

ORIGINAL ARTICLE

## Recurrent posterior reversible encephalopathy syndrome in mitochondrial disorder

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### Abstract

**Objectives.** Recurrent posterior reversible encephalopathy syndrome (PRES) has not been reported in association with multi-system mitochondrial disorder (MID). **Case report.** In a 60-year-old HIV-negative, Caucasian female with short stature, double vision, struma, memory impairment, chronic renal failure requiring hemodialysis, seizures, intermittent atrial fibrillation, arterial hypertension, hyperlipidemia, anemia, hypacusis, tinnitus, and a daughter with multiple sclerosis, short stature and hypothyroidism, another daughter with schizophrenia, and a son who died from encephalopathy at age 3 months, an MID was suspected. At age 53 years, she experienced sudden, transient blindness for 2 days bilaterally during an episode of high blood pressure with complete recovery within 2 weeks. At age 60 years, a similar episode occurred. Four weeks later, she experienced a third PRES episode with high blood pressure, seizures, impaired consciousness and reversible blindness for 2 days. MRI at the second episode was indicative of a PRES, and MRI at the third episode additionally revealed occipital bleedings, acute embolic stroke and features indicating PRES. **Conclusions.** This case indicates that MID may be associated with recurrent PRES, triggered by recurrent episodes of high blood pressure. Whether high blood pressure was a manifestation of the MID or related to other causes remains speculative. PRES does not seem to be a primary but is rather a secondary manifestation of an MID.

**Key Words:** Blood pressure, encephalomyopathy, MELAS, metabolic myopathy, multi-system disease, neuromuscular disorder, stroke

### Introduction

Mitochondrial disorders (MIDs) are progressive conditions, affecting a single or multiple organs, depending on the stage of the disease. The organs most frequently affected are the central and peripheral nervous system (1). Central nervous system manifestations of MIDs include primary manifestations, such as stroke-like episodes, cognitive impairment, epilepsy, pyramidal and extra-pyramidal disorders, or secondary manifestations. Posterior reversible encephalopathy syndrome (PRES) is an increasingly recognized condition, most frequently triggered by long-term elevation of blood pressure and predominantly affecting the posterior cerebral circulation (2). Recurrent PRES has not been reported in association with an MID.

### Case report

The patient is a 60-year-old HIV-negative, Caucasian female, height 154 cm, weight 82 kg, with a history of recurrent herpes genitalis infections, and lichenoid condylomata and fibroma at the labia majora and perianally from age 20 years; arterial hypertension and hyperlipidemia from age 20 years; hypacusis and tinnitus mainly on the left side from age 25 years; conization at age 30 years for a Papanicolaou smear IV; hepatosplenomegaly related to steatosis hepatis in the absence of an alcohol history from age 40 years; paroxysmal atrial fibrillation from age 40 years; myalgias from age 40 years; struma without requiring substitution or suppression therapy from age 48 years; recurrent double vision from age 50 years; increasingly impaired memory from age 50 years; sudden, transient confusion

and blindness for 2 days bilaterally during an episode of high blood pressure and complete recovery within 2 weeks at age 53 years, retrospectively interpreted as first PRES episode; chronic renal failure of unknown etiology from age 55 years, requiring chronic hemodialysis from age 55 years; secondary hyperparathyroidism; anemia from at least age 57 years, occasionally requiring blood transfusions; depression from at least age 57 years; a first tonic clonic seizure at age 57 years without initiation of a long-term therapy with anti-epileptic drugs; disc prolapse L4/5 from at least age 59 years without requiring surgery so far; recurrent muscle cramps enhanced after dialysis from age 59 years; and spondylodiscitis L3/4 at age 60 years, for which she received vancomycin and long-term meropenem with success. Four weeks prior to the actual admission, she experienced a second episode of a PRES syndrome, this time manifesting as confusion and impaired vision during a prolonged episode of arterial hypertension. MRI of the cerebrum showed spot-like and garland-like T2-hyperintensities of the subcortical U-fibers, most extensively in the parieto-occipital regions bilaterally, without other abnormalities. PRES was diagnosed upon the clinical presentation, the radiological findings and the transient nature of the abnormalities. Her family history was noteworthy for a son, who had died 3 months after birth from “acute encephalopathy of unknown etiology”, for a daughter who was said to suffer from “multiple sclerosis” and was of short

stature (160 cm) and had hypothyroidism, for a second daughter, who was said to suffer from “schizophrenia”, and for a third daughter with anemia.

At age 60 years, she was admitted after a series of tonic clonic seizures, associated with prolonged disturbed consciousness and severe arterial hypertension up to 260 mmHg systole, requiring urapidil, nitroglycerin and labetalol (Figure 1). Under this regimen, high blood pressure partially resolved, but the patient remained soporous. Seizures were successfully stopped by valproic acid. Serum sodium on admission was 124 mmol/l (*n*, 136–145 mmol/l) and there was anemia. At the intensive care unit, the patient developed tachycardious atrial fibrillation, for which she received sedacorone and digitalis, with success. A CT scan of the cerebrum showed a single occipital bleeding on the right side. MRI of the cerebrum a few hours later, however, showed several bleedings in both occipital lobes, two acute ischemic lesions, and vasogenic edema predominantly over the occipital lobes (Figure 2). Since the patient developed high fever and remained soporous, a lumbar puncture was carried out revealing normal cell count, increased CSF lactate of 2.88 mmol/l (*n*, 0–2.1 mmol/l), and increased CSF protein but otherwise normal values. Two days after the seizure, the patient awoke but complained about visual loss bilaterally. After another 3 days, vision progressively improved. Some days after the seizures, she again developed

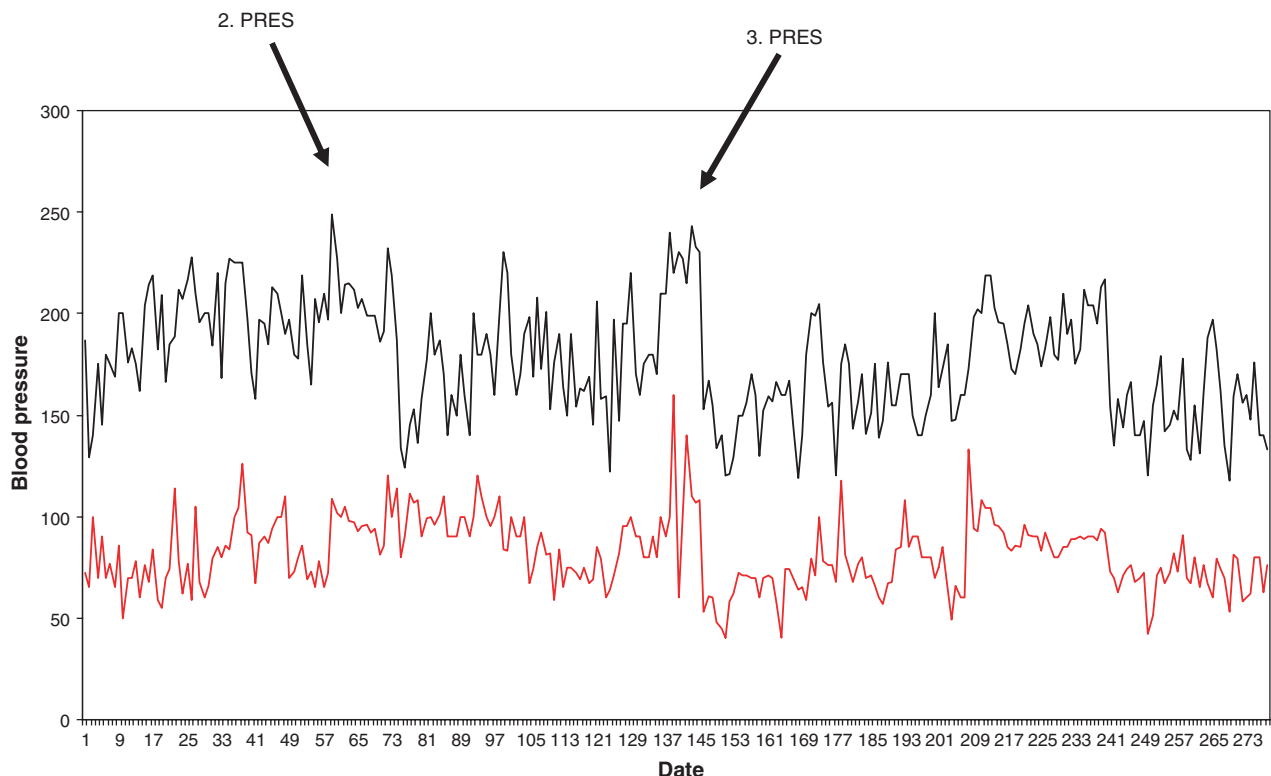


Figure 1. Course of blood pressure during admission at which the third PRES episode occurred. The data show that blood pressure was particularly high when PRES became symptomatic.

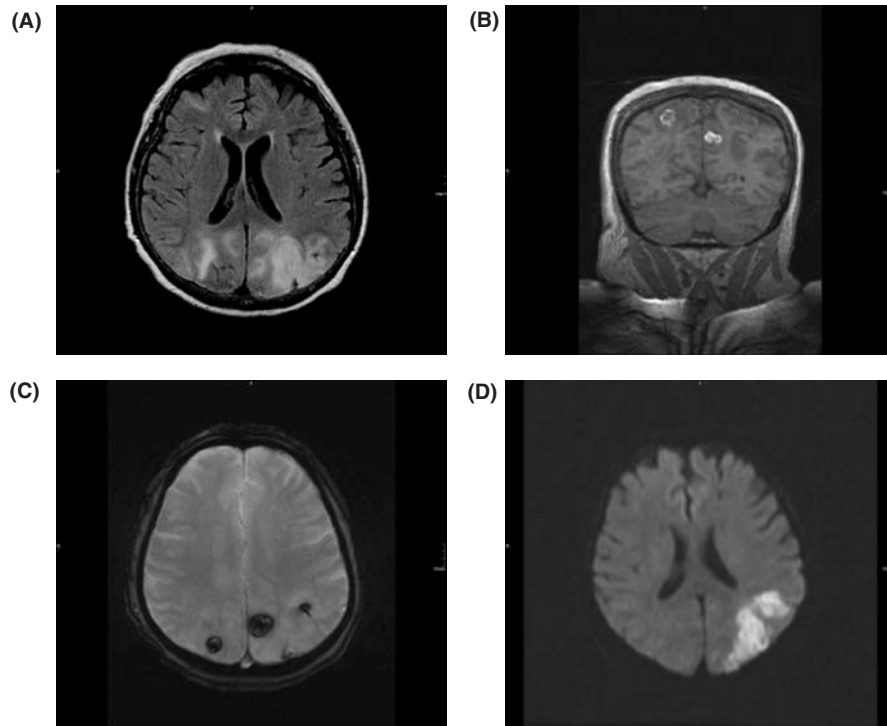


Figure 2. MRI of the cerebrum at the third PRES episode showing cortical and subcortical hyperintensities in the occipital regions on FLAIR, which were hyper-intense on ADC and hypo-intense on  $b=1000$  (A). Bleeding in the occipital regions was visible on T1-weighted (B) and T2-weighted images (C). During episodes of altered vigilance a few days later, diffusion weighted imaging ( $b=1000$ ) showed a hyper-intensity in the left posterior border-zone (D), being interpreted as ischemic stroke.

impaired vigilance. Cerebral MRI this time revealed an extensive hyperintensity on T2-weighted images over the left parieto-temporo-occipital region, sparing the cortex, and an acute left-sided, posterior border-zone infarction. Clinical neurologic examination after recovery from the third PRES episode revealed a fully alert patient with facial dysmorphism, hemianopsia to the left, bilateral ptosis, hypacusis, diffuse weakness M4– to M4 with right-sided predominance, absent deep tendon reflexes, bilateral dysmetria on the upper limbs, and on the lower limbs diffuse weakness M4 to M4+, wasting of the thighs, and absent deep tendon reflexes. Based upon the history and clinical findings, an MID was suspected in addition to the PRES. The electroencephalogram (EEG) days after the seizures showed continuous theta–delta activity over the left hemisphere and sharp waves over the left fronto-temporal projections, which was why valproic acid was increased. Visually evoked potentials were slightly abnormal on the left side. Within a few days, the patient regained her previous state without residual deficits from the actual episode. Cerebral MRI normalized with 3 weeks.

## Discussion

PRES is a clinically and radiologically transient condition related to vasogenic edema most frequently in the posterior circulation, which is often associated with high blood pressure, renal disease (3–7),

obstetric disease, such as pre-eclampsia and eclampsia (8,9), auto-immune disease (4), immunosuppressive medication, allogenic bone marrow transplantation, solid organ transplantation, alcohol withdrawal, anaphylaxis to contrast media, or high-dose cancer chemotherapy (10). Clinically, PRES manifests as seizures, altered mental state, headache, focal neurological deficits, visual disturbances or vomiting (11,12). Radiologically, PRES presents as occipito-temporal hypo-intensity on T1-weighted, hyper-intensity on T2-weighted and FLAIR images, as hypo-intensity on diffusion weighted images ( $b=1000$ ), and as hyper-intensity on apparent diffusion coefficient (ADC) (13). Atypical radiological findings in PRES include contrast enhancement, restricted diffusion or hemorrhage (14). Clinical and radiological abnormalities usually resolve within 1–4 weeks after onset (4).

The mechanism underlying the vasogenic edema is unknown but two main theories have been proposed (15): (i) severe arterial hypertension exceeding auto-regulatory limits with subsequent, forced hyperperfusion with endothelial injury and vasogenic edema or (ii) vasoconstriction and hypoperfusion leading to cerebral ischemia and subsequent vasogenic edema (10,11,15). According to the hypertension theory, PRES results from sustained high-grade fluctuations in blood pressure, leading to reduced cerebral vascular autoregulatory function with failure of compensatory vasoconstriction to prevent

hyperperfusion and fluid extravasation into the occipital lobes (16). An argument against the hypertension/hyperperfusion theory, however, is that there are number of patients who did not develop increased blood pressure during PRES. An argument for the vasoconstriction/hypoperfusion theory is that PRES is associated with a state of T-cell or endothelial cell activation that may be the basis of leukocyte trafficking and systemic/cerebral vasoconstriction (10). PRES has been also associated with vasculopathy resulting in reduced cortical regional cerebral blood flow within the PRES lesions (15). Although PRES is usually transient and completely reversible, ischemic injury and irreversible damage have been reported (12). In single cases, recurrent PRES has been described (6).

Though the cause of PRES in the described patient remains speculative, it could be attributed to arterial hypertension, kidney disease, or to the suspected MID. Arguments for arterial hypertension are that each of the three PRES episodes was associated with markedly elevated blood pressure and that blood pressure was badly controlled even between the PRES episodes. Whether autoregulatory functions are principally impaired in MID is unknown. So far, there are no indications that MID patients more frequently develop PRES than patients without an MID. It is not even known if PRES patients more frequently suffer from arterial hypertension than the normal population. However, impaired oxidative phosphorylation could also affect autoregulation of the cerebral vasculature and thus contribute to the pathogenesis of PRES. Whether the intravenous administration of nitroglycerin for lowering blood pressure enhanced or prolonged the PRES episode, as has been previously reported (9), remains speculative. Epilepsy was most likely a manifestation of the PRES syndrome, since the patient did not report seizures outside the PRES episodes and since epilepsy is a key feature of PRES in many patients. However, it cannot be definitively excluded that seizures were also a manifestation of the MID, since MIDs are frequently associated with epilepsy. Irrespective of the cause of seizures in the described patient, however, a long-term anti-epileptic therapy was initiated. Transient deterioration of vigilance was attributed to an acute left border-zone stroke, possibly relate to arterial hypotension during recovery from the third PRES episode.

This case indicates that MID may be associated with recurrent PRES, possibly initiated by recurrent episodes of high blood pressure or kidney failure. Whether high blood pressure was a manifestation of the MID or related to other causes remains speculative. Patients with PRES associated with elevated blood pressure require close blood pressure monitoring and tight pharmacological blood pressure regulation.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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