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BRIEF REPORT

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Reversible posterior leukoencephalopathy in a patient with Wegener granulomatosis

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Abstract A 14-year-old girl with rapidly progressive glomerulonephritis was transferred to our hospital because of acute renal failure. A diagnosis of Wegener granulomatosis was made according to the symptom triad of a renal biopsy demonstrating crescentic glomerulonephritis, severe sinusitis, and serological findings of raised proteinase 3 anti-neutrophil cytoplasmic antibody level. In spite of combination therapy with methylprednisolone, cyclophosphamide, and plasma exchange, her renal function gradually deteriorated. Thereafter, she suffered a severe headache and generalized seizures. Brain computed tomography (CT) scan revealed bilateral low-density areas in the parieto-occipital lobes. Magnetic resonance imaging (MRI) disclosed a high-intensity area on T2-weighted images and a low-signal intensity area on T1-weighted images in the same lesion. Follow-up brain CT scan 3 weeks and MRI 2 months after the first studies showed complete resolution of the abnormal lesions, which indicated reversible posterior leukoencephalopathy syndrome. In addition to renal failure, hypertension, and cyclophoshamide, the primary disease may have played a role in the development of this uncommon syndrome in our patient.

Keywords Hypertension · Chronic renal failure · Reversible posterior leukoencephalopathy syndrome · Wegener granulomatosis · Anti-neutrophil cytoplasmic antibody

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Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare neurological syndrome characterized by headache, altered mental status, seizures, and visual disturbance, associated with reversible white matter changes [1]. It has been commonly reported in patients with severe hypertension and pre-eclampsia [1, 2, 3]. To date, there are only a few cases of RPLS with systemic vasculitis. We report a patient with Wegener granulomatosis (WG) complicated by RPLS.

Case report

Recurrent polyarthritis involving the knees and ankles developed in a 14-year-old girl without a previous history of neurological manifestations. Two weeks after the first manifestation, she was admitted to a local hospital with a tentative diagnosis of post-streptococcal acute glomerulonephritis. She had no fevers and no respiratory symptoms or signs. On admission to the hospital, laboratory studies revealed a blood urea nitrogen (BUN) of 60.9 mg/dl and serum creatinine 3.0 mg/dl. Eleven days later, she was referred to our hospital for further evaluation and treatment.

Her clinical course in our hospital is shown in Fig. 1. On admission to our hospital, physical examination showed several erythematous lesions in the second and third proximal interphalangeal joints and her blood pressure was 90/40 mmHg. Laboratory studies revealed a serum sodium of 139 mEq/l, serum potassium 4.1 mEq/l, serum chloride 103 mEq/l, BUN 80.1 mg/dl, serum creatinine 6.0 mg/dl, bicarbonate 24.1 mmol/l, serum creatine kinase 63 U/l, and C-reactive protein 1.9 mg/dl. The levels of proteinase 3 anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor, and anti-nuclear antibody were more than 500 U/ml (normal, less than 3.5 U/ml), 576 IU/ml, and 1:320, respectively. Serum anti-glomerular basement membrane antibody, anti-DNA

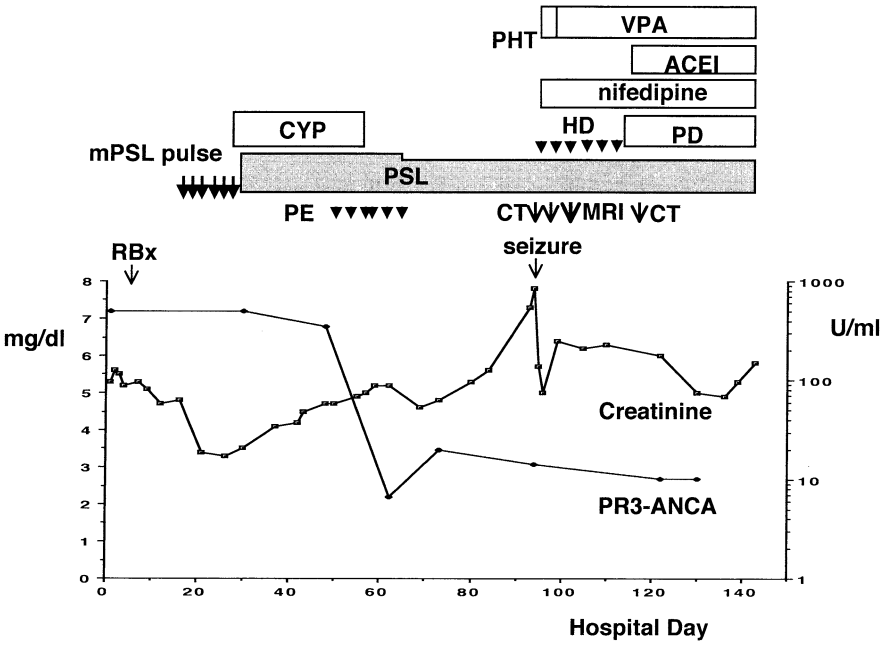

Fig. 1 Clinical course of the patient in our hospital. (*mPSL* methylprednisolone, *PSL* prednisolone, *CYP* cyclophosphamide, *PE* plasma exchange, *ACEI* angiotensin-converting enzyme inhibitor, *PHT* phenytoin, *VPA* valporate sodium, *HD* hemodialysis, *PD* peritoneal dialysis, *CT* computed tomography, *MRI* magnetic resonance imaging, *RBx* renal biopsy, *PR3-ANCA* proteinase 3 anti-neutrophil cytoplasmic antibody)

antibody, anti-Sm antibody, anti-SS-A antibody, anti-SS-B antibody, myeloperoxidase ANCA, and cryoglobulin were all negative. The urine gave a 2+ test for protein; the sediment contained 50–100 red blood cells per high-power field and red blood cell casts. She underwent a renal biopsy, which demonstrated diffuse and global fibrous or fibrocellular crescents. Although chest computed tomography (CT) failed to show any abnormality, severe chronic sinusitis was confirmed clinically and radiographically. Therefore, a diagnosis of WG was made. She received intravenously six pulses of methylprednisolone at a dose of 1,000 mg, followed by oral prednisolone (1 mg/kg body weight per day) and oral cyclophosphamide (2 mg/kg body weight per day), with little effect. Cyclophosphamide was withdrawn at 6 weeks because of leukopenia and diffuse alopecia. Thereafter, her renal function deteriorated gradually in spite of six sessions of single plasma exchange.

On the 94th hospital day, she developed a severe headache and her blood pressure was 180/92 mmHg. She was treated successfully with nifedipine. The following day she experienced sudden generalized tonic-clonic seizures seven times and became lethargic. The seizures were treated successfully with intravenous diazepam. At that time, she was afebrile and her blood pressure was 158/100 mmHg. Laboratory studies revealed a serum creatinine of 7.8 mg/dl, BUN 126.1 mg/dl, and hemoglobin 7.2 g/dl. Blood glucose, electrolytes, and bicarbonate were in the normal range. Cerebrospinal fluid examination showed no abnormality, with negative testing for myelin basic protein. Thus, she underwent emergency hemodialysis with a tentative diagnosis of uremic encephalopathy. Although emergency brain CT scan failed to reveal any abnormal findings, brain CT scan 2 days later disclosed bilateral low-density areas in the parieto-occipital lobes. Magnetic resonance imaging (MRI) showed a high-signal intensity area on T2-weighted fluid-attenuated inversion-recovery images and a low-signal intensity on T1-weighted images in the same lesions (Fig. 2A). Electroencephalography conducted 1 month after the first seizure showed diffuse slow activity without any sharp wave. Phenytoin was given intravenously for 7 days after the first seizure, followed by per os valproate. Follow-up CT scan at 3 weeks and MRI at 2 months (Fig. 2B) after the first studies showed complete resolution of the abnormal lesions in the bilateral parieto-occipital lobes, which was compatible with the diagnosis of RPLS. She gradually recovered consciousness and had no additional episodes of convulsions. No neurological abnormality was present and her blood pressure was well controlled with nifedipine and an angiotensin-converting enzyme inhibitor when she left our hospital on peritoneal dialysis 3 months after the first seizure.

Discussion

RPLS has been characterized by headache, altered mental function, seizures, and visual disturbance, associated with reversible white matter lesions, predominantly in the posterior region of the cerebral hemispheres on brain CT scan or MRI [1]. The cause of this syndrome remains unknown. However, the rapid resolution of clinical and neuroradiological abnormalities suggests that cerebral edema, caused by impaired cerebrovascular autoregulation and endothelial injury, is the main pathophysiological mechanism. Mukherjee and McKinstry [2] reported 12 cases with RPLS, including 2 cases of lupus nephritis, 2 of thrombotic thrombocytopenic purpura, 1 of acute renal failure, 1 of end-stage renal disease, 1 of eclampsia, 1 of focal segmental glomerulosclerosis, and 3 of ciclosporine administration. Of the 12 cases, 11 manifested with mild-to-severe hypertension. It is likely that hypertension played a major role in the pathogenesis in these patients.

Patients with end-stage renal disease have a dysfunction in vasopressor homeostasis and endothelial function related to elevations in lipoproteins, blood pressure, uremia, and as a result of drug therapy. Therefore, end-stage renal disease is also an important factor in RPLS. RPLS has also been reported after administration of ciclosporine, tacrolimus, and cytotoxic agents, which may have a direct toxic effect on the cerebral vasculature [4, 5]. Thus, our patient also had several known causative factors, i.e., renal failure and increased blood pressure, together with recent chemotherapy.

To our best knowledge, the patient we present here is the first clinically and radiographically demonstrated case

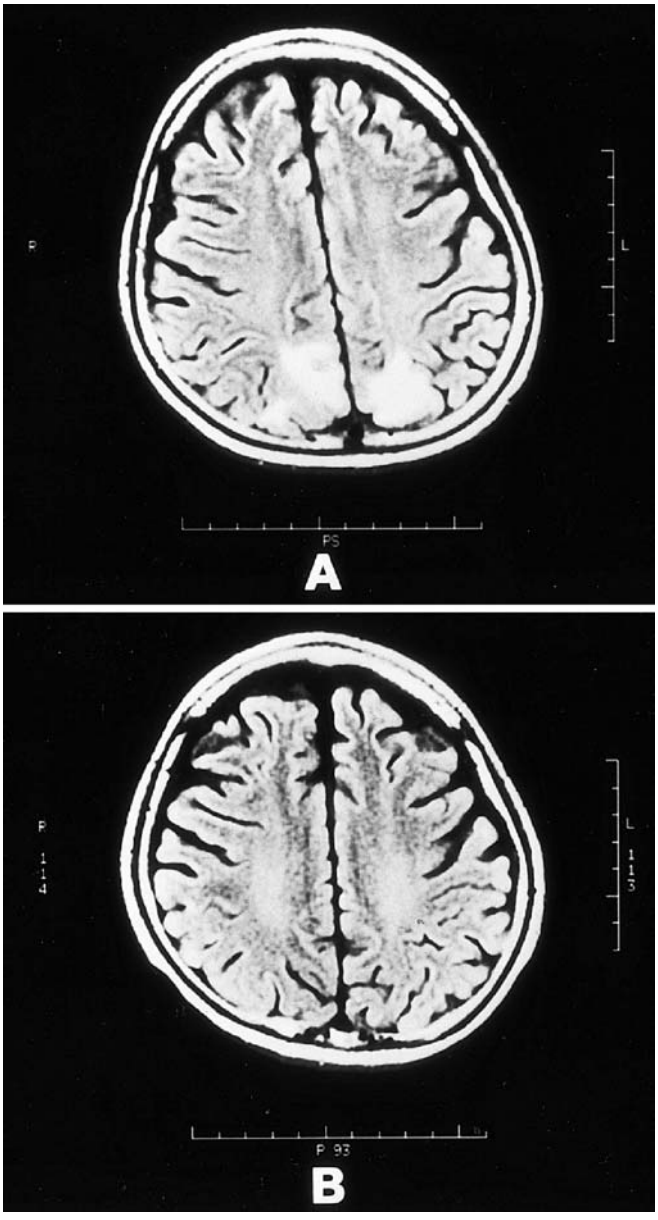

Fig. 2 T2-weighted MRI scans. **A** Areas of hyper-intense signals on T2-weighted fluid-attenuated inversion-recovery images involving parieto-occipital lobes bilaterally. The follow-up MRI (**B**) reveals the complete resolution of abnormal signals

of RPLS associated with WG. The central nervous system has rarely been affected in patients with WG in the literature. In two large pediatric series of WG, seizure was noted in 2 of 40 patients [6, 7]. In the largest series of WG, central nervous system abnormalities, which included stroke, cranial nerve abnormalities, and diabetes insipidus, occurred in 8% of patients [8]. However, it is unclear whether thorough neuroimaging studies were conducted in these patients. Recently, with the widespread use of MRI, RPLS is becoming more common. Some of the above patients might have been misdiagnosed because RPLS may have been overlooked with only an emergency CT evaluation. It is likely that WG played a role in the progression to RPLS in our patient because the serum from patients with WG contains ANCA, which can activate neutrophils and cause endothelial cell injury [9]. In general, the important points of successful treatment for WG are early diagnosis and early intense immunosuppressive therapy, including several cytotoxic agents [9]. Moreover, Ellis et al. [10] suggested that pediatric patients with WG had rapid progression to end-stage renal disease. Therefore, RPLS should be considered in patients, especially pediatric patients, with end-stage renal disease due to systemic vasculitis, including WG.

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