

# Spontaneous posterior fossa hemorrhage associated with low-molecular weight heparin in an adolescent recently diagnosed with posterior reversible encephalopathy syndrome: case report and review of the literature

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## Abstract

**Background** Posterior reversible encephalopathy syndrome (PRES) constitutes a well-described clinical entity, classically entailing characteristic edematous lesions on imaging studies in a patient with altered mental status, visual disturbances, headache, and seizures. PRES is reversible in the vast majority of cases, although progression to ischemia and hemorrhage has been documented.

**Methods** We report a case of a 16-year-old male with chronic renal failure who developed PRES during a hypertensive crisis. The hypertension was successfully managed and PRES-associated symptomatology showed complete regression. However, approximately 2 months later, the patient returned with a spontaneous posterior fossa hemorrhage. Two weeks before this second admission, treatment with low-molecular weight heparin had been initiated. The patient finally succumbed, despite surgical evacuation. The pertinent literature is reviewed.

**Conclusion** We suggest that the administration of low-molecular weight heparin in the setting of recent PRES might increase the risk for the development of intracranial hemorrhage.

**Keywords** Hemorrhage · Heparin · Low-molecular weight · Magnetic resonance imaging · Posterior fossa · PRES · Reversible encephalopathy

## Introduction

Posterior reversible encephalopathy syndrome (PRES) is a well-recognized clinical entity characterized mainly by headache, blurred vision, altered mental status, and seizures, along with typical imaging features, primarily in the territories of the brain supplied by the posterior circulation [1]. An associated factor, most commonly hypertension, is identified in the vast majority of cases.

Prompt treatment usually reverses the clinical symptoms and the radiological findings and the patients have an overall good prognosis. However, PRES may be complicated during its course by ischemia, infarcts, and less commonly, hemorrhage in the posterior fossa [2–4].

In our current communication, we present a case of a 16-year-old male with chronic renal failure, who developed a left cerebellar hemorrhage more than 2 months after the successful management of a hypertensive crisis complicated with PRES. The patient was started on low-molecular weight heparin 2 weeks before the incident. The possible association between anticoagulation in the setting of recent PRES and intracerebral hemorrhage is discussed and the pertinent literature is reviewed.

## Case report

A 16-year-old African American male with a history of chronic renal failure, due to focal glomerular sclerosis, presented with increasing headache, blurred vision, and difficulty of breathing. The patient was receiving dialysis three times a week and had undergone bilateral nephrectomy 2 months earlier. He was diagnosed with hypertension 6 months before this episode and was receiving antihyper-

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tensive treatment. Upon admission, his blood pressure was 220/160 mmHg. Neurological examination revealed no focal deficits. The patient became progressively incoherent and combative. No seizure activity was documented. Chest X-ray showed signs of pulmonary edema. Antihypertensive treatment was initialized and dialysis was planned for the following day. The patient showed progressive clinical improvement and his blood pressure was normalized. A magnetic resonance imaging (MRI) showed subtle zones of increased signal intensity in the cerebellar hemispheres and over the occipital lobes bilaterally on T<sub>2</sub>-weighted images (Figs. 1 and 2) and on fluid-attenuated inversion recovery (FLAIR) images (Figs. 3 and 4), consistent with PRES. The patient was discharged 2 days after admission free of symptoms and with a blood pressure of 140/80 mmHg.

Two months later, the patient returned to the ER; his mother gave an account of severe headache and vomiting that had started a few hours ago. He was started on low-molecular weight heparin 2 weeks ago due to clotting of the tip of his dialysis catheter in the right atrium. On admission, the patient was unresponsive and intubation was required. His pupils were dilated and nonreactive, and his blood pressure was 130/76 mmHg. According to the patient's mother, his blood pressure had been well controlled since the previous hypertensive crisis. Prothrombin time, partial thromboplastin time, and platelet count were within normal limits and no electrolyte disturbances were noted. Computerized tomography (CT) of the brain revealed a left cerebellar hemorrhage measuring 3.4×4.8 cm with mass effect (Figs. 5 and 6). Administration of Vitamin K and protamine was initiated. The patient was immediately taken to the operating room and posterior fossa craniectomy for evacuation of the hematoma was undertaken. A right occipital external ventricular drain was left at the conclusion of the case. There were no complications during the procedure. The



**Fig. 2** Axial T<sub>2</sub>-weighted MR images showing areas of increased signal intensity bilaterally in the cerebellar hemispheres

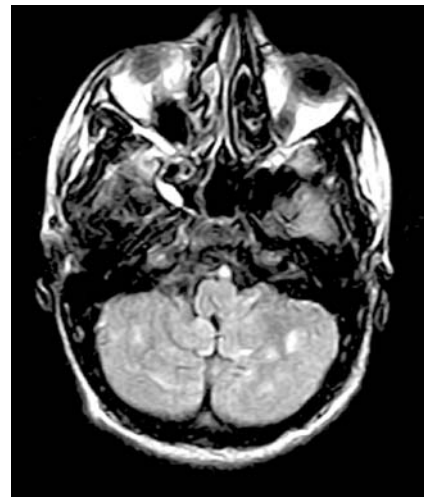
patient's condition did not improve postoperatively, and he succumbed to the disease 3 days after admission.

## Discussion

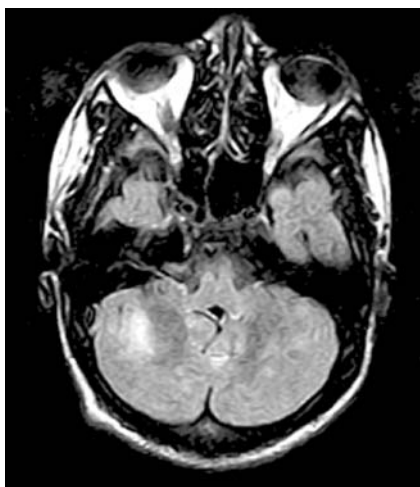
Hypertensive encephalopathy as a distinct clinical entity was described as early as 1928 by Oppenheimer and Fishburg [5]. In recent years, a variety of diseases and therapeutic agents have been found to produce a similar clinical syndrome and imaging findings, leading to the introduction of a large number of terms used to describe the same syndrome. In 1996, Hinchey et al. [1] suggested the term reversible posterior leukoencephalopathy syndrome to describe a disorder in a group of patients with neurological



**Fig. 1** Axial T<sub>2</sub>-weighted MR images showing areas of increased signal intensity bilaterally in the cerebellar hemispheres



**Fig. 3** Axial FLAIR MR images demonstrating patchy zones of increased signal intensity in the cerebellar hemispheres

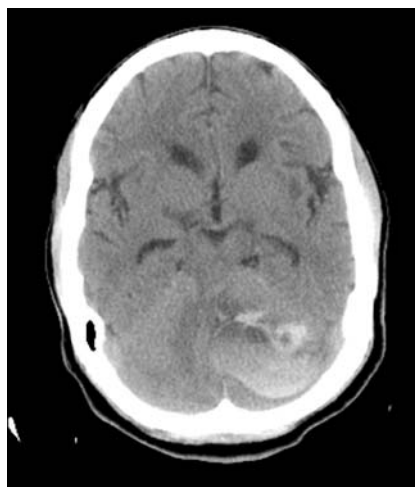


**Fig. 4** Axial FLAIR MR images demonstrating patchy zones of increased signal intensity in the cerebellar hemispheres

findings and CT and MRI abnormalities in the posterior regions of the brain; those patients had associated hypertension or renal insufficiency or were immunocompromised. They called it “leuko”-encephalopathy, based on their belief that only the white matter was involved, and “reversible” due to the reversibility of symptoms after the treatment of the underlying disorder or the withdrawal of the triggering agent. A few months later, Pavlakis et al. [6] suggested that the term occipital–parietal encephalopathy is more appropriate because the gray matter can also be affected. The nomenclature has further been complicated by terms such as reversible posterior cerebral edema syndrome [7] and vascular autoregulatory dysfunction [8]. In 2002, Schwartz [9] suggested the introduction of “hyperperfusion encephalopathy” as a general term for describing hyperten-



**Fig. 5** Axial CT images without contrast demonstrating left cerebellar hemisphere hemorrhage with significant mass effect, obliteration of the fourth ventricle, and midline structure shift



**Fig. 6** Axial CT images without contrast demonstrating left cerebellar hemisphere hemorrhage with significant mass effect, obliteration of the fourth ventricle, and midline structure shift

sive encephalopathy and all other related encephalopathies sharing the same pathophysiologic mechanism regardless of the causative agent, in an effort to simplify the existing nomenclature. The term posterior reversible encephalopathy syndrome has become widely accepted in the last few years, and this is the term used by the authors in their text.

The clinical spectrum of PRES comprises mainly the classical tetrad of altered mental status, headache, seizures, and visual disturbances; Pavlakis et al. [10] reported that three of these four symptoms are present in 76% of patients. Altered mental status may range from somnolence to stupor and coma. Visual disturbances usually occur in the form of blurred vision and papilledema, but visual hallucinations, hemianopia, and cortical blindness may develop [11]. Antunes et al. [12] have described a patient who presented with oculogyric crisis as the sole clinical manifestation of the syndrome. Seizures are usually multiple and often become generalized [1]. Bakshi et al. [13] reported on two cases, where occipital lobe seizures were the major manifestations of PRES. Other associated symptoms include vomiting, nausea, weakness, and incoordination of the limbs [14], whereas focal neurological signs may occasionally appear [11].

PRES is most commonly encountered in the setting of hypertension [1, 9, 10], but a variety of associated conditions and triggering factors have been recently identified. Renal insufficiency, eclampsia, immunosuppression with cyclosporine or tacrolimus, and various cytotoxic agents, such as cisplatin, cyclophosphamide, and granulocyte colony stimulating factor are not infrequently encountered [15, 16]. Porphyria [17], systemic lupus erythematosus [3], hemolytic uremic syndrome [18], and thrombotic thrombocytopenic purpura [19] have also been implicated. Kastrup et al. [15] reported two cases in which the only

identifiable abnormality was elevated serum calcium levels.

The pathophysiology behind the reversible changes seen in PRES is not thoroughly understood. Earlier findings of cerebral vasospasm in patients with eclampsia led to the hypothesis that cerebral vasoconstriction in response to systemic hypertension was the mechanism of PRES [20]. There is not much support for this theory today. Contrariwise, the changes observed in PRES are attributed mostly to vasodilation. Autoregulatory mechanisms in the brain result in constriction of cerebral arterioles in the setting of systemic hypertension. There is a threshold though, after which this mechanism is lost and the arterioles are forced to dilate, leading to extravasation of fluid and formation of edema [3, 4, 20, 21]. Results obtained by MR perfusion imaging performed on a patient in a study reported by Jones et al. [20] provide further evidence in support of vasodilation. Cytotoxic and immunosuppressive agents might disrupt the blood brain barrier, thus facilitating the development of edema [10]. When hypertension is adequately managed and possible causative agents removed, fluid reenters the vessels and edema disappears. The predilection for the territories supplied by the posterior circulation is further explained by the sparse distribution of adrenoreceptors in the posterior circulation, resulting in a decreased contractility, thus easier hyperperfusion and development of vasogenic edema [3, 4].

The diagnosis of PRES requires positive imaging findings, primarily attributed to brain edema, mainly, but not exclusively, in the white matter [4, 22]. Casey et al. [23] demonstrated in a study utilizing FLAIR MRI that 94% of patients with PRES had cortical involvement. CT reveals hypodense areas in the posterior regions of the cerebral hemispheres. The diagnostic modality of choice in cases of PRES is MRI. The lesions demonstrate high signal intensity on T<sub>2</sub>-weighted and FLAIR images [3]. They are usually symmetrical, most often in the parieto-occipital region. It is interesting to note that Covarrubias et al. [2] documented frontal lobe affection in 82% of patients. The brain stem may also be involved, though isolated brain stem affection is rare [17]. The lesions appear isointense on diffusion-weighted images (DWI) and show increased signal intensity on apparent diffusion coefficient (ADC) maps. These findings are of paramount importance because they aid in the differentiation from infarction, which shows high signal intensity on DWI and low on ADC maps [3, 24]. “Top of the basilar” embolism may also mimic PRES; sparing of the calcarine and paramedian occipital lobe, typical of PRES, contributes to establishing the correct diagnosis in these cases. Thrombosis of the superior sagittal or the transverse sinus may also pose diagnostic difficulties; magnetic resonance angiography (MRA) is then the modality of choice [4]. Vasogenic edema produced due to neoplastic

and inflammatory abnormalities may be differentiated from edema in PRES mainly due to its asymmetric and unilateral extension, its typical gadolinium enhancing, as well as its irreversibility with treatment [9].

Management of PRES consists of removal of the suspected causative agent, such as immunosuppressive and cytotoxic medication, and treatment of the underlying disorder, usually hypertension. Reversal of neurologic symptoms is then expected to occur within a few days to weeks. Rarely, progression to ischemia, infarction, or hemorrhage may occur [2–4]. However, Covarrubias et al. [2] reported that as high as 27% of their patients had evidence of ischemia on DWI. In the same study, a correlation between the extent of lesions on T<sub>2</sub>-weighted images or DWI and prognosis was noted. Furthermore, it has been suggested that chronic hypertension leads to elevation of the upper limit of cerebral autoregulation; aggressive antihypertensive treatment may, in these cases, result in persistence of cerebral vasoconstriction, which, in combination with the decreased systemic blood pressure is responsible for paradoxical ischemia in the brain [4].

In our patient, posterior fossa hemorrhage occurred more than 2 months after reversal of the neurological symptoms. Furthermore, the patient’s blood pressure had been within normal limits and dialysis was being regularly performed during that period of time. Jones et al. [20] supported in their article that children have a lower range of cerebral blood flow autoregulation than adults. Lower blood pressure, in the range of 180/130 mmHg, could thus precipitate hypertensive encephalopathy in younger patients. Our patient presented the second time with a blood pressure of 130/76 mmHg, which by no means can be considered beyond the range of autoregulation. Conclusively, at the time of hemorrhage, our patient had neither the clinical findings of PRES, nor a blood pressure that could trigger another episode of PRES.

One could postulate that our patient’s hemorrhage was a result of hemodialysis, which is a well-known risk factor for hemorrhagic complications, especially subdural hematomas [25, 26]. Although this is a valid suggestion, we do not feel comfortable with attributing a spontaneous posterior fossa hemorrhage in a young patient solely to renal failure and hemodialysis, without taking into consideration the recent PRES findings in the very same anatomical region.

Our patient was started on low-molecular weight heparin 2 weeks before the fatal hemorrhage. Intracranial hemorrhage associated with administration of low-molecular weight heparin has been reported in children [27]. However, clotting studies in our patient were within normal limits at the time of the second admission to the hospital. This, in association with the fact that the hemorrhage occurred at

exactly the same region of the brain where the edematous changes of PRES had been noted some 2 months earlier, raises the suspicion that low-molecular weight heparin in the setting of recent PRES might have precipitated the hemorrhagic event, even with normal clotting studies. MRI of the brain before the bleeding would have demonstrated any possible findings in the posterior fossa. Unfortunately, such an MRI was not obtained.

In conclusion, we have presented a case of fatal intracranial hemorrhage in a patient receiving low-molecular weight heparin, almost 2 months after an episode of PRES. Although the exact mechanism of hemorrhage cannot be fully elucidated, we suggest that the administration of low-molecular weight heparin may increase the risk of intracranial hemorrhage in patients recently diagnosed with PRES.

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