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Development of epilepsy after posterior reversible encephalopathy syndrome

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ABSTRACT

Purpose: This study was intended to describe the risk of epilepsy subsequent to posterior reversible encephalopathy syndrome (PRES) and the clinical features of post-PRES epilepsy.
Method: We retrospectively identified all patients with PRES who were admitted to Severance Hospital and consulted with the Department of Neurology between 2001 and 2013 and the subgroup of these patients who subsequently developed epilepsy. We also describe clinical features of patients who were not treated with PRES as inpatients at our center but who presented later with post-PRES epilepsy during the study period. We studied clinical characteristics during the acute symptomatic phase of PRES and after the development of epilepsy.
Results: During the study period 102 patients were treated at our center during the acute phase of PRES. Four of these patients (3.9%) subsequently developed epilepsy. Two additional patients with a history of PRES presented to our hospital after the acute phase of their illness with post-PRES epilepsy. During the acute phase, five of six patients had acute symptomatic seizures and four had convulsive or nonconvulsive status epilepticus (SE). Acute phase MRI showed cytotoxic edema in five patients, and follow-up MRI showed focal atrophic changes including hippocampal sclerosis in four. Presumptive epileptogenic foci were located in the left-side temporal, parietal and occipital lobes, corresponding to the regions that showed cytotoxic edema or severe vasogenic edema as well as with the location or lateralization of EEG abnormalities during the acute phase.
Conclusion: Our findings indicate a small but not insignificant risk for the development of epilepsy after PRES. The presence of cytotoxic edema and severe, acute symptomatic seizures, such as SE suggests irreversible brain damage and may predict the development of epilepsy.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) presents with various neurological signs and symptoms, including seizures, and is characterized by a pattern of abnormalities in brain imaging studies. The prognosis in patients with PRES is favorable as most cases completely resolve without any sequelae [1] if the underlying conditions responsible for PRES are treated promptly. Recently, two studies showed that the development of epilepsy is uncommon in patients who recover from PRES [2,3]. However, cytotoxic edema (bright signals on diffusion weighted imaging, dark signals on apparent diffusion coefficient map images), hemorrhage, contrast enhancement on MRI during the acute symptomatic phase, and residual lesions on follow-up MRI are not infrequently found in PRES [4–8]. As well, pathologic evidence of partial irreversible damage has been documented in PRES in spite of radiographic resolution of abnormalities [9], suggesting the potential for irreversible brain damage. Although seizures occurring during the acute symptomatic phase, are generally well controlled by short-term antiepileptic drug (AED) treatment [10], severe seizures such as status epilepticus (SE), and delayed or non-aggressive treatment of seizures may produce irreversible injury. Herein, we attempted to investigate the risk of epilepsy subsequent to PRES, describe the clinical characteristics of patients who

Abbreviations: PRES, posterior reversible encephalopathy syndrome; AED, antiepileptic drug; SE, status epilepticus; HS, hippocampal sclerosis; GTCS, generalized tonic-clonic seizure; PLED, periodic lateralized epileptiform discharge; FLAIR, fluid-attenuated inversion recovery; DW, diffusion-weighted; HE, hypertensive encephalopathy; TLE, temporal lobe epilepsy.

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developed epilepsy after PRES, and discuss associated risk factors for this condition.

2. Methods

In order to estimate the incidence of epilepsy development stemming from PRES, we retrospectively identified all patients with PRES who were admitted to Severance Hospital and consulted with the Department of Neurology between January 2001 and December 2013 from data maintained by our department. Diagnosis of PRES was based on clinical features (predisposing conditions, headache, seizures, alterations in consciousness, and visual abnormalities); multifocal lesions on MRI, mainly suggesting vasogenic edema; clinical recovery; and when available, reversibility of MRI lesions. We identified six patients with epilepsy following PRES, who visited the epilepsy clinic of Severance Hospital between January 2001 and December 2014. Additionally, we searched the medical records of patients with PRES who were admitted to our hospital, and investigated evidence of seizure or epilepsy occurrence. Clinical information was collected for these six patients including demographics, co-morbid illnesses, medication histories, neurological manifestations, brain MRI, and EEG during the acute symptomatic phase of PRES. Clinical information on seizure semiology, EEG, brain MRI and prognosis after the development of epilepsy was investigated in detail. This study was approved by the Institutional Review Board of Severance Hospital.

3. Results

3.1. Overall incidence of epilepsy in patients with PRES

We identified 102 patients who were treated at our hospital during the acute phase of PRES. Four of these patients (3.9%) developed epilepsy subsequent to PRES. We did not find evidence of seizure or epilepsy occurrence in any other patients among the medical records of our hospital. Two additional patients (Patients 2 and 3) suffering from PRES who were admitted to other hospitals, developed intractable epilepsy and a single seizure, respectively, and visited the epilepsy clinic of our hospital.

3.2. Clinical features of patients in the acute phase of PRES

The clinical data for the patient cohort are described in Table 1. All patients except for Patient 3 had acute symptomatic seizures. Four patients (Patients 1, 2, 5 and 6) had convulsive or nonconvulsive SE. Patient 1 had recurrent episodes of deviation of the head and eyes to the right and hand automatisms without responsiveness for one day. Patient 2 showed a continuous state of the head and eyes to the right or motionless staring without responsiveness for 4 h. In Patient 5, recurrent episodes of deviation of the head and eyes to the right and clonic movements of bilateral shoulders (more prominent in the right side) with intermittent generalization were found in a state of persistent deterioration of consciousness for 2 days.

Acute phase MRI revealed cytotoxic edema in five patients (except for Patient 2). The MRI of Patient 2 showed all lobar involvement predominantly in the left hemisphere on MRI without cytotoxic edema during the acute phase although the brain MRI scans were not available due to the disposal of the old data. Patient 6 developed four generalized tonic-clonic seizures for 1 h in the initial period of PRES, followed by recurrent episodes of eye and head deviation to the right side, intermittently evolving to convulsive movements of the right face and arm in the state of persistent deterioration of consciousness for a prolonged time. He received delayed and non-aggressive AED treatment. Frequent

Table 1
Clinical features during the acute phase of PRES.

Patient number		1	2	3	4	5	6
Sex/Age (years)		F/47	F/18	F/12	F/12	M/64	M/42
Medical history		Aplastic anemia, massive transfusion	Acute lymphoblastic leukemia, sepsis, granulocyte-colony stimulating factor, hypertension	IgA nephropathy, methylprednisolone (pulse), cyclophosphami-de, hypertension	Femur osteosarcoma, cisplatin, ifosphamide, adriamycin, acute renal failure, hypertension	Liver transplantation, sepsis, tacrolimus	Liver transplantation, tacrolimus
Acute symptomatic seizures		Nonconvulsive SE	Nonconvulsive SE	No seizure (headache and drowsy mental state)	Two GTCSs	Convulsive SE	Convulsive SE
MRI (Fig. 1)	Cytotoxic edema	Left parieto-occipito-temporal regions	Absent	Left parieto-occipital regions	Left hippocampus	Bilateral mesial frontal and left temporo-parietal regions	Left temporo-occipital regions
	Vasogenic edema	Right parieto-occipito-temporal regions	Multifocal involvement in bilateral cerebral hemispheres with left-sided dominance	Right parieto-occipital regions	Multifocal involvement in bilateral cerebral hemispheres	Right temporal and frontal regions	Right temporo-occipital and bilateral frontal regions, and pons
EEG		Repetitive ictal discharges and PLEDs in the left posterior region	NA	Posteriorly dominant diffuse slowing, more prominent in the left side	Diffuse background rhythm slowing with slower frequency and higher amplitude in the left side and intermittent PLEDs-like activity in the left posterior region	Recurrent ictal discharges in the left posterior quadrant region	PLEDs in the left posterior quadrant region, and continuous waxing and waning pattern of 1–1.5 Hz repetitive and periodic pattern of delta activities in the left hemisphere

Abbreviations: PRES, posterior reversible encephalopathy syndrome; F, female; M, male; SE, status epilepticus; GTCS, generalized tonic-clonic seizure; NA, not available; PLED, periodic lateralized epileptiform discharge.

seizures persisted for approximately 1 month although his high blood pressure was controlled, tacrolimus was temporarily stopped and then its dose was decreased. The MRI of Patient 6, performed 24 days after the initial MRI during the acute phase of PRES, showed a slight improvement of the lesions noted on the initial MRI; however, increases in the size or new lesions in the left temporo-occipital lobes (which exhibited cytotoxic edema on the initial MRI) were considered as seizure-induced changes superimposed on unresolved PRES (Fig. 1). Additional clinical information on Patient 1 was described in detail in our previous paper [11].

3.3. Clinical features of patients after the development of epilepsy

As shown in Table 2, the duration from PRES to the development of epilepsy varied and was within 1 year of the acute phase of PRES, except for Patient 3. Patient 3 who did not have acute symptomatic seizure or residual MRI changes, developed her first seizure 7 years after PRES. All patients, except for Patient 6, developed seizures in the absence of AED treatment. Patient 6 with prolonged SE and additional seizure-induced MRI changes during the acute phase developed habitual seizures immediately after PRES. Patient 1 had residual focal neurological deficits of the right homonymous inferior quadrantanopia and numbness in her right lower extremity. Patient 2 who underwent neuropsychological testing, had borderline or low-average verbal memory but better visual memory. Patient 6 complained of decreased memory function, difficulty finding words, and right homonymous hemianopsia. Follow-up MRI after epilepsy development showed focal atrophic changes including hippocampal sclerosis (HS) in four patients (Patients 1, 2, 4 and 6). Presumptive epileptogenic foci were located in the left-side temporal, parietal and occipital lobes, corresponding to the regions that showed cytotoxic edema (Patient 1, 3, 4, 5 and 6) or severe vasogenic edema (Patient 2) on MRIs as well as with the location or lateralization of EEG abnormalities during the acute phase.

Brain MRIs obtained during the acute phase and follow-up are shown in Fig. 1.

3.4. Seizure outcome

Patient 1 had experienced intermittent auras only or simple partial seizures over a period of 13 years and 3 months with phenytoin treatment, which began after a single secondarily generalized tonic-clonic seizure, and attained seizure freedom with levetiracetam treatment over the past 7 months. Patient 2 had visited our epilepsy clinic because of drug-resistant epilepsy for 10 years. She declined epilepsy surgery because of concerns about the risk of surgical treatment. She showed a significant

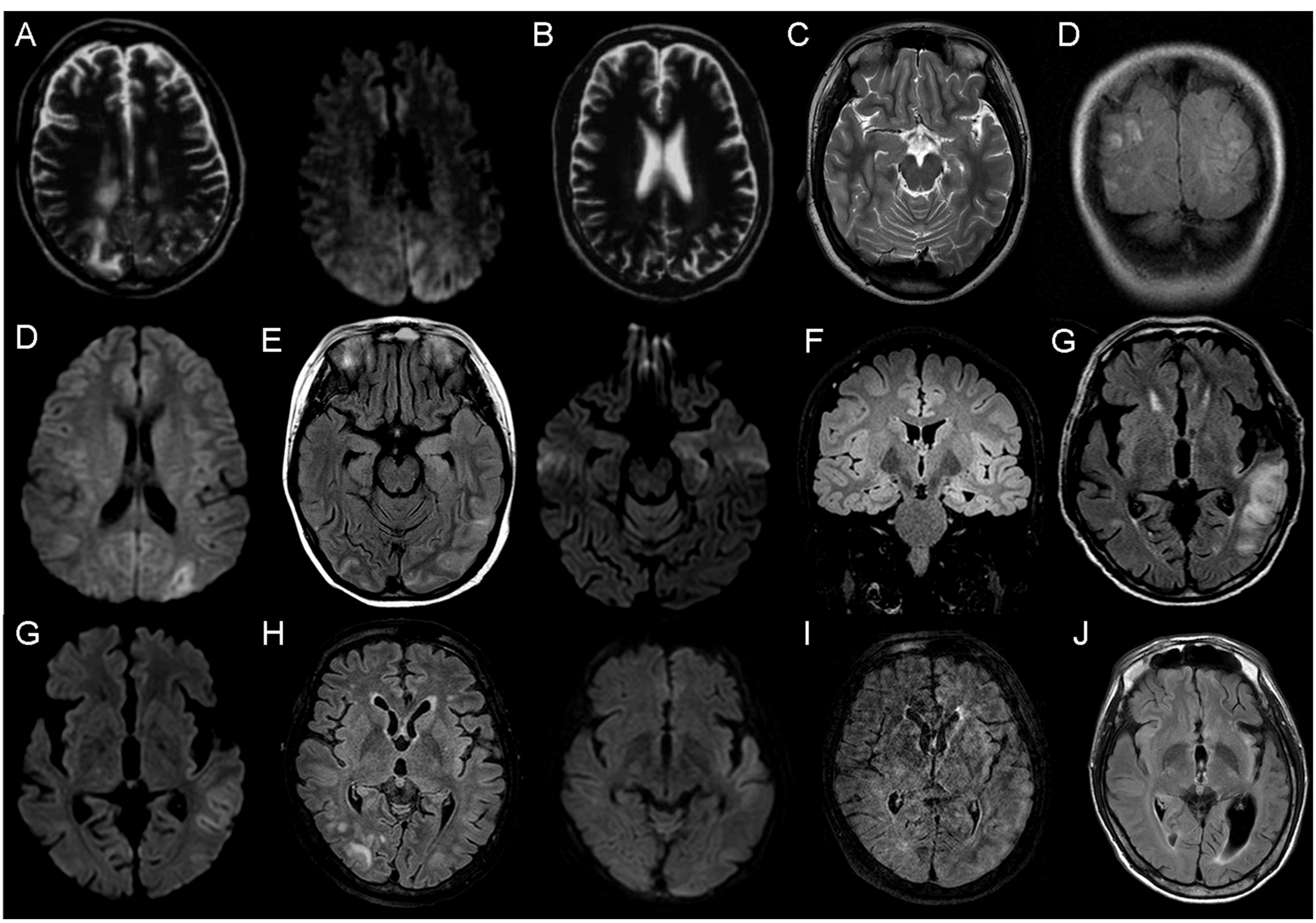

Fig. 1. Brain magnetic resonance images (MRIs) during the acute period and follow-up. (A) T2-weighted and diffusion-weighted (DW) images of Patient 1 with posterior reversible encephalopathy syndrome (PRES). Reproduced from reference [11] with permission from Karger. (B) T2-weighted image of Patient 1 after the development of epilepsy. Reproduced from reference [11] with permission from Karger. (C) T2-weighted image of Patient 2 after the development of epilepsy. (D) Fluid-attenuated inversion recovery (FLAIR) and DW images of Patient 3 with PRES. (E) FLAIR and DW images of Patient 4 with PRES. (F) FLAIR image of Patient 4 after the development of epilepsy. (G) FLAIR and DW images of Patient 5 with PRES. (H) FLAIR and DW images of Patient 6 with PRES. (I) FLAIR image of Patient 6, 24 days after the initial MRI. (J) FLAIR image of Patient 6, 2 years after the initial MRI. See Tables 1 and 2, and text for information.

Table 2
Clinical features after the development of epilepsy.

Patient number	1	2	3	4	5	6
Time to epilepsy after PRES	7 months	2 months	7 years	4 months	3 months	Since acute symptomatic seizures
Seizure semiology	Brief electric sensation involving the right extremities, intermittently with convulsive movements (a single GTCS)	Palpitation, dyspnea, visual blurring, dysphasia, eye blinking, and motionless staring	Visual hallucinations in the right visual field, alexia, and postictal throbbing headache in the left occipital region	Palpitation, motionless staring, and lip smacking, intermittently evolving to GTCS	Aphasic status with auditory comprehension difficulty, decreased verbal output, and paraphasic speech	Version to right and convulsive movements of right face and arm with loss of consciousness
EEG	Persistent small volume of slowing in left posterior region	Interictal: sharp waves in the left posterior temporal and occipital and mesial temporal regions Ictal: rhythmic theta activity in the left posterior temporal region	Normal	Left temporal sharp waves, maximum at nasopharynge-al and T1 electrodes and left temporal slowing	Frequent brief or prolonged episodes of rhythmic (about 1 Hz) sharply formed slow waves in the left hemisphere with temporal emphasis (during aphasic status)	Left temporal sharp waves maximum at T1 and T3 electrodes and delta slowing in the left hemisphere
Follow-up MRI (Fig. 1) (interval from initial MRI)	A focal infarction in the left medial occipital region and slight atrophic change in the left occipito-parietal regions (7 months)	Slight atrophic change of the left hippocampus and temporo-occipital regions (10 years)	Normal (7 years)	Left hippocampal sclerosis (5 years)	Normal (4 years)	Marked atrophic change in the left temporo-occipital regions and insular cortex (2 years)
Presumptive epileptogenic focus	Parietal lobe	Posterior temporal lobe	Occipital lobe	Mesial temporal lobe	Lateral temporal lobe	Lateral temporal lobe

Abbreviations: PRES, posterior reversible encephalopathy syndrome; GTCS, generalized tonic-clonic seizure.

improvement in seizure frequency and severity with further AED treatment (lacosamide, lamotrigine, topiramate and valproic acid) over the past 3 years and 10 months. Patient 3 had maintained seizure freedom over the past 3 years and 7 months with lamotrigine treatment, which began after a single seizure. Patient 4 had experienced intermittent complex partial seizures or auras only over the past 3 years and 9 months with AED treatment, which began after a single secondarily generalized tonic-clonic seizure; she attained seizure freedom with carbamazepine and topiramate treatment over the past 8 months. Patient 5 was diagnosed as having epilepsy after his second episode of aphasic status and had maintained seizure freedom with levetiracetam treatment over the past 5 years and 10 months. Patient 6 experienced monthly complex partial seizures over the past 3 years and 2 months with polytherapy (lamotrigine, levetiracetam, topiramate, and valproic acid).

4. Discussion

Our findings suggested that PRES may lead to the development of epilepsy in patients, particularly those with severe brain damage during the acute phase although there is a small risk of epilepsy for patients with PRES. In a nationwide population-based study from the National Health Insurance Research Database of Taiwan, the incidence of subsequent epilepsy was 2.25-fold higher in patients with hypertensive encephalopathy (HE) than in hypertensive patients without a history of HE (4.17 versus 1.85 per 1000 person-years), with an adjusted hazard ratio of 2.06 (95% confidence interval = 1.66–2.56) [12]. However, the study cohort only included patients with HE, did not include all patients with PRES and did not provide any detailed information on patients with epilepsy. In a retrospective study of 127 patients with PRES, whose median duration of follow-up was 3.2 years, three (2.4%) patients developed subsequent unprovoked seizures, and one of them had recurrent seizures and was considered to have developed epilepsy [2]. In another retrospective study of 75 patients with PRES, four (5.3%) patients had seizures later than one month beyond their hospitalization for PRES, and two of them developed chronic epilepsy [3]. These findings suggest that PRES may be associated infrequently with subsequent development of unprovoked seizures and epilepsy.

Our study had several significant limitations, including the patient population from a single center, the small number of patients, referral bias toward unusual or severe cases at a large tertiary hospital, insufficient capture of cases that might have led to an underestimation of patients with PRES or epilepsy subsequent to PRES, lack of a pediatric population, and a short follow-up period. Therefore, although the true incidence of the development of epilepsy following PRES could not be assessed accurately, we estimated the incidence of seizure or epilepsy following PRES to be 3.9%.

Six cases of temporal lobe epilepsy (TLE) with HS or occipital lobe epilepsy following PRES or HE have been reported [13–16]. One of the five patients with HS had cytotoxic edema in the left temporal lobe, including the mesial temporal structures on MRI obtained during the acute phase [14], as seen in Patient 4 in our study. One patient with HS did not have any MRI change in the hippocampus on MRI during the acute phase [16]. The other three patients with HS did not have an MRI performed during their acute disease [13]. One patient with occipital lobe epilepsy had two bilateral hematomas in the parieto-occipital region [15]. As well, a retrospective study investigated 26 female patients with HS who had no identifiable risk factors or seizures following pregnancy, and found that nine had a history of eclampsia [17]. This finding suggested that eclampsia might be a risk factor for TLE and HS, although information from MRIs that can be performed during the eclamptic episodes was not described.

Evidence of irreversible damage may not be detected in most of patients with PRES. However, cytotoxic edema and severe vasogenic edema, which occur in some patients with PRES, may suggest irreversible tissue damage that may or may not be detectable on follow-up MRI. In this study, cytotoxic edema was found in five out of six patients. Follow-up MRI showed focal atrophic changes including HS in four patients. Presumptive epileptogenic foci corresponded to the regions that showed cytotoxic edema on MRIs during the acute phase.

Also, the role of SE in potential irreversible brain injury should not be ignored. In this study, SE occurred in four patients. SE itself may contribute to cytotoxic edema, which was found in three patients. A previous report described the case of a boy who presented with PRES and nonconvulsive SE after the initiation of intrathecal methotrexate, who subsequently developed TLE with HS [14]. Initial MRI revealed a patchy, relatively symmetric, T2 signal increase in subcortical regions of the posterior portions of the cerebral and cerebellar hemispheres when the patient developed PRES symptoms with probably several (although the number of seizures was not described accurately) complex partial seizures on day 8 after the first dose of chemotherapy. Four days later the patient developed nonconvulsive SE along with increased blood pressure. Another MRI indicated extensive restriction of diffusion signal involving the entire left temporal lobe, including the mesial temporal structures, insular cortex and posterior thalamus. As seen in Patient 6, SE or frequent seizures related to delayed and non-aggressive treatment may contribute to brain damage. On the other hand, the degree of PRES itself may be an important factor for irreversible brain injury. Patients 4 and a previously reported patient [16] had just two generalized tonic-clonic seizures and probably several complex partial seizures, respectively, suggesting that PRES itself could produce HS. Irrespective of a lack of comparison with patients who did not develop epilepsy, our findings suggest that cytotoxic edema on MRI and SE during the acute phase may be risk factors for the development of epilepsy. Therefore, prompt control of acute symptomatic seizures associated with PRES, as well as general treatment strategies for PRES, such as reduction of high blood pressure, withdrawal or dose reduction of offending drugs, and control of other associated underlying conditions or diseases, is important for preventing the development of epilepsy.

Seizure outcome in patients with epilepsy following PRES may not be benign. In this study, long-term seizure freedom was attained in only two out of six patients, although an unfavorable prognosis may be related to referral bias.

5. Conclusion

In conclusion, the results of this study suggest that the risk of the development of epilepsy after PRES might be small but not insignificant, although this study had several significant limitations. The presence of cytotoxic edema on MRI and severe, acute symptomatic seizures, such as SE during the acute phase, may indicate and enhance irreversible brain damage and may predict the development of epilepsy. Additional large prospective studies are required to accurately determine the incidence of epilepsy following PRES and to identify biological markers predictive of epilepsy development.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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