CASE REPORT

Generalised reversible encephalopathy syndrome: a variant of posterior reversible encephalopathy syndrome (PRES)

Julia Kunzmann, Hubert Wolf, Stefan Oberndorfer

Department of Neurology,
University Clinic St Pölten, KLI-
Neurology and
Neuropsychology, St Poelten,
Austria

Correspondence to
Professor Stefan Oberndorfer,
Stefan.Oberndorfer@stpaelten.
lknoe.at

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SUMMARY

Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiological syndrome characterised by headache, visual disturbance, seizures and altered consciousness. Radiological findings show hyperintense T2-lesions on MRI, predominantly located in the subcortical white matter of the posterior occipital and parietal lobes. We report the case of a 74-year-old woman with adenocarcinoma of the gastric cardia who developed severe neurological signs and symptoms. MRI of the brain showed atypical generalised hyperintense lesions on T2 and fluid-attenuated inversion recovery sequences. Under symptomatic treatment, the radiological changes as well as neurological signs and symptoms improved. Several potential risk factors for PRES, such as hypertensive crisis, blood transfusions, infection and cancer, were identified in our patient, whereby perhaps the coexistence of these risk factors led to the unusual radiological and clinical manifestation of a generalised PRES variant.

BACKGROUND

Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiological condition.¹ Clinical manifestation is characterised by headache, visual disturbance, alteration of consciousness and seizures.¹⁻³ Seizures are often the presenting symptom; these can occur in series and are mostly generalised tonic-clonic.⁴ Other neurological signs such as paresis are uncommon.² The classical imaging findings on MRI are hyperintense lesions on T2 sequences and fluid-attenuated inversion recovery (FLAIR), predominantly located in the subcortical white matter of the posterior occipital and parietal lobes.^{1 5 6} MRI manifestation of PRES can also occur in atypical locations involving the cerebellum, brainstem, basal ganglia, deep white matter and the cortex.³

Diagnosis of PRES can only be established in the case of concordant clinical and radiological findings.¹ While the exact pathogenesis remains unclear, several causes and risk factors are known, including hypertension, pre-eclampsia, renal failure, severe infection/sepsis, immunosuppressive therapy and autoimmune diseases.^{3 7 8} Treatment of PRES is targeted at identifying and eliminating the potential underlying causes, as well as symptomatic management.^{1 9} In the majority of patients, symptoms completely resolve within a few weeks.^{1 10} We report a patient with generalised reversible encephalopathy syndrome resembling PRES, with severe neurological signs and symptoms.

CASE PRESENTATION

A 74-year-old woman was admitted to the department of internal medicine, with anaemia due to an adenocarcinoma of the gastric cardia with metastases to the abdominal lymph nodes and liver, which was diagnosed a few weeks previously. Prior to admission, she had received no antitumour treatment. Medical history revealed hypertonia, which was treated with propranolol, as well as a recent urinary tract infection, for which antibiotics (ciprofloxacin) were administered. Ciprofloxacin was switched to sulbactam/ampicillin 2×3 g parenterally due to ongoing elevated infection parameters (CRP 5.91 mg/dL; leucocytes: 11.3 G/L). The patient's blood pressure was reported to be normal to mildly elevated on admission.

Owing to anaemia (haemoglobin: 7.0 g/dL), the patient received 2 units of packed red blood cells and major bleedings were ruled out as possible causes of blood loss.

On day 5 after admission, the patient experienced a generalised tonic-clonic seizure. Within the next 24 h, she had a series of complex-focal seizures. At this time, physical examination revealed fever (39.2°C), atrial flutter (160 bpm) and severe hypertension (200/100 mm Hg). Neurological examination showed a somnolent patient with homonymous hemianopsia, flaccid tetraparesis with hyporeflexia and a positive Babinski sign on both sides. Laboratory findings exhibited mild renal and liver failure (serum creatinine: 1.18 mg/dL; blood urea nitrogen: 17.4 mg/dL; aspartate aminotransferase: 87 U/L; alanine transaminase: 50 U/L; lactate dehydrogenase: 713 U/L; γ-glutamyl transpeptidase: 537 U/L; alkaline phosphatase: 381 U/L; serum albumine: 3.6 g/dL) mild anaemia (haemoglobin: 11.6 g/dL) and elevated infection parameters (C reactive protein: 6.62 mg/dL, leucocytes: 12.8 G/L).

CT imaging of the brain showed diffuse, bihemispheric white matter hypodensity. MRI demonstrated widespread, almost symmetric, hyperintense lesions, predominantly in the white matter on fluid attenuated inversion recovery (figure 1). Diffusion-weighted imaging showed no evidence of infarction and imaging with gadolinium showed no pathological enhancement. Based on radiological findings and neurological signs and symptoms, PRES was diagnosed and the patient was transferred to the department of Neurology. At this time, her neurological condition was unchanged.

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Figure 1 Brain MRI. Development of multiple, generalised hypertense lesions on axial fluid-attenuated inversion recovery (FLAIR) at diagnosis, at day 10 and day 20.

DIFFERENTIAL DIAGNOSIS

1. MRI changes possibly caused by seizures.
2. Progressive Multifocal Leukoencephalopathy.

TREATMENT

Initial treatment comprised of antihypertensive therapy with intravenous application of urapidil as well as antiepileptic

therapy with levetiracetam and clobazam. Antibiotic therapy was changed to meropenem 3×1 g per day, which finally proved clinically effective.

Although cerebrospinal fluid examination was unremarkable, due to the unusual generalised appearance of leucoencephalopathy, the patient received corticosteroids for possible immune-mediated leucoencephalopathy syndrome.

OUTCOME AND FOLLOW-UP

Within a few days, concurrently with the normalisation of blood pressure, the patient's impairment of consciousness as well as the flaccid tetraparesis improved. Follow-up MRI performed at days 10 and 20 also showed improvement of hyperintense lesions on FLAIR (figure 1). Based on the clinical and radiological development, the diagnosis of PRES was reinforced. The patient was discharged 21 days after the onset of neurological symptoms. She was alert and fully oriented, with persistent mild to moderate tetraparesis and normal blood pressure. The patient died 11 days later due to adenocarcinoma of the gastric cardia. No autopsy was performed.

DISCUSSION

This case study reports an unusual generalised reversible encephalopathy syndrome. Although the diagnosis resembles PRES, possible synergistic factors contributing to the unusual and generalised presentation should be discussed.

In PRES, hyperintense lesions are predominantly located in the subcortical white matter of the posterior occipital and parietal lobes.^{1 5} Despite its name, as a 'posterior' encephalopathy syndrome, PRES can also occur in atypical locations. While involvement of the frontal lobe and cerebellum are commonly reported, the brainstem, cortex, basal ganglia and deep white matter are less frequently affected.^{3 5} A detailed list of site-dependent frequencies of MRI changes in PRES is reported by McKinney *et al*⁶: posterior frontal, 78.9%; temporal, 68.4%; thalamus, 30.3%; cerebellum, 34.2%; brainstem, 18.4%; and basal ganglia, 11.8%. In the present case, MRI of the brain showed generalised, widespread hyperintense FLAIR and T2-lesions involving the occipital, temporal, parietal and frontal lobes, as well as the cerebellum, pons and splenium.

The association between PRES and arterial hypertension is well documented,^{1 2 8} although patients without hypertension are also reported to develop PRES.^{5 6} Seventy to eighty per cent of patients with PRES present with hypertension at time of symptom onset.^{2 3} Although our patient presented mild hypertension during the previous days, blood pressure was only severely elevated at the time of symptom onset. Under intravenous hypertensive therapy, clinical symptoms, especially consciousness, improved, as did radiological findings. Several studies showed that T2-hyperintense lesions are more extensive in patients with normal blood pressure compared to those with severe hypertension.^{7 11} In our patient, we found generalised T2 hyperintensity, meaning that hypertensive crisis was probably not the major underlying cause.

Bartynski *et al*⁷ showed an association between PRES and infection, sepsis and shock, occurring 2 weeks after bacteraemia or organ/tissue infection. Prior to admission, our patient was treated with ciprofloxacin due to a urinary tract infection. At the time of the clinical manifestation of PRES, she presented with fever, and laboratory findings revealed elevated parameters of infection. Although no focus could be found, antibiotic therapy was changed at the same time as when intravenous anti-hypertensive therapy was initiated. Therefore, a possible association between clinical and radiological improvement after antipyretic as well as antibiotic treatment may also be considered.

The patient also received 2 units of packed red blood cells due to anaemia. The literature also suggests an association between blood transfusion followed by PRES.^{12 13} All reported cases affected patients with chronic anaemia who received a large volume of blood within a short time, whereby

haemoglobin increased by about 5 g/dL. In all cases, PRES occurred 2–7 days after blood transfusion. In our case, the patient received a lesser volume and the haemoglobin level only increased by 3 g/dL. Despite the small volume, blood transfusion may have triggered the development of PRES, coexisting with other risk factors such as hypertension and infection.

Chemotherapy is a well-documented risk factor of PRES.^{2 9} Moreover, tumour lysis syndrome and hypercalcaemia due to cancer have been reported as risk factors for PRES.^{14 15} Our patient received no anticancer treatment, while serum-calcium was also normal. It remains unclear whether there is a correlation between PRES and malignancy by itself.

Transient MRI changes after seizures, such as contrast enhancement, increased T2 fluid-attenuated inversion recovery and diffusion weighted imaging, have been reported.^{16 17} These MRI changes are often cortically accentuated, and have a more unilateral distribution and involvement of hippocampal structures; also, an association with meningeal enhancement is reported.^{16–18} To what extent the initial series of complex partial seizures in our patient contributed to the signal changes on MRI remains unclear. However, the characteristics of MRI changes due to seizures show a different pattern as compared to the generalised MRI changes predominately in the white matter without meningeal contrast enhancement in our patient.

Another differential diagnosis is the progressive multifocal leucoencephalopathy syndrome (PML). PML typically shows widespread, asymmetric, hyperintense T2-lesions and FLAIR-lesions of the white matter, especially in parieto-occipital and frontal lobe.^{19 20} PML is usually associated with an immunosuppressive state and shows, in contrast to our case study, a clinical and radiological progression.^{19 21}

Learning points

- Posterior reversible encephalopathy syndrome (PRES) can also occur in atypical locations.
- Several risk factors can cause PRES.
- The coexistence of several risk factors may lead to unusual clinical and radiological findings of PRES.

Contributors JK is the author of the case report. HW is co-author. SO is senior author and corresponding author.

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