Cyclic seizures with automatisms occurring during non-convulsive status epilepticus with lateralized periodic discharges caused by hyponatremia

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Abstract

Lateralized periodic discharges (LPDs) have been known to be one of the ictal electroencephalography (EEG) activities in non-convulsive status epilepticus (NCSE). Cyclic seizures represent a special form of status epilepticus in which seizures recur at regular intervals. We treated a patient who suffered from NCSE with LPDs which developed under hyponatremia. The patient showed cyclic seizures with automatisms during NCSE. The cyclic seizures were associated with high-frequency rhythmic discharges on EEG, and the NCSE was associated with LPDs. Our patient showed that cyclic seizures with motor symptoms can occur on the background of NCSE with LPDs. The rhythm of LPDs abruptly changed at the initiation and the ending of the seizures, implying the possibility of replacement of one pacemaker by another pacemaker, which triggers seizures associated with the ictal high-frequency rhythmic activities. We discuss the pathophysiology underlying the evolution of these two types of seizures.
Introduction
Non-convulsive status epilepticus (NCSE) is a form of status epilepticus, and its ictal period is characterized by sustained impaired consciousness with minimal or no motor symptoms [1-3]. Lateralized periodic discharges (LPDs) (formerly referred to as periodic lateralized epileptiform discharges) have been known to be associated with status epilepticus of various forms, including NCSE [1, 4]. Cyclic seizures represent a special form of status epilepticus in which seizures recur at regular intervals [5]. We treated a patient who suffered from NCSE with LPDs which developed under hyponatremia. The patient showed a peculiar NCSE in which seizures with automatisms and high-frequency rhythmic discharges on electroencephalograms (EEG) appeared as cyclic seizures during a sustained stuporous state with LPDs. We investigated the temporal features and transition of the two types of seizures on EEG, and we discuss their pathophysiology.

Case Presentation
Our patient was an 86-year-old right-handed woman, requiring some support for everyday life, with a 20-year history of diabetes mellitus, hypertension and possible Alzheimer’s disease. She had had an episode of hyponatremia three months before admission to another hospital, and she had been prescribed hydrocortisone 10 mg daily since then on suspicion of potential adrenal insufficiency. She subsequently developed mild hemiparesis and numbness on the left side and visited the emergency center with her family. Neurological examination revealed mild weakness and decreased touch and pinprick sensation in the left extremities, and her symptoms fluctuated. She was alert and did not show any seizure. Results of the routine blood and urine analysis were normal, except for a blood sugar of 292 mg/dL and serum sodium of 132 mEq/L (135-147 mEq/L). MRI taken 11 hours after onset showed no abnormality, except for mild-to-moderate atrophy of the medial temporal lobe and the frontal lobe. Oral hydrocortisone 10 mg daily was discontinued on admission. On Day 3, her consciousness was gradually impaired without seizure, and her serum sodium was revealed to be as low as 108 mEq/L. On follow-up examination, her serum sodium was 113 mEq/L, serum osmolality was 234 mOsm/kg (275-295 mOsm/kg), urine sodium was 130 mEq/L and urine osmolality was 663 mOsm/kg (500-800 mOsm/kg). She was diagnosed as having inappropriate secretion of anti-diuretic hormone (SIADH). Hormonal examination revealed no hypothyroidism or adrenal insufficiency. Her sodium was corrected slowly through hypertonic saline infusion (4-8%) and fluid restriction (700 ml/day). Her serum sodium improved to 130 mEq/L on Day 8 (the average sodium correction rate, 4 mEq/L/day), but her consciousness disturbance continued with fluctuating responsiveness. She began to show intermittent seizures associated with automatisms composed of right arm elevation in the air, right hand groping and soliloquy. The seizures with automatisms occurred at fairly regular intervals on Day 9. Brain 3T MRI was taken on the same day and revealed areas of high intensity in the temporooccipital, precuneus and posterior thalamic regions on the
right side on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) images, and the same areas showed low intensity on apparent diffusion coefficient map (ADC map). The arterial spin-labeling (ASL) perfusion MRI with a post-labeling delay of 2525 ms showed marked hyperperfusion in the same areas (Figure 1A, B, C). EEGs recorded on the same day revealed LPDs dominantly in the right hemisphere approximately at 0.4 Hz with the focus at the right occipital lead (Figure 2A, B). Every 3-4 min, the frequency of the LPDs abruptly became higher at approximately 0.9 Hz, associated with some changes in the shape of the single epileptiform discharges. The new periodic discharges were sustained for several seconds and then changed to another ictal pattern; that is, showing irregular 8-10 Hz rhythmic activities. These ictal activities continued for 30-40 seconds and were abruptly replaced again by the LPDs at approximately 0.4 Hz. The patient was lying still during the LPD phase and started arm elevation with groping on the right side and soliloquy at the beginning of the high-frequency rhythmic activity phase, which continued until the return of the LPDs (Figure 2B). The seizures recurred at fairly regular intervals, once every 3-4 min, as

Figure 1. MRI taken on Day 9. High-signal areas in the temporoooccipital, precuneus and posterior thalamic areas were demonstrated on DWI (A) and on FLAIR (B), and the areas showed marked hyperperfusion on ASL (C). MRI taken on Day 18 showed normalization of the areas with abnormal signal, except for a part of the occipital area on DWI (D), on FLAIR (E) and on ASL (F).
demonstrated by the compressed spectral array (CSA), in which the frequency spectral data were calculated for the central and occipital leads on both sides and combined (Figure 2C). We diagnosed her as having NCSE with a seizure focus in the right temporooccipital areas and cyclic seizures with a focus in the same areas.

We initiated treatment with continuous intravenous infusion of midazolam under in-
termittent EEG monitoring. The initial dose of midazolam was 0.1 mg/kg/hour, and the dose was increased to 0.4 mg/kg/hour and maintained for 5 days. The seizures with high-frequency rhythmic discharges on EEGs promptly disappeared, but she remained stuporous with LPDs. The LPDs gradually changed to irregular and smaller epileptic discharges. Midazolam infusion was tapered off and replaced by oral levetiracetam 1000 mg per day and lacosamide 100 mg per day. The patient recovered with some cognitive dysfunction after discontinuation of midazolam infusion. MRI taken on Day 18 showed near normalization of the signal changes in the right temporooccipital and thalamic areas, except for a part of the right temporooccipital area which showed high signal intensity on FLAIR, and the hyperperfusion of these areas were almost resolved on ASL perfusion MRI (Figure 1D, E, F).

Discussion
The initial symptoms of the patient; that is, mild hemiparesis and numbness on the left side, could have been a stroke mimic [6, 7], because the later clinical course and laboratory findings suggested that they had been caused by seizure. We estimated that NCSE had started at the time when the patient entered a sustained delirious state with concomitant hyponatremia. It has been reported that hyponatremia can cause status epilepticus, including NCSE [8, 9] or focal impaired awareness seizure status epilepticus [10]. Furthermore, possible Alzheimer's disease suggested by the MRI findings might underlie the evolution of the seizure. Her serum hyponatremia was caused by SIADH, which was probably induced by discontinuation of the steroids after admission.

Our patient showed a unique SE pattern that was composed of two types of seizures during status epilepticus: one type was seizure with automatisms and high-frequency rhythmic discharges on EEG; the other was NCSE associated with LPDs. Although the LPDs at 0.4 Hz in our case did not meet the Salzburg Criteria for NCSE [1], clinical and EEG improvements from intravenous antiepileptic drug and decrementing termination suggested “possible NCSE”. The seizure with automatism can be considered a phenomenon involved in the NCSE according to the diagnostic criteria of NCSE [3]; however, the two types of seizures had different ictal EEGs in our patient. Periodic epileptiform discharges have been classified in several ways, and, among them, lateralized epileptiform discharges and generalized epileptiform discharges are distinguished based on diffuse or local brain injuries [4]. Based on the EEG and MRI findings, our patient was assessed to have LPDs. An increase of cerebral blood flow on ASL perfusion MRI was demonstrated in the period of the two-seizure patterns. As has been reported in a case of status epilepticus which showed hyperperfusion of the focus area of the brain in relation to LPDs [11], seizures of the two patterns could have contributed to the hyperperfusion.

As the seizure with automatisms recurred at fairly regular intervals in our patient, we may refer to this condition as “cyclic seizures” [5]. Friedman et al. [5] analyzed 13 patients who showed a pattern of seizures recurring in a cyclic fashion and referred to them as cyclic seizures. All of the cyclic seizures were
NCSE, except for one patient who showed facial twitching during seizures in their study. The mean duration of each seizure was 48 seconds (range 15-90 seconds), and the mean duration of inter-seizure interval was 7.6 min (range 0.25-47 min). The features of the seizures with automatisms in our case fell within the ranges of Friedman’s cases.

The cyclic seizure pattern allowed us to confirm the transition of the seizure on EEGs from the LPD background. The changes in the EEGs were as follows: 0.4 Hz LPDs $\rightarrow$ 0.9 Hz LPDs $\rightarrow$ irregular 8-10 Hz rhythmic activity $\rightarrow$ 0.4 Hz LPDs. Little is known regarding the pathophysiology of periodicity of LPDs. Enhanced synchrony, changes in neural excitability and pacemaker are key words in elucidating the mechanism of the electrogensis of LPDs [4]. A pacemaker exerts function of rhythm generation under modulation of the membrane properties, synaptic interactions and neural networks [12, 13]. The electrogenesis of the two types of seizures may include a dependent mechanism and an independent mechanism. From the standpoint of ictal-interictal continuum [14], the seizure with automatisms and high-frequency rhythmic discharges may be ictal, and the NCSE with LPDs may be interictal; these two types of seizures may be generated by identical background electrical activities. On the other hand, the abrupt changes in the rhythm of LPDs at the beginning and the end of the seizures in our case may imply replacement of the pacemaker of the LPDs by another pacemaker, which triggers seizures associated with the ictal high-frequency rhythmic activities. It is possible that the seizure with automatisms and the seizure with the LPDs could have simultaneously proceeded in the brain, and the dominant activity of these two activity patterns may appear as the ictal phenomenon.

Our patient showed that cyclic seizures with automatisms can occur on a background of NCSE with LPDs. Although the pathophysiology underlying the periodicity of cyclic seizures is not yet known, future study of detailed phenomenology and electrophysiology of this peculiar condition will help clarification of the initiation and termination of individual seizures.

**Ethical statement**

This study has been carried out in accordance with the Declaration of Helsinki. Informed consent was obtained for the examinations.

**Disclosures**

None of the authors have any conflict of interest to declare.

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