

# Diagnosis and Treatment of Patients with Concurrent Non-Convulsive Status Epilepticus and Sporadic Creutzfeldt-Jakob Disease

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## Abstract

**Background:** Sporadic Creutzfeldt-Jacob disease (sCJD) and non-convulsive status epilepticus (NCSE) may show similar clinical features and occur concomitantly. The diagnosis and treatment for patients with both sCJD and NCSE are challenging without current proposed management in clinical practice.

**Case presentation and review of literature:** Two women (52 and 61 years old) developed subacute onset of progressive conscious change, unsteady gait and involuntary movements. The results of brain MRI (hyperintensities in cerebral cortex and basal ganglia) and persistent elevation of 14-3-3 and tau protein levels in cerebrospinal fluid (CSF) supported a diagnosis of sCJD. Electroencephalography showed epileptiform discharges with temporospatial evolution that met the diagnostic criteria of NCSE. Treatment with antiepileptic medication (AED) led to clinical improvement in one patient. We searched PubMed and MEDLINE for articles between 1977 and February 2018 and found the other 11 patients of sCJD who had concurrent NCSE.

**Conclusion:** To distinguish between sCJD and NCSE, the involvement of basal ganglia on MRI and persistent elevation of 14-3-3 and tau proteins in CSF are suggestive of sCJD. Meanwhile, a fluctuated clinical course, epileptiform discharges with temporospatial evolution and clinical response to AED treatment are characteristics of NCSE. Treating NCSE in patients with sCJD is difficult but worth trying for the chance of clinical improvement.

**Keywords:** Cerebrospinal fluid; Creutzfeldt-Jacob disease; Electroencephalography; Magnetic resonance imaging; Non-convulsive status epilepticus

## Introduction

Sporadic Creutzfeldt-Jacob disease (sCJD) is a fatal prion disease that commonly presents with rapidly progressive dementia, ataxia, and myoclonus [1]. Non-convulsive status epilepticus (NCSE) refers to prolonged seizures manifested primarily as impaired consciousness and behavioral changes rather than generalized tonic-clonic convulsions. Because of similar clinical manifestations and laboratory findings between sCJD and NCSE, misdiagnosis of sCJD as NCSE or erroneously recognizing patients of NCSE as sCJD have been recorded previously [2,3]. Specifically, patients with sCJD or NCSE may both present with altered mental status. The diagnostic hallmark of NCSE includes focal or generalized rhythmic epileptiform discharges with evolutionary changes in distribution and frequency in the electroencephalography (EEG) study that resemble EEG pattern as periodic sharp wave complexes (PSWC) is usually seen in sCJD [2]. In addition, cortical ribbon signs on brain magnetic resonance imaging (MRI) and increased 14-3-3 and tau protein levels in cerebrospinal fluid (CSF) could also present in both conditions [2]. Since sCJD is a lethal disease with no current effective treatment, it is important to distinguish sCJD from any treatable diseases such as NCSE.

About 15% of patients with sCJD had seizure episodes with most of them occurred in the later stage of sCJD and in patterns of focal or generalized motor convulsions [4]. Notably, some patients with sCJD may develop concurrent NCSE [5-14], which result in the diagnosis for either one even more difficult. Until now, there is still no standardized approachable method to make a diagnosis of concurrent sCJD and NCSE. There is also lack of sufficient experiences to guide the treatment of NCSE in sCJD patients. Here, we present two patients of sCJD with concomitant NCSE and review previous studies to discuss the diagnosis and treatment of NCSE in sCJD.

## Case Presentation and Literature Review

### Case 1

The 51-year-old woman developed progressive cognitive impairment, unsteady gait, and intermittent fluctuated consciousness with subtle stereotypic involuntary movements for two months. Upon examination, she had obtunded consciousness and myoclonus. The results of serial laboratory studies were normal (vitamin B12, tumor markers, autoimmune profiles, electrophoresis, syphilis and human immunodeficiency virus screening, and antibodies specific for limbic encephalitis). Brain MRI/ diffusion-weighted imaging (DWI) revealed diffuse cortical ribbon sign. A CSF study showed normal protein level without pleocytosis. Therapeutic trial with methylprednisolone (500 mg/day for 3 days) was given for autoimmune encephalopathy, bringing no clinical or electrophysiological improvement.

The CSF 14-3-3 protein analysis revealed a negative result and the level of tau protein was only slightly increased (1512 pg/ml; cutoff point at 1200 pg/ml), which did not support a diagnosis of sCJD. An EEG study showed periodic lateralized spike-and-wave complexes or sharp waves at 2-3 Hz with secondary generalization (Figure 1A). Video EEG monitoring demonstrated that the patient had rhythmic subtle

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jerky movements accompanied with generalized periodic epileptiform discharges (GPED) at 2-2.5 Hz. Notably, intravenous lorazepam could transiently suppress the clinical seizures and turn EEG pattern to periodic lateralized epileptiform discharges (PLED) or diffuse slow waves. Under a diagnosis of NCSE, we used multiple anti-epileptic drugs (AED) and anesthetic agents (Table 1). Although seizure was finally controlled, the patient did not recover her consciousness.

Two months later, follow-up CSF 14-3-3 protein analysis revealed a positive result and the level of tau protein raised markedly to 14604 pg/ml. Brain MRI/DWI depicted more widespread hyperintensities that involved diffuse cortical areas, bilateral caudate nuclei and the left putamen (Figure 2A). The EEG revealed a typical PSWC pattern at 1 Hz. A diagnosis of probable sCJD was made.

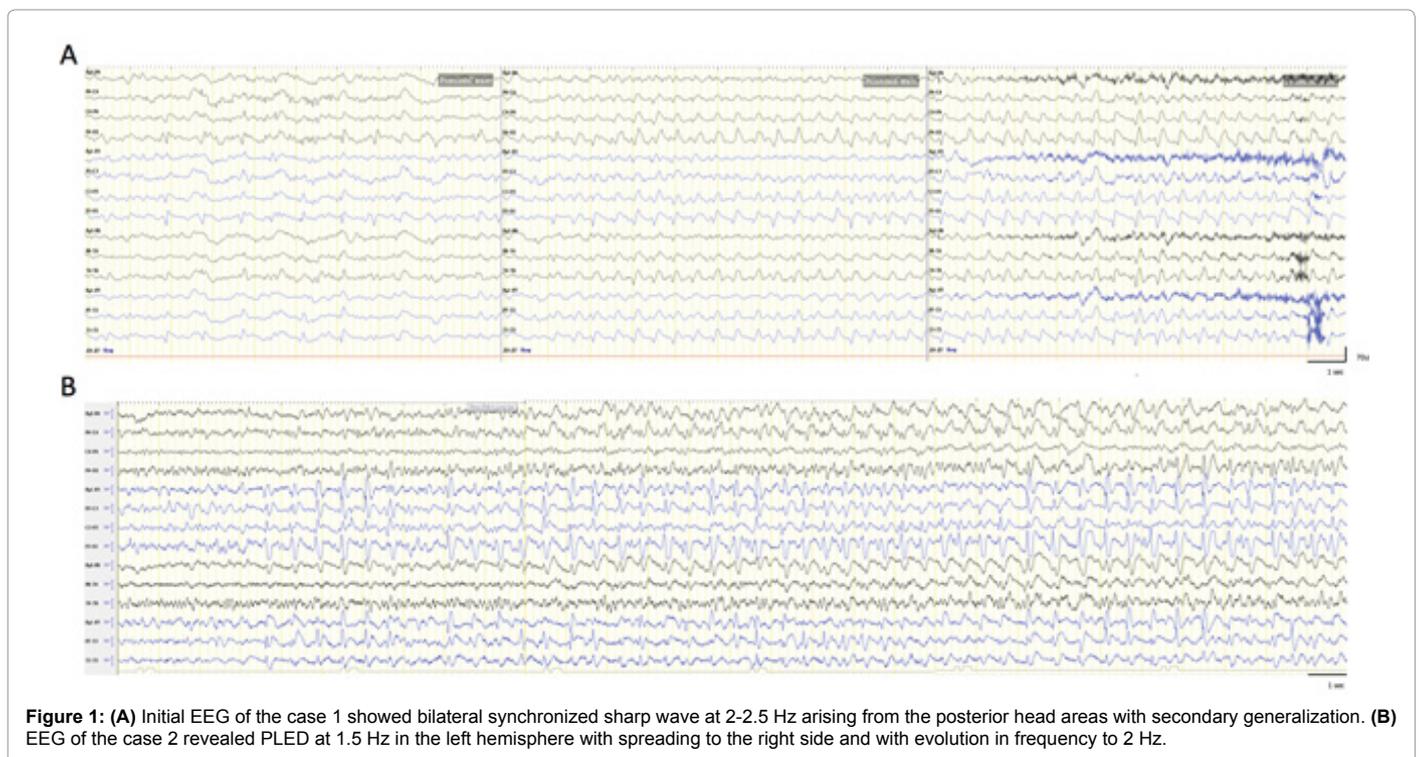
### Case 2

The 62-year-old woman suffered from progressive memory, language, and visuospatial impairment for 2 months. Serial serum

and CSF studies all showed normal results. Methylprednisolone (500 mg/day for 3 days) was given without clinical or electrophysiological improvement. Brain MRI/DWI demonstrated multiple hyperintensities, involving basal ganglia (Figure 2B). CSF study revealed positive 14-3-3 protein and elevated tau protein (9256 pg/ml). Therefore, a diagnosis of probable sCJD was made. However, EEG showed PLED at 1.5-3 Hz with frequent generalization (Figure 1B), indicating NCSE. For seizure control, we tried multiple AED treatment, which did not change the clinical condition or EEG pattern.

### Literature review

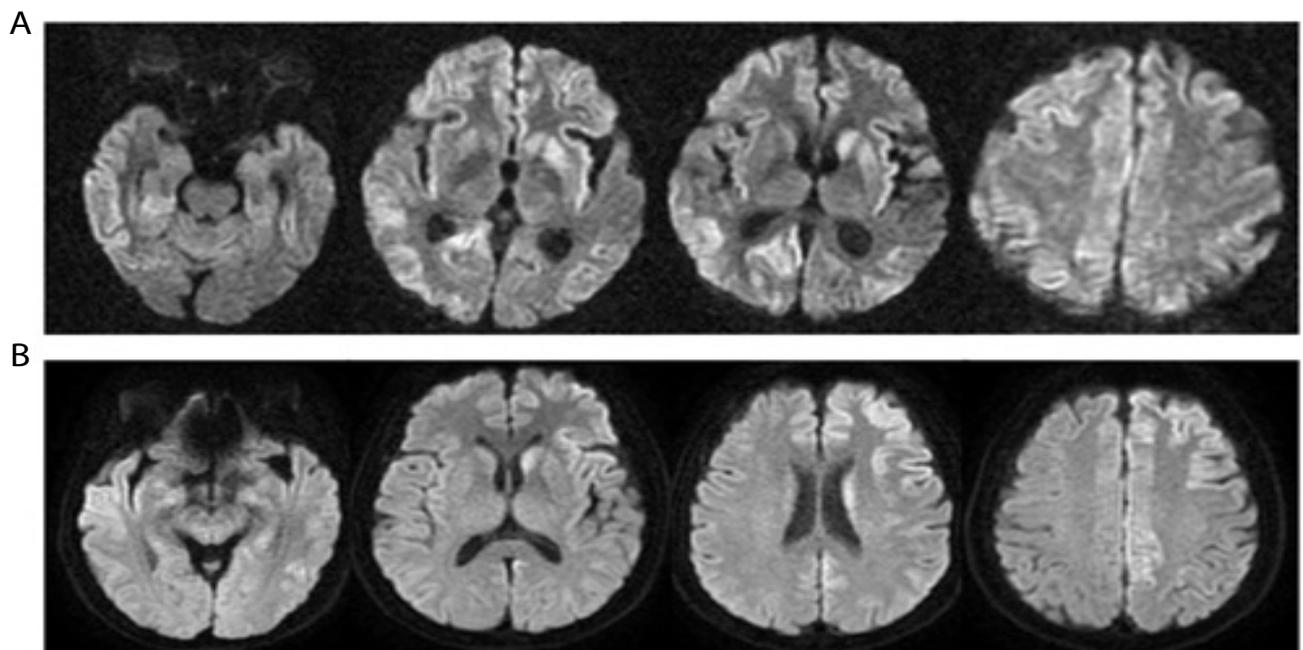
Between 1977 and February 2018, there were 11 reported cases with concurrent sCJD and NCSE [5-14] (Table 1). Including our two patients, all the 13 patients shared common clinical presentation of progressive cognitive impairment. The cortical ribbon sign frequently accompanied with basal ganglia hyperintensities on MRI (62%) and elevated 14-3-3 protein level in CSF (54%) were usually recorded.



**Figure 1:** (A) Initial EEG of the case 1 showed bilateral synchronized sharp wave at 2-2.5 Hz arising from the posterior head areas with secondary generalization. (B) EEG of the case 2 revealed PLED at 1.5 Hz in the left hemisphere with spreading to the right side and with evolution in frequency to 2 Hz.

Variables	Age (yrs) / Sex	Clinical symptoms	EEG during seizure	Seizure presentation	Seizure treatment and clinical results	Areas of DWI hyperintensities	14-3-3 protein	Pathology
Rees et al. [4]	58, F	Cognitive impairment, unsteady gait and mood disturbance	Continuous semi-rhythmic sharp waves at 2 Hz	-	PHT, VPA; no improvement	-	ND	sCJD
Rees et al. [4]	68, M	Cognitive impairment	PLED and GPED	-	PHT, VPA; no improvement	ND	ND	NP
Cohen et al. [5]	26, M	Cognitive impairment	Focal rhythmic delta waves intermixed with sharp waves and biPLEDs	-	FPT, VPA, TPM, PB, OXC, LEV; no improvement	BG, Cx	ND	sCJD
Shapiro et al. [6]	71, F	Left hemiparesis, depression, and cognitive impairment	Focal repetitive sharp waves at 2 Hz and disorganized background	Fluctuated consciousness	LZP, PHT, VPA with clinical improvement	Cx	ND	sCJD
Fernandez-Torre et al. [7]	75, F	Cognitive impairment, unsteady gait, and visual hallucination	Continuous diffuse spikes, rhythmic sharp waves, sharp-and-wave complexes; PSWC	Forced head deviation and clonic jerks in upper limbs	DZP, PHT, CZP, VPA, PB; no improvement	-	+	sCJD

**Table 1:** Patient characteristics, clinical presentations, examination results and treatment in our cases and the previous reported patients of concurrent NCSE and sCJD.



**Figure 2:** (A) In the case 1, DWI demonstrated diffuse cortical ribbon signs and hyperintensities involving bilateral caudate nuclei and left putamen. (B) In the case 2, DWI depicted hyperintensities involving left caudate nucleus, left parietal and frontal, and right insular and temporal areas.

PSWC was only noted in 6 patients, possibly because the epileptiform discharges of NCSE masked the potential underlying PSWC. Clinical ictal phenomena of NCSE were reported in 6 patients with common manifestations of fluctuated consciousness and subtle repetitive movements. In 12 patients who received AED treatment, 1 had clinical improvement in consciousness.

## Discussion

NCSE is a rare presentation in sCJD patients [5-14]. To distinguish NCSE and sCJD is sometimes difficult for their similar clinical manifestations and laboratory findings (altered mental status, epileptiform discharges in EEG, cortical ribbon signs on MRI, and elevation of 14-3-3 and tau proteins in CSF). In this study, we reported 2 patients with concomitant sCJD and NCSE, and found the other 11 patients through literature review. By analyzing the 13 patients, we discussed the clinical diagnostic clues and treatment course in this challenging situation.

Diagnosing NCSE requires clinical and EEG correlations. Several clinical presentations, which appear rapidly and unexplainably may suggest NCSE [15], e.g. impaired mental status (ranging from mild confusion to coma), cognitive impairment (including aphasia, temporospatial disorientation, hallucination, etc.), abnormal eye movements, focal myoclonus (involving face, eyelids, or limbs), automatism (presented with lip smacking or orofacial movement), and autonomic dysfunction [15]. The clinical manifestations of NCSE may show a fluctuating pattern, which is different from the progressive course in sCJD [1-15]. In 6 of 13 patients having clinical seizures from our review, 3 subjects showed fluctuating consciousness. Current electrographical diagnostic criteria for NCSE includes repetitive epileptiform discharges with frequency above 2.5 Hz, or below 2.5 Hz but with clinical and EEG improvement after AED given, or below 2.5 Hz and with focal ictal phenomena [15]. Rhythmic waves with

temporospatial evolution also fulfill the criteria [15]. On the other hand, the EEG hallmark of sCJD is PSWC, which consists of periodic sharp waves or complexes with mixed spikes, polyspikes, and slower waves with a duration of 100 to 600 ms and frequency at 0.5-2 Hz, without temporospatial evolution [4]. In our two patients, EEG either showed GPED or PLED at 1.5-3 Hz with temporal and/or spatial evolution; one patient had EEG-correlated clinical seizure, which can be suppressed by AED treatment. These results all feature a diagnosis of NCSE. Under treatment with AED, the EEG patterns could be attenuated in both sCJD and NCSE [2,4]. However, the clinical improvement could be observed in NCSE but not in sCJD [2] though no response to AED does not exclude NCSE diagnosis. Taken together, the diagnosis of NCSE in sCJD patients mainly depends on fluctuating clinical manifestations, higher frequency of epileptiform discharges with temporospatial evolution in EEG, and existence of clinical improvement under AED treatment.

Current diagnosis of definite sCJD requires brain biopsy or autopsy for neuropathological, immunocytochemical, or biochemical confirmation [1]. In previous reports of 11 patients with both sCJD and NCSE, sCJD was diagnosed pathologically in 9 subjects, which indeed unequivocally demonstrated potential concurrent of sCJD and NCSE. However, the laboratory studies are more practical to assist in making a diagnosis of sCJD apart from NCSE in clinical setting. Typical PSWC in EEG supports a diagnosis of sCJD. Furthermore, the characteristic MRI findings in sCJD include cortical ribbon sign and hyperintensities involving thalamus, caudate, and putamen [16]. In NCSE, brain MRI may depict hyperintensities in cortical areas and thalamus, but rarely in basal ganglia [2]. If the initial MRI study only reveals cortical ribbon sign, a follow-up imaging study is useful if the diagnosis of sCJD is still uncertain. As for our patient 1, the second MRI study demonstrated hyperintensities in caudate nucleus and putamen, which was not illustrated in the first MRI. Moreover, the concentrations of 14-3-3 and tau proteins in CSF have high sensitivity and specificity for sCJD

diagnosis [16]. While both 14-3-3 and tau proteins could transiently increase in patients of NCSE if extensive neuronal damage occurs [16], follow-up measurement may be helpful for sCJD diagnosis to detect the raise of 14-3-3 and tau protein levels in CSF as in our patient 1. Recently, a new technique, real time quaking-induced conversion, has been developed to detect the abnormal form of prion protein directly from CSF or nasal brushings [16], which may simplify the diagnostic process and increase the diagnostic accuracy of sCJD.

Unlike sCJD, NCSE is a treatable condition. Therefore, in sCJD patients with NCSE, AED is worthy trying for potential clinical improvement. However, NCSE in sCJD is difficult to control that under multiple AEDs with or without anesthetic agents in 12 of 13 patients from our review, only 2 patients achieved clinical improvement and only 1 got recovery of consciousness [7]. Since the prognosis of NCSE largely depends on the degree of structural brain damage caused by underlying etiologies [15], the aggressiveness of AED treatment may depend on the stage of sCJD assessing by clinical course and MRI findings [4]. More evidences are needed to decide whether and how to treat NCSE in patients with sCJD.

## Conclusion

In conclusion, NCSE may occur concurrently in patients with sCJD, which increases the diagnostic difficulty. The diagnosis of NCSE should be suspected in sCJD patients with fluctuating clinical manifestations, higher frequency of epileptiform discharges with temporospatial evolution in EEG, and existence of clinical improvement under AED treatment. The appearance of PSWC in EEG, hyperintensities involving basal ganglia in addition to cortical ribbon sign on MRI/DWI, and serial elevation of 14-3-3 or tau protein levels in CSF all support a diagnosis of sCJD for patients with NCSE. NCSE in sCJD is not easy to control even using multiple AEDs. Future large studies are mandatory to standardize the diagnostic process and optimize the AED treatment in patients with concurrent sCJD and NCSE.

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