Case Report

Immunosuppressive Drugs, an Emerging Cause of Posterior Reversible Encephalopathy Syndrome: Case Series

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Background: Posterior reversible encephalopathy syndrome (PRES) is a well-recognized complication of hypertensive encephalopathy. Recently, pre-eclampsia, connective tissue disorders, and immunosuppressive drugs have been reported to be the etiologies of this rare syndrome. *Methods:* We evaluated 9 cases of PRES whose diagnosis were confirmed based on clinical and radiologic evidence between July 2011 and December 2013 in a tertiary center, Imam Khomeini Hospital, Tehran, Iran. *Results:* Immunosuppressive drugs, especially cyclosporine, and hypertension were the main precipitating factors. In this study, seizure was the most common clinical presentation (100%), whereas other common clinical presentations were confusion (78%), visual loss (67%), and headaches (67%). With conservative management and elimination of predisposing factor, the patients improved gradually except for 2 cases who experienced prolonged recovery period because of delayed diagnosis. *Conclusions:* With timely diagnosis, PRES generally has a good prognosis with complete recovery. However, in missed conditions, it could be associated with catastrophic burden especially in organ transplantation after a prolonged time spending to find matched donors or in chronic immunosuppressive conditions. Thereupon, physicians should be aware of clinical and radiologic manifestations of this preventable but potentially disabling syndrome. **Key Words:** Posterior reversible encephalopathy syndrome—hypertension—immunosuppressive drugs—organ transplantation.

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiologic diagnosis developing in a setting of heterogeneous etiologies including hypertensive encephalopathy, eclampsia, and immunosuppressive drugs.[1,2] Despite a growing body of investigations in this area, its pathogenesis is a topic of debate. It usually presents with headache, confusion, visual impairment, and seizure secondary to cortical and subcortical vasogenic edema preferentially in parieto-occipital region. Hypertension is the well-known predisposing factor for PRES. However, immunosuppressive and cytotoxic drugs which recently have been used increasingly appears to become one of the main causes of PRES. Nonetheless, unfortunately, physicians generally have limited

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information about drug-related PRES. We introduced 9 cases of PRES that mainly happened in a setting of use of immunosuppressive drugs.

Patients and Methods

Patients with clinically diagnosed PRES were identified prospectively during their admission to Imam Khomeini hospital between July 2011 and December 2013.

We applied the following factors as definition of the syndrome and inclusion criteria for the patients: (1) neurologic manifestations including headache, encephalopathy, seizure, visual disturbance, or focal deficit; (2) evidence of focal vasogenic edema in brain imaging; and (3) reversibility of clinico-radiologic manifestations after elimination of precipitating factor.

Case Series

During a period of 28 months (July 2011 and December 2013), we diagnosed 9 cases of PRES, manifestations of which were summarized in Tables 1 and 2. Immunosuppressive drugs especially cyclosporine, in patients with a history of solid organ transplantation was the most common precipitating factor. In most cases, hypertension preceded clinical signs and symptoms (about 67%). In contrast to hypertension-related PRES, patients without evidence of severe hypertension (2 cases of cardiac transplantation on cyclosporine and 1 patient with a history of liver cirrhosis) developed slowly progressive headache, visual field defect, and psychiatric manifestations (especially visual hallucination) several days before seizure and other focal neurologic deficits. Nonetheless, the first neurologic consultation was requested for seizure control and evaluation of loss of consciousness.

Brain magnetic resonance imaging of all patients disclosed cortical and subcortical vasogenic edema (preferentially in parieto-occipital region) except for a case of rituximab-related illness (Figure 1, A,B,C). The latter patient (case 8) was a 52-year-old man with underlying disease of hypertension and intractable idiopathic thrombocytopenic purpura who developed headache and sudden onset blindness during infusion of second dose of rituximab. At this time, blood pressure was 185/105. First dose of rituximab was infused about 1 month before recent admission. After 10 minutes, he developed generalized tonic clonic seizure. Rituximab was discontinued immediately, and blood pressure well managed with labetalol. Seizure was treated with diazepam and phenytoin. Of interest, the patient achieved his vision within 2 hours without evidence of relapse of symptoms. Brain magnetic resonance imaging showed no pathologic change other than minimal abnormal signal intensity in subcortical white matter of right occipital lobe, which appeared to be old, and more importantly, did not explain patient's complaints (Figure 1, D). Probably, prompt therapeutic intervention (rituximab discontinuation and timely management of hypertension) stopped progression of endothelial leakage and development of vasogenic edema and thereby radiologic manifestations of disease.

Seizures mainly were controlled with diazepam and phenytoin. We prescribed levetiracetam because of intractable seizure for one of the patients with cyclosporine-related PRES (case 5) and in a patient with underlying liver cirrhosis (case 9). Antiepileptic drugs were discontinued after resolution of brain pathology. Likewise, in patients with cyclosporine-induced PRES, cyclosporine was replaced with tacrolimus.

All patients other than cases 5 and 9, who have been associated with worse prognosis because of delay in diagnosis, improved during 2 weeks. Case 5 was a 42-year-old man, a case of heart disease and cardiac transplantation, who developed PRES in a setting of cyclosporine consumption. He had complained of visual impairment and headache since 2 weeks before the first neurologic consultation that was requested because of recurrent seizure and left hemiparesis. Seizures were controlled with levetiracetam. Cyclosporine was substituted with tacrolimus. However, the patient had a prolonged recovery time. He suffered from visual field defect and left hemiparesis for several weeks. Case 9 was a 53-year-old woman a known case of end stage cryptogenic cirrhosis who was in relatively good health until 2 weeks before admission when presented with headache, mild visual disturbance, visual hallucination, and confusion associated with repeated focal and generalized tonic clonic seizure. She was referred to gastroenterology ward with impression of hepatic encephalopathy. Brain Fluid-Attenuated Inversion Recovery and T2-weighted imaging disclosed diffuse cortical and subcortical hypersignal intensity with preferential involvement of parieto-occipital lobes characteristic for PRES (Figure 1, C). PRES diagnosis delayed because of similarities between clinical manifestations of PRES and hepatic encephalopathy. This patient had worse prognosis with prolonged recovery period, too.

In this study, all patients were followed for 1 year. No evidence of relapse was detected.

Discussion

Hinchey et al[1] described PRES for the first time as hypertension-related neurologic complication. Despite its deceptive name, even with timely diagnosis, PRES may be associated with irreversible sequels and is always not limited to posterior white matter region.[2] Its pathophysiology is a topic of debate; so far, several aspects of its pathogenesis remained to be elucidated. According