



Case Report

Paroxysmal sympathetic hyperactivity and the later development of epilepsy in a chemotherapy-associated brain damage

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Abstract

Background: Chemotherapy in childhood leukemia potentially induces brain lesions and neurological sequelae. Paroxysmal sympathetic hyperactivity (PSH) is known as a treatment-associated complication; however, the full clinical spectra of PSH remain to be elusive.

Case report: A 5-year-old girl was diagnosed of acute myeloid leukemia (AML) M5. After the intensification therapy, she developed recurrent symptoms of episodic tachycardia, hypertension and perspiration lasting for several hours per day. The low-frequency-high-frequency ratio on Holter electrocardiography was rapidly increased from 0.84 to 2.24 at the onset of the paroxysmal event, whereas the video-monitoring electroencephalography (EEG) never identified ictal patterns of epileptiform discharges during the episodes. Thus, the diagnosis of PSH was given at 7 years of age. Myoclonic and generalized tonic-clonic seizures frequently appeared from 10 years of age, which poorly responded to anticonvulsants. EEG showed diffuse slow-wave bursts with multifocal spikes. Serial head magnetic resonance imaging (MRI) revealed diffuse cerebral and hippocampal atrophy, but not inflammatory lesions in the limbic system.

Conclusion: We first demonstrate a pediatric case with PSH who developed drug-resistant epilepsy 3 years after the onset of PSH. Our data suggest the pathophysiological link of persistent PSH with chemotherapy-associated brain damage.

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1. Introduction

Paroxysmal sympathetic hyperactivity (PSH) represents a deregulated condition of autonomic system char-

acterized by episodic hyperthermia, tachycardia, hypertension, tachypnea, and diaphoresis [1,2]. PSH most frequently occurs in association with severe traumatic brain injury (TBI), while encephalitis, brain tumors and other causes have been reported in fewer cases [1].

Pathophysiology of PSH remains to be elusive. However, former studies identified aberrant discharges in the diencephalon, but not in the cerebral cortex [2]. These electrophysiological data may rationalize the mechanism underlying autonomic bursts of PSH. Thus, PSH is currently understood as a distinct brain disorder from epilepsy. On the other hand, no information is available for the comorbidity of PSH with epilepsy in childhood. We herein describe a child who developed PSH after chemotherapy for leukemia and drug-resistant epilepsy 3 years later.

2. Case report

A 5-year-old girl was an only child of healthy, unrelated parents. She presented with polyarthralgia from one month before. Complete blood counts revealed leukocytosis of $51.90 \times 10^9/\text{L}$, low hemoglobin concentration of 9.3 g/dl and thrombocytopenia of $50.0 \times 10^9/\text{L}$. Myeloperoxidase-negative, esterase-positive leukemic cells were identified in the peripheral blood and bone marrow. Flow-cytometry analysis confirmed the diagnosis of acute myeloid leukemia (AML) M5 at intermediate risk. G-band karyotyping detected 46,XX,t(9;11) (p22;q23)/47,idem,+8.

This patient obtained a complete remission after the first induction therapy. During the third course of intensification chemotherapy on continued remission, a convulsion occurred on transient hyponatremia ($\text{Na} 120 \text{ mEq/L}$). Lumbar puncture showed a marginal increase of total protein to 43 mg/dl without pleocytosis (3/4 μl) in cerebrospinal fluid. Viral infections and the reactivation of human-herpesvirus 6 (HHV6) were not screened with polymerase chain reaction. A tentative diagnosis of inappropriate antidiuretic hormone secretion was given, and the serum sodium level was appropriately corrected.

After this event, however, she began to experience daily attacks of hypothermia ($34\text{--}35^\circ\text{C}$), hypertension with systolic blood pressure (BP) 160–180 mmHg and diastolic BP 100–120 mmHg, tachycardia (150–180/min), and episodic increase in perspiration at age 5 years and 9 months (Fig. 1A). These symptoms started without apparent triggers, typically lasting for three to four hours per day. Each episode accompanied restless behaviors, loss of social interactions and outspoken words. Head magnetic resonance imaging (MRI) detected the mild cerebral atrophy and symmetrical T2-hyperintense lesions in the cerebral white matters (Fig. S1). While chemotherapy-associated brain damage was suspected, serum anti-voltage-gated potassium

channel (VGKC) complex antibodies were elevated to 121 pmol/L (reference range: <100 pmol/L).

Because the condition of paroxysmal dysautonomia persisted over one year, she was referred to our department at 7 years of age for further evaluation. During the episodic attack of dysautonomia, plasma catecholamine levels were elevated to adrenaline 307 pg/ml (reference range: $\leq 100 \text{ pg/ml}$), noradrenaline 424 pg/mL (100–450 pg/ml) and dopamine 28 pg/ml ($\leq 20 \text{ pg/ml}$). A heart rate variability test on Holter electrocardiogram showed that the low-frequency (LF: 0.04–0.15 Hz) to high-frequency (HF: 0.15–0.4 Hz) ratio was rapidly elevated at the onset of dysautonomia (Fig. 1B). We confirmed that the average LF/HF ratio (2.24) during the event was higher than that (0.84) obtained from non-episodic period. Thus, her autonomic system was shifted to the sympathetic nerve dominance [3]. Video-monitoring EEG did not show ictal patterns during the episodes of dysautonomia (Fig. 2A). Taken together, she was considered being under PSH. We used β -blocker, angiotensin-converting enzyme inhibitor or anticonvulsants (clonazepam and carbamazepine) for PSH [4], but either of them did not improve these symptoms. Serum anti-VGKC antibody was negative at 9 years of age. Wechsler Intelligence Scale for Children 4th (WISC-IV) showed mildly impaired cognitive functions with intelligence quotient 77 at this age.

Epileptic seizures were initially recognized as myoclonic, involuntary movements of upper limbs at 10 years of age. However, in one month after the onset of myoclonic movements, she began to show recurrent generalized tonic-clonic seizures (GTCS) with or without precedent focal signs. We therefore considered the onset of these seizures to be “combined generalized and focal”; and classified the epilepsy types into “myoclonic seizure” and “tonic-clonic seizure”, according to the International League Against Epilepsy Classification 2017 [5]. Myoclonic seizures occurred at the frequency of 5–10 attacks per day, while GTCS did once in 1 or 2 weeks. Multifocal spike-and-wave complexes on interictal EEG (Fig. 2B) suggested that she had “combined generalized and focal epilepsy”. The epileptogenic focus remained unknown from the history and serial recordings of EEG (Fig. 2B). However, video-monitoring EEG at 12 years recurrently identified ictal patterns recurrently identified the precedent focal epileptiform discharges, which emerged from the right frontal region and evolved into the generalized activities (Fig. S2A). In contrast, no focal activities preceded the generalized discharges associated with myoclonic seizures (Fig. S2B). Myoclonic seizures did not appear to induce GTCS. These data confirmed that she had “combined generalized and focal epilepsy” [5]. Follow-up MRI excluded the progressive hippocampal sclerosis (Fig. 3). Because seizures were uncontrollable with combined anticonvulsant treatments, she received surgical corpus

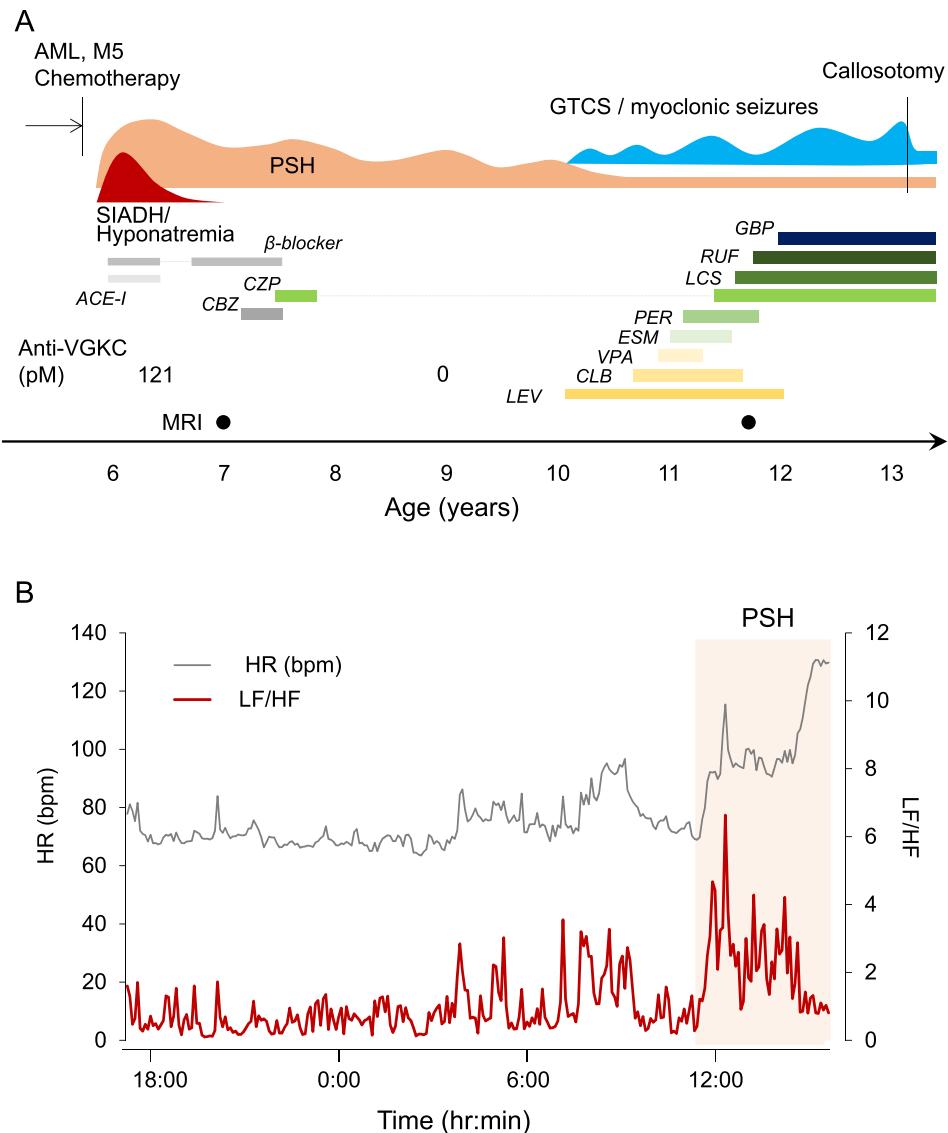


Fig. 1. Clinical course and the heart rate variability test for the present case. (A) During 7 years of follow-up period, the present case continued to show variable degree of PSH. Myoclonic and generalized tonic-clonic seizures were resistant to the combined treatments with anticonvulsants. Carbamazepine (CBZ), clonazepam (CZP), levetiracetam (LEV), clobazam (CLB), valproic acid (VPA), ethosuximide (ESM), perampanel (PER), lacosamide (LCS), rufinamide (RUF) and gabapentin (GBP), angiotensin-converting enzyme inhibitor (ACE-I). Generalized tonic-clonic seizures (GTCS). She received corpus callosotomy at 13 years of age. (B) The oscillations of heart rate (HR) and the low frequency to high frequency ratio (LF/HF). HR (gray line) was averaged every 5 min. LF/HF (red line) was calculated on the short-term heart rate variability within the same interval. Shaded area represents the period of PSH (11:25 to 15:40). Note that the LF/HF value showed a rapid increase in the early phase of PSH (11:45 to 12:45). The Holter-ECG recording was terminated in the middle of PSH (15:40).

callosotomy at 13 years of age (Fig. 1). Corpus callosotomy was effective for controlling GTCS, but myoclonic seizures recurred in one month after surgery. At presently 13 years of age, she still has symptoms of PSH with milder degree in duration, tachycardia, and perspiration than those at initial presentation. Her motor, social and language skills have never regressed or stagnated throughout the observation period.

3. Discussion

This report described a girl presenting with acute leukemia and PSH after the intensification chemotherapy. The primary finding in this case was that she had persistent symptoms of PSH. From this observation, chemotherapy-associated PSH in childhood may not follow self-limiting time course, as typically observed

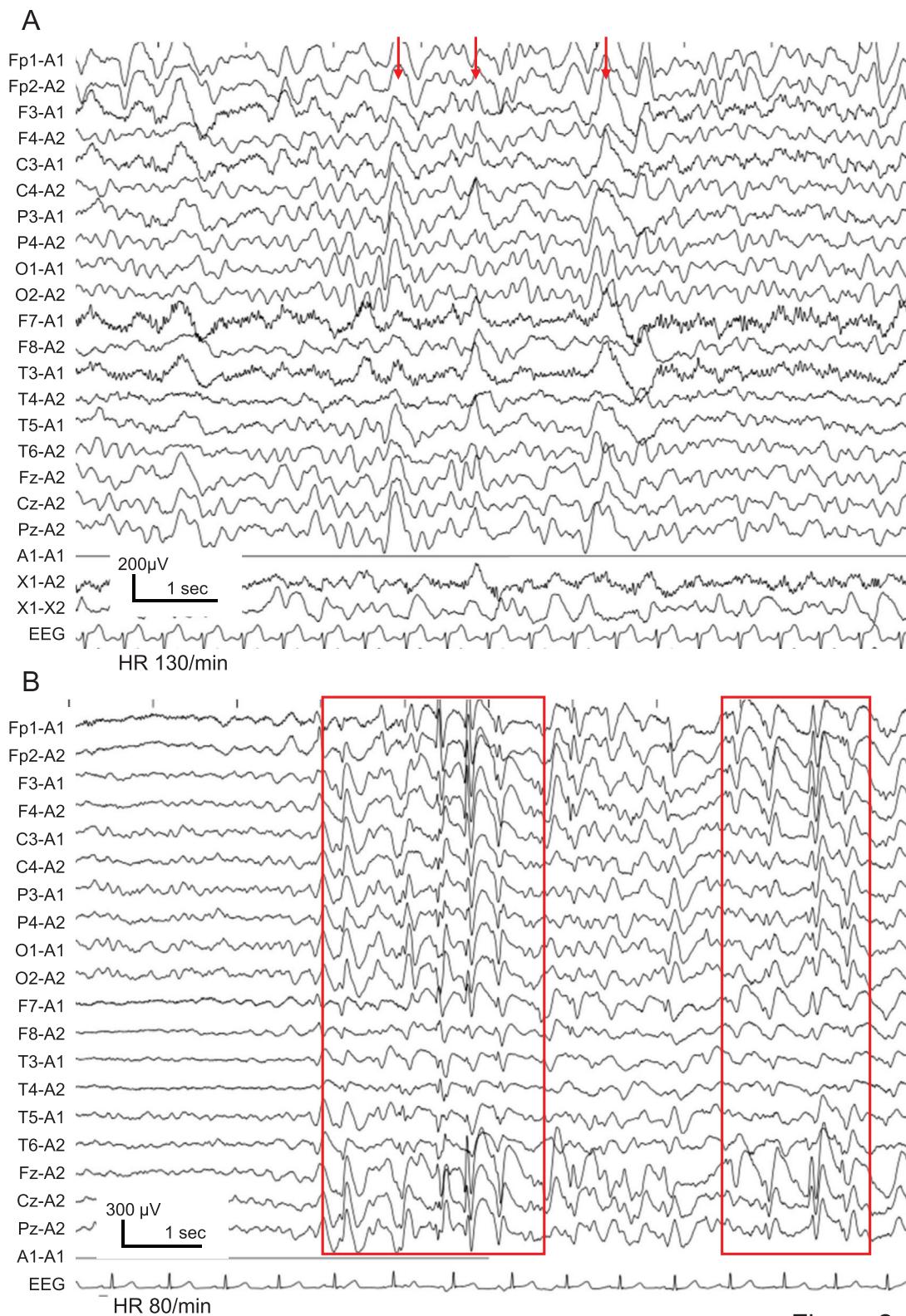


Figure 2

Fig. 2. Electroencephalography of the present case. (A) Electroencephalography at the onset of PSH (7 years of age). The EEG detected a transient increase in irregular, slow-wave components (arrows). (B) An interictal electroencephalography after the onset of epileptic seizures (10 years of age). Note that high-voltage slow waves with spike components are diffusely observed (red squares). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

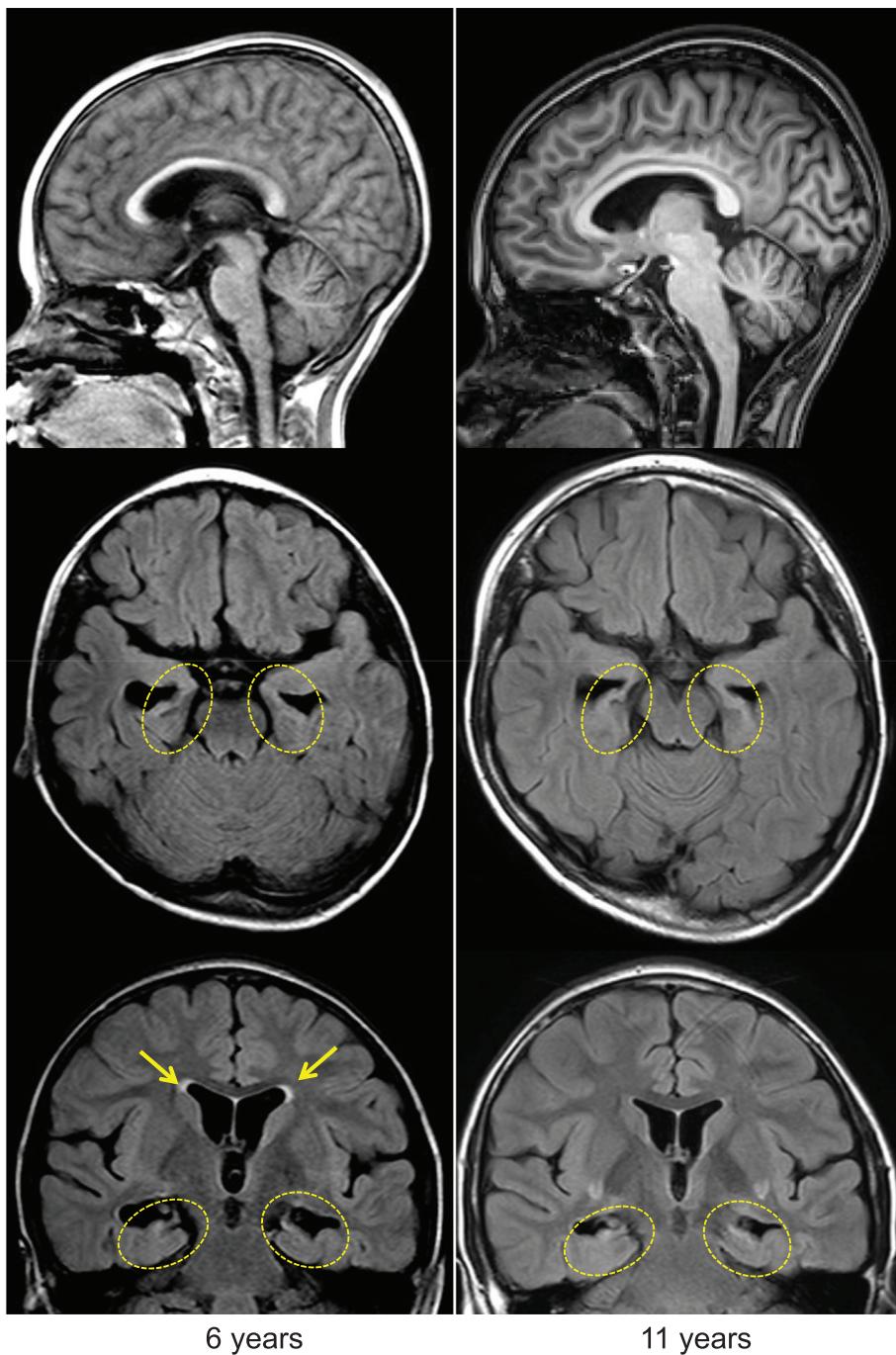


Fig. 3. Head MRI of the present patient. T1-weighted images (top, sagittal) and fast fluid-attenuated inversion-recovery (FLAIR; middle and bottom) show the neuroimaging data at the indicated ages. Arrows indicate the chemotherapy-associated white matter lesions. Note that hippocampal atrophies (dashed circles) were already present from 6 years of age and that the hippocampal atrophy was not progressive during the follow-up period.

in those with TBI [1]. Second, this patient also developed combined generalized and focal epilepsy three years after the onset of PSH.

The majority (80%) of PSH occurs in association with TBI, while 8–33% of TBI have been shown to cause the variable degree of PSH [1,2]. Duration of symptoms may range from a few days to months, in which a pro-

longed form of PSH has been documented [6]. The appearance of PSH in intensive care represents the high morbidity after TBI and unfavorable neurological outcomes [7,8]. To date, however, it remains unknown whether chemotherapy causes PSH with more prolonged symptoms than TBI, and whether the duration of PSH reflects the severity of brain damage. In cancer

chemotherapy, activation of microglia and induction of reactive astrocytes are involved in the pathogenic process of leukoencephalopathy [9,10]. Because these cells provoke proinflammatory signals in both innate and acquired immune system, symptoms of PSH in chemotherapy may advance more slowly and progressively than those of TBI-associated PSH. Notably, our patient presented with hypothermia, but not hyperthermia, as a prodromal sign to other symptoms of PSH. Such a complex presentation might be defined as a clinical feature of PSH in childhood or PSH after chemotherapy.

No previous reports have documented patients who developed epilepsy several years after the onset of PSH. The present patient did not show epileptiform discharges associated with the clinical events of dysautonomia. Considering the later development of generalized seizures with diffuse epileptiform discharges, epileptogenic circuits were unlikely to involve the cerebral cortex at the onset of PSH. Thus, PSH in this case was speculated to harbor two distinct phases: the first three years without epilepsy and the second phase with frequent epilepsy. We also demonstrated that the LF/HF value was a useful parameter for detecting PSH.

Recent studies have shown that PAG was impaired in a rodent model of status epilepticus, resulting in an increased susceptibility to generalized seizures [11,12]. We therefore hypothesize that the dysfunction of PAG might be involved not only in the development of PSH, but also in the epileptogenic process after chemotherapy. On the other hand, the pathogenic mechanisms of PSH cannot be fully explained only from the loss of PAG function [13]. In this context, it will be valuable to investigate whether PSH precedes the onset of epilepsy in other cases with chemotherapy-associated brain damages.

Neuroimaging studies did not find brainstem lesions; however, we cannot exclude the possibility that the autonomic center was functionally deregulated in the brainstem of this case. Of note, the insular cortex, paraventricular nucleus and other subcortical structures form the afferent pathway regulating the parasympathetic outflow to the cardiac rhythms [13,14]. Thus, we speculated that she had profound damages in these regions during or after chemotherapy.

Neuroinflammatory findings in this patient may partly explain the pathogenic mechanisms of chemotherapy-associated PSH [9,15]. Recent reports have supported evidence that the presence of anti-VGKC represents neuroinflammation but not always indicates autoimmune-associated mechanisms [15,16]. In agreement with this concept, focal inflammatory lesions were absent in the limbic system of our patient. For the same reason, we speculated that reactivation of HHV-6 was less likely to be involved in the patho-

genic process of hyponatremia and epileptic seizures in this patient.

We herein conceptualize that chemotherapy and/or transient hyponatremia disrupted the connectivity of periaqueductal grey matter (PAG) in the midbrain with other regulatory centers of sympathetic tone [1]. As recently reported, impaired descending inhibition contributed not only to increase in the sympathetic output, but also to deregulating the excitation-inhibition balance in thalamocortical connectivity [1,2]. Neurophysiological studies may further identify the pathogenic mechanisms of chemotherapy-associated PSH and its critical difference from those of TBI-associated PSH [2,9,10].

In conclusion, we demonstrated a girl who developed intractable epilepsy three years after the onset of chemotherapy-associated PSH. Because this is a single-case report, extensive studies may find more patients who show similar conditions to our patient in association with anticancer chemotherapy. Different time courses and outcomes between children with PSH after TBI and those after chemotherapy will be the potential target of investigation. Future works for uncovering pathogenic mechanisms will provide alternative options to prevent the development of epilepsy in PSH after chemotherapy.

Acknowledgments

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Conflict of interest

All authors have no conflicts of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.braindev.2021.07.001>.

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