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# Redefining periodic patterns on electroencephalograms of patients with sporadic Creutzfeldt–Jakob disease

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HIGHLIGHTS

- We redefined various periodic patterns in the EEG of sCJD using the ACNS criteria.
- iPDs+R, RSWs and PDs appeared at different time point during the disease course.
- Periodic patterns might be a predictive factor of a rapid progression of sCJD.

ABSTRACT

*Objective:* We aimed to redefine various periodic patterns (PPs) observed on electroencephalography (EEG) in patients with sporadic Creutzfeldt–Jakob disease (sCJD) using the American Clinical Neurophysiology Society's (ACNS) Criteria.
*Methods:* We analyzed EEG data of 23 patients with sCJD were admitted to two university hospitals between August 2005 and September 2015.
*Results:* We classified PPs on EEG data into three types: irregular periodic discharges (PDs) with superimposed rhythmic activities, appearing at a median of 8 weeks after onset (w.a.o.); rhythmic sharp-and-wave, at a median of 11 w.a.o.; and PDs with biphasic or triphasic morphology, at a median of 17 w.a.o. Of 16 patients presenting with PPs, 14 had widespread lesions in both cortical and subcortical areas with clinical stage III at admission, and shorter time intervals for admission to hospital from disease onset than patients without PPs (Patients with PP, 11.6 ± 12.2 weeks; without PP, 18.2 ± 8.3 weeks; $p = 0.033$).
*Conclusions:* PPs largely presented as three types at different stages of disease progression, and patients who had PPs had more wide spread lesions and rapid disease progression.
*Significance:* Our redefinition of PPs demonstrated on EEG using the ACNS criteria may contribute to further understanding of the pathological mechanisms of sCJD, and PPs might be a predictive factor of a rapid sCJD progression.


## 1. Introduction

Sporadic Creutzfeldt–Jakob disease (sCJD) is a rare and fatal neurodegenerative disease, which is typically diagnosed based on the results of electroencephalography (EEG) findings and cerebrospinal fluid (CSF) analysis. The most commonly used diagnostic criteria were revised in 1998 by the World Health Organization (WHO) (Asher et al., 1999).

However, these revised criteria still presented some issues and needed to be updated. First, the WHO criteria did not include the results of magnetic resonance imaging (MRI), despite the fact that MRI, especially diffusion-weighted imaging (DWI), has been shown to be very sensitive and specific for sCJD. Therefore, Zerret al. proposed new clinical diagnostic criteria for sCJD that included the findings from MRI scans (Zerr et al., 2009). Second, EEG findings in revised 1998 WHO criteria had not been updated for two decades. For two decades, EEG has been the method of choice to substantiate the clinical diagnosis of sCJD (Wieser et al., 2006). About two thirds of patients with sCJD had periodic sharp wave complexes (PSWC) in their EEG findings, as reported by many

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studies (Puoti et al., 2012); PSWC, defined as a sharp wave or sharp bi- or tri-phasic complexlasting from 100 to 500 ms and repeated at intervals of 500–2000 ms, was included in the 1998 revised WHO criteria as a sign of sCJD. However, this definition of PSWC typically arises in the middle and late stages of the disease and does not include other types of periodic patterns (PPs) that may appear at various disease stages, including the early stage. It is necessary to investigate other PPs that would appear at earlier stage before they develop into PSWCs at advanced stage. For several years, there has been no unified definition of these PPs. The characterization and systemic organization of PPs including PSWC will serve as the foundation for future research, in which PPs, especially appearing at the early stage, are related to ongoing neuronal injury or a specific genotype. Moreover, a better understanding of these PPs will be helpful to clinical diagnostic approach for CJD, especially at earlier stages.

Recently, the American Clinical Neurophysiology Society (ACNS) announced new criteria to standardize the terminology describing periodic and rhythmic EEG patterns in the critically ill to aid communication and future research on such patterns (Hirsch et al., 2013), and Ayyappan and Seneviratne (2014) previously described PSWCs in detail using ACNS criteria. We analyzed the EEG findings of various PPs, including PSWC, in patients with sCJD using the ACNS Standardized Critical Care EEG Terminology: 2012 version. Furthermore, we compared the clinical features of patients who did or did not present with PPs on their EEG findings.

## 2. Methods

### 2.1. Patients

In this retrospective study, we reviewed the EEG and DWI data of patients with sCJD who were admitted at two hospitals between August 2005 and September 2015. The study was approved by the Institutional Review Board of each institution. The patients were included in the study if they met the updated MRI-CJD Consortium criteria for sCJD (Zerr et al., 2009). The criteria were the following: (i) clinical signs: dementia, cerebellar or visual, pyramidal or extrapyramidal, akinetic mutism; (ii) diagnostic tests results: PSWCs on the EEG findings, 14-3-3 proteins detected in the CSF, high signal abnormalities in the caudate nucleus and putamen or in at least two cortical regions (temporal, parietal, oroccipital) observed with either DWI or fluid-attenuated inversion recovery (FLAIR) imaging. Probable sCJD was diagnosed if the patients had at least two clinical signs and at least one positive test result. Possible sCJD was diagnosed if the patients had at least two clinical signs and duration less than two years.

### 2.2. Patients characteristics and sCJD stages

Electronic medical records were used to acquire baseline demographics and clinical characteristics of each patient, including sex, age at presentation and at the time of diagnosis, and clinical symptoms/sign. We used the staging criteria described by Roos et al. (1973) to determine the stage of the disease based on clinical symptoms and signs (Ayyappan and Seneviratne, 2014). The stage I sCJD was characterized by neurologic or psychiatric symptoms, but only with minor neurologic signs. These patients usually did not have impairment in their day-to-day activities. The stage II sCJD was a distinct neurologic syndrome with marked impairment of daily activities, but dementia per se was not evident. The stage III was defined by dementia, progressing to marked akinetic mutism and death. DWIs acquired with a 1.5T MRI scanner were obtained for all patients.

### 2.3. EEG

Routine EEG recordings were obtained for at least 30 min from each patient, while awake and sleeping, using a digital EEG machine (EEG-2100, NihonKohden, Tokyo/Natus Neurology Incorporated – Grass Products, Warwick, RI, U.S.A.). The EEG recordings were made using 21 electrodes (Fp1, F7, T5, F3, T3, C3, P3, O1, Fp2, F8, T6, F4, T4, C4, P4, O2, Fz, Cz, Pz, A1, and A2) placed on the scalp according to the international 10–20 system. The electrode impedance was maintained at less than 5 kΩ. The band pass filter setting was 0.5–70.0 Hz, with a sampling rate of 200 Hz. All EEGs were reviewed and classified by two investigators who were blinded to the patient's clinical information independently. We classified the EEG findings according to the ACNS's Standardized Critical Care EEG Terminology: 2012 version (Hirsch et al., 2013). According to this classification, rhythmic or periodic patterns consist of a main term #1 event followed by a main term #2 event. Main term #1 events include generalized, lateralized, bilateral independent, or multifocal patterns. Main term #2 events include periodic discharges (PDs), rhythmic delta activity (RDA), and rhythmic spike-and-waves or sharp-and-waves (RSWs) patterns. Briefly, PDs are defined as repetition of a waveform with relatively uniform morphology and duration with a quantifiable interdischarge interval between consecutive waveform and recurrence of the waveform at nearly regular interval. RDA is defined as the repetition of a waveform that is rhythmic activity $\leq$4 Hz with relatively uniform morphology and duration, and without an interval between consecutive waveforms. RSWs pattern is defined as a polyspike, spike, or sharp wave consistently followed by a slow wave in a regularly repeating and alternation pattern, with no interval between one spike-wave complex and the next. "Triphasic" morphology applies to both PDs and SWs, and it is either two (positive–negative) or three phases (negative–positive–negative) with the positive phase of highest amplitude. Anterior-posterior lag applies if a consistent measureable delay of >100 ms exists from the most anterior to the most posterior derivation in which is seen.

### 2.4. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software for Windows (version 21.0; SPSS Inc., Armonk, NY, U.S.A.). Categorical data were compared using Fisher's exact test. Continuous data were compared using the Mann–Whitney *U* test and Jonckheere–Terpstra test. Differences or associations with $p$ values < 0.05 were considered statistically significant.

## 3. Results

### 3.1. Demographics

Table 1 shows the demographic and clinical characteristics of the analyzed patients, including the genetic subtype of the 14-3-3 proteins found in their CSF. All patients ($n$ = 23, 11 men and 12 women) were diagnosed with probable sCJD, and they presented as stage III on clinical sign at admission. The age at disease onset ranged from 38 to 83 years, and the median age was 66 years. At hospital admission, all patients had symptoms of cognitive decline and were clearly impaired in their daily activities. Of 23 patients, 21 (91.3%) had pyramidal/extrapyramidal signs, 15 (65.2%) cerebellar dysfunction, 15 (65.2%) akinetic mutism, 11 (47.8%) myoclonus, and 7 (30.4%) visual symptoms. Two patients had a history of psychotic symptoms, manifesting as hallucinations and delusions. The CSF was examined in 19 patients and was positive for 14-3-3