was diabetic and hypertensive. His family history was unremarkable.

Neurological examination revealed that he was disorientated with regards to time and place. He was alert, but failed to pay attention and cooperate thoroughly. He had severe dysarthria, truncal ataxia and dysmetria in both upper extremities. Continuous jerks, most prominent in his right hand, extended proximally, occurring once every 2-3 seconds and were also apparent in the lower extremity, provoked by standing. There was not any pyramidal sign. On physical examination, neither skin or mucosal lesion, nor any other sign of intoxication were detected.

Blood chemistry and complete blood count analysis, vitamin B12 level and thyroid hormone levels were normal. On EEG, there was background slowing on the left hemisphere and PLEDs on the fronto-centro-temporal region *(figure 1)*. He also had rhythmic myoclonic activity in the right hand during EEG recording *(see video sequence)*. A brain MRI demonstrated restricted diffusion in bilateral caudate nuclei, more apparent on the left side; on the left frontal, temporal, and parietal cortical gyri involving the primary motor area and insular cortex *(figure 2)*.

With these clinical and EEG findings supported by diffusion MRI, the patient was diagnosed with probable sporadic Creutzfeldt-Jakob disease (World Health Organisation, 1998). Serological investigations excluded any alternative diagnosis for progressive dementia. No further toxicological investigations were performed since physical and neurological examinations did not suggest any intoxication. A brain biopsy, lumbar puncture or hospitalisation was refused by the patient himself as well as by the family. Thus, we were unable to perform tests for paraneoplasia and infections based on cerebrospinal fluid. However, this was not primarily considered in differential diagnosis since clinical and radiological findings were inconsistent. Levetiracetam at a dose of 1,000 mg/day was initiated for seizures. We learned, by phone interview, that

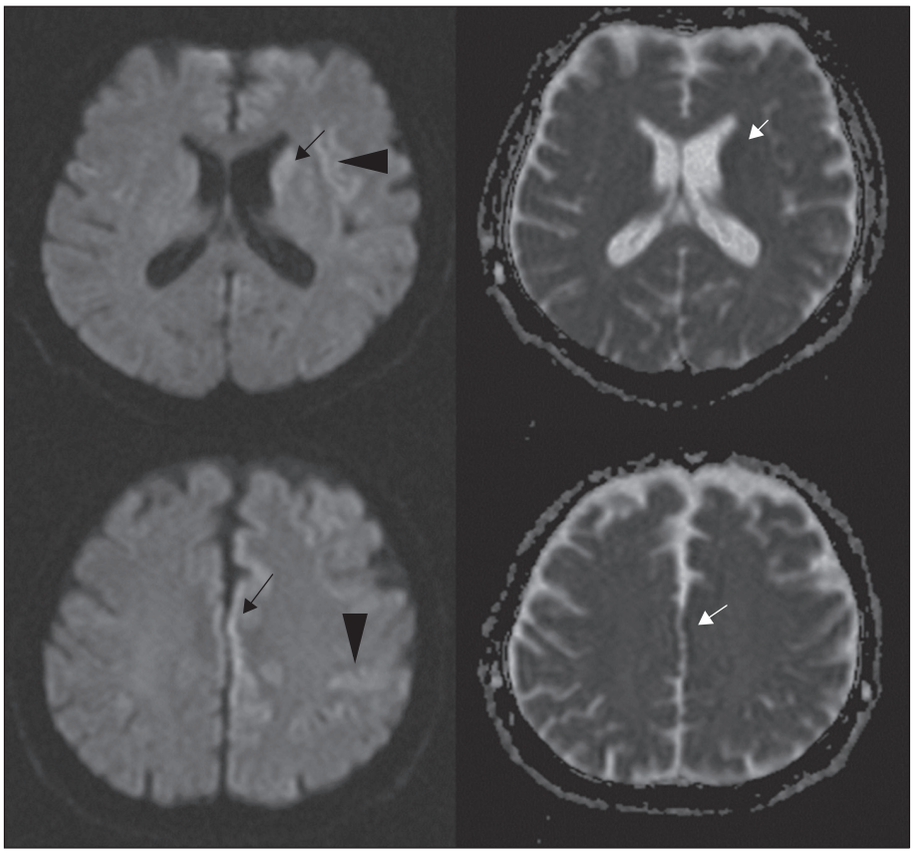

Figure 2. Brain MRI demonstrates restricted diffusion in bilateral caudate nuclei, predominantly on the left side; on the left frontal, temporal, and parietal cortical gyri, involving the primary motor area and insular cortex, as evidenced by diffusion-weighted imaging hyperintensity and ADC hypointensity. Arrows indicate caudate nucleus and cortical gyri; arrow-heads indicate insular cortex and primary motor area.

there was a beneficial effect over two weeks, however, the patient died at home two months following the onset of the first symptoms.

Discussion

In this report we have described a very rare presentation of probable sCJD with EPC. The clinical evolution of CJD has been previously subdivided into three stages (Wieser *et al*., 2006). In stage one (mean duration of nine weeks; range 1-52), mild neurological or psychiatric symptoms such as dizziness, vertigo, headache, depression, or anxiety are seen. Myoclonus can very rarely (in 6% cases) be seen. In stage two (mean duration of ten weeks; range 1-104), higher cortical functions are affected and visual disturbances and gait problems occur. Myoclonus is an uncommon finding in this stage. In stage three (mean duration of 14 weeks; range 1-116), severe myoclonus and dementia are typical findings.

According to current WHO criteria, progressive dementia, myoclonus and cerebellar signs, along with typical EEG and a clinical duration to death of less than two years, suggest a *probable* diagnosis of sporadic CJD (World Health Organisation, 1998). Due to a lack of neuropathological examination, our diagnosis was probable sCJD, in parallel with these criteria. Although the lack of cerebrospinal fluid studies precludes a definite diagnosis, any paraneoplastic or inflammatory condition is quite unlikely given the patient's clinical and laboratory findings. Moreover, MRI of the patient was not enhanced with gadolinium, reducing the likelihood of an inflammatory process.

EPC is defined as regular or irregular clonic muscular twitches affecting a limited part of the body, occurring for a minimum of one hour and recurring at intervals of no more than 10 seconds (Thomas *et al*., 1977). In mild cases of EPC there may be focal inter-ictal abnormalities on EEG, without any correlation between spikes or sharp waves and myoclonic jerks. In cases with an underlying degenerative process, the background

Table 1. Summary of findings of the five reported sCJD patients who presented with EPC in the early stage of the disease.

	Age/ Gender	Other findings	EEG	Time-to-EPC	MRI	Biopsy	Prognosis
Lee, 2000	42/M	Forgetfulness, mild hemiparesia, dementia, incoordination, ataxia, spasticity, aphasia	L sided PLEDs	Onset	Hyperintensity on left occipital cortex	Presence of protease resistant prion protein (PrP*res*)	Rapid deterioration in dementia
Parry, 2001	67/F	Dystonic posture, myoclonus, GTCS, dysphasia, dementia	Bilaterally synchronous PSW	Onset (first month)	None	Multifocal spongiform degeneration of the cortex with focal neuronal loss, astrocytosis	Coma, exitus in 3,5 months
Donmez, 2005	47/F	Chorea, dystonic posture, myoclonus, anxiety, ataxia, mild hemiparesia, cognitive decline	Diffuse slowing, biphasic and triphasic sharp waves	4 weeks	Hyperintensity in basal ganglia on DWI (after 3 weeks)	Not performed	Coma, exitus in 5 months
Lowden, 2008	49/F	Right upper extremity weakness, gait disturbance	R sided PLEDs	3 weeks	Hyperintensity in bilateral caudate, putamen, pulvinars and occipital lobes	E200K-129M mutation in PrP gene	Exitus in 2 months 3 weeks
Taskiran, 2010	70/M	Sensorial deficits, dysarthria, ataxia, incoordination, memorial deficits	PLEDs on L fronto-centro-temporal	Onset (1 week)	Restricted diffusion in bilateral caudate (more on L), and L hemispheric cortices including primary motor area and insula	Not performed	Exitus in 2 months

sCJD: sporadic Creutzfeldt-Jakob disease; DWI: diffusion weighted imaging; EPC: epilepsia partialis continua; GTCS: generalised tonic clonic seizure; PSW: periodic sharp waves; L: left; R: right.

activity is slowed and more extensive epileptiform discharges may be seen (Pandian *et al*., 2002). In some patients with EPC, EEG reveals PLEDs. Among adults, infections and cerebrovascular disease constitute the commonest aetiologies for EPC (Gurer *et al*., 2001; Pandian *et al*., 2002).

In the literature, EPC is reported as a presenting feature of CJD, with or without other findings, based on four case reports *(table 1)* (Lee *et al*., 2000; Parry *et al*., 2001; Donmez *et al*., 2005; Lowden *et al*., 2008). Our case is the fifth patient with CJD presenting with EPC. On the basis of the neuroimaging evidence we speculate that his initial sensory symptom resulted from the parietal cortical lesion whereas disease progression to the primary motor area resulted in *focal motor status*. The irritative, rather than destructive, nature of the damage may be the reason for the absence of paresis and continuous jerks at the early stage of the disease. Basal ganglia lesions leading to EPC are also reported in the literature (Colamaria *et al*., 1988; Hess and Sethi, 1990; Veggiotti *et al*., 1995; Cockerell *et al*., 1996). Cockerell *et al*. (1996) were inclined to classify these jerks separately from those originating in the cortex. They speculated that the loss of basal ganglia influence on brain stem results in muscular twitches. In our patient, there was obvious hemispheric cortical damage which was more likely to be responsible for the epileptic activity.

In the other previously reported cases of CJD presenting with EPC (Lee *et al*., 2000; Parry *et al*., 2001; Donmez *et al*., 2005; Lowden *et al*., 2008), rapidly progressive fatal diseases were reported *(table 1)*. This feature may imply that the early presentation of CJD with EPC could be a sign of bad prognosis. Although in our case follow-up was lacking and death occurred outside the hospital, the disease process also involved the insula, arousing suspicion of sudden unexpected death in epilepsy (SUDEP) with its critical role in respiratory physiology. Seizures (either electrical or clinical), which arise from or spread to areas in the central autonomic network involving the insula, cingulate gyrus, amygdala, hypothalamus and brain stem, can mimic stimulation of autonomic afferents leading to arrhythmia (Penfield, 1929). On the other hand, the radiological finding of insular involvement is not present in the rest of cases of EPC and sCJD. Another possibility might be the intense use of antiepileptic drugs and their toxicity in these patients due to EPC. Although our patient was on levetiracetam monotherapy, more than one antiepileptic drug was used for three of the other four cases with refractory EPC. Antiepileptic polytherapy is also a risk factor for SUDEP (Surges *et al*., 2009).

The hallmark EEG features in patients with CJD are the periodic sharp waves or complexes with mixed spikes, polyspikes, and slower waves with a typical duration of 100-600 ms, recurring every 0.5-2 seconds (Gloor, 1980). The discharges are diffuse and generally symmetrical, but may initially be asymmetrical and occasionally lateralized (Au *et al*., 1980). In the early stages and terminal stage of the disease, typical periodic EEG activity may be lacking.

Radiological findings are not included in the diagnostic criteria defined by WHO, but diffusion weighted imaging (DWI) represents a very important premortem diagnostic tool. In 2009, the MRI-CJD Consortium criteria were established for diagnosing sporadic Creutzfeldt–Jakob disease (Zerr *et al*., 2009). These criteria recommended the modification of the current WHO criteria to include either a combination of at least two cerebral cortical regions (temporal, occipital, or parietal) with increased signal or both the putamen and the caudate nucleus with high signal intensity on FLAIR or DWI, since this yields the highest diagnostic accuracy. When neuropathological confirmation is not available, it seems reasonable to combine radiological data with clinical findings and EEG for optimum identification of the disease.

As a concluding remark, EPC can be an early manifestation of CJD and may also be a possible sign of bad prognosis; a reliable non-invasive measure to diagnose EPC in this early stage of CJD may involve DWI. □

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

Legend for video sequence

The patient has irregular twitching in his right hand occurring for several hours, and recurring at intervals of a few seconds.

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