Polish Annals of Medicine

journal homepage: https://www.paom.pl

Case report

Posterior reversible encephalopathy syndrome (PRES) in the course of immunosuppressive therapy in a 45-year-old male with normal blood pressure – case study

Rakesh Jalali[1,5], Izabela Godlewska[1,5], Grzegorz Dałek[2], Justyna Chormańska[1,5], Elżbieta Bandurska-Stankiewicz[3,5], Adam Kern[4,5]

[1] *Clinical Emergency Department, Regional Specialist Hospital in Olsztyn, Poland*
[2] *Clinical Neurology Department, Regional Specialist Hospital in Olsztyn, Poland*
[3] *Clinical Department of Endocrinology, Diabetology and Internal Diseases, Regional Specialist Hospital in Olsztyn, Poland*
[4] *Cardiology Department, Regional Specialist Hospital in Olsztyn, Poland*
[5] *School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland*

ARTICLE INFO

Article history
Received 23 May 2017
Accepted 22 June 2017
Available online 2 February 2018

Keywords
Posterior reversible encephalopathy syndrome
PRES
Emergency department
Immunosuppressive therapy
Normal blood pressure

Doi
10.29089/2017.17.00005

ABSTRACT

Introduction: Posterior reversible encephalopathy syndrome (PRES) is an entity characterized by acute neurological symptoms including headache, quantitative disturbances of consciousness or vision and seizures, accompanied by radiological findings. Most of the time it is induced by high blood pressure in predisposed patients.

Aim: The aim of the study is to spread the knowledge of PRES and emphasize its risk factors.

Case study: 45-year-old male with a history of hypertension and nephrotic syndrome was admitted to the emergency department after seizure. Although the patient was normotensive, his numerous risk factors were considered and he was diagnosed with PRES. Initial diagnosis was confirmed in MRI.

Results and discussion: Normotensive patients develop compensatory mechanisms within the central nervous system to ensure constant cerebral blood flow despite blood pressure fluctuations. Abnormal compensatory response in patients with PRES is related to increased permeability of blood vessels and culminates in vasogenic brain oedema, however, chronic hypertension is a relative protective factor in the development of PRES. It is essential to distinguish between PRES, ischaemic cerebral stroke, uremic encephalopathy and cerebral venous sinus thrombosis. The treatment of PRES involves elimination of the predisposing factor and arterial pressure reduction.

Conclusions: PRES is characterized by symptoms resembling stroke which makes the differential diagnosis difficult. Due to the differences in the management of ischemic stroke and PRES, as well as the time factor, which brings forward the preservation of neurological symptoms in both cases, a prompt and accurate diagnosis followed by urgent implementation of therapeutic procedure in the hospital emergency department is essential.

Corresponding author: Rakesh Jalali, Clinical Emergency Department of Regional Specialist Hospital in Olsztyn, Żołnierska 18, 10-561 Olsztyn, Poland. Phone: +4889 538 62 99.
E-mail address: rakesh.jalali@uwm.edu.pl.

1. INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinical entity characterized by acute neurological symptoms including headache, quantitative disturbances of consciousness (ranging from somnolence, through stupor, to coma), seizures and vision disturbances (such as blurred vision, visual field defects and cortical blindness), accompanied by radiological findings.[1] Most of the patients diagnosed with PRES are hypertensive, however, incidence of PRES in normotensive patients has been reported.[2]

Neuroimaging, i.e. computed tomography (CT) and magnetic resonance imaging (MRI), is the mainstay in the diagnosis of PRES. The most common CT and MRI findings mainly consist of white matter oedema in the occipital and parietal lobes, sometimes involving also other locations such as the frontal lobes, the cerebellum or the thalamus.[3]

The aim of the treatment is to manage the cause leading to PRES and reduce blood pressure, thus leading to alleviation of the clinical symptoms and normalization of radiological image.

2. AIM

The aim of the study is to spread the knowledge of posterior reversible encephalopathy syndrome and emphasize its risk factors and management in emergency department.

3. CASE STUDY

A 45-year-old male with a history of hypertension and nephrotic syndrome (status after kidney transplantation in 1997, chronically treated with cyclosporine and prednisone) was admitted to the Clinical Emergency Department (ED) of the Regional Specialist Hospital in Olsztyn, Poland, around 9.30 a.m. after the first seizure in his life. As his wife reported, on the same day at work he suffered from dizziness, which lasted for about 30 minutes and preceeded the seizure. At the scene patient was treated with 1 mg of clonazepam by emergency medical team (EMT), which resulted in resolving convulsion. On admission, the patient was conscious, confused but oriented as to the place and himself, with retrograde amnesia. He was complaining of impaired visual acuity of the right eye.

On admission patient was hemodynamically stable. His vital signs were as follows: blood pressure (BP) 136/87 mmHg, heart rate 87 bpm, respiratory rate 12 breaths/min, SpO2 98% while breathing ambient air. On physical examination, the breath sounds were normal. The abdomen was normal, and there was no peripheral oedema at none of lower extremities. On neurological assessment pupils were round, symmetrical and reactive to light, binocular visual defect with predominance of right visual field. Meningeal and Babinski's signs were negative. Muscle strength of both upper and lower limbs was symmetrical and deep tendon reflexes normal. The results of hematologic and other laboratory tests are shown in Table 1.

Table 1. Patient's laboratory test results.

Variable	Results	Normal
Hematocrit, %	44.2	41–53
White blood cells, 103/μL	8.97	4.1–10.9
Platelets, 103/μL	199	150–400
Glucose, mg/dL	130	60–99
Sodium, mmol/L	139	136–145
Potassium, mmol/L	3.8	3.5–5.1
Urea, md/dL	57	10.50
Creatinin, mg/dL	2.0	0.7–1.2
eGFR, mL/min	36.7	>60
CRP, mg/dL	0.62	<0.5
Troponin T, ng/mL	0.006	<0.010
APTT, s	28	26–36
INR	1.02	0.8–1.2
D-dimer, mg/L	1.32	<0.5

The abnormalities observed in laboratory data included increased creatinine and urea levels and decreased eGFR. D-dimer values were requested to rule out cerebral venous thrombosis. Although its range was higher than normal, the patients previous electronic medical records showed that its level had been elevated for the last couple of years and ranged from 1–2 mg/L. Hence the D-dimer value was ruled out as a diagnostic measure for PRES.

Every patient admitted to our hospital after first episode of seizures is having head CT scan taken (with and without contrast enhancement) in order to confirm/exclude any vascular malformations, aneurysms, tumours, hematomas or other abnormalities which can lead to epileptic attacks. However, while confusion following seizures is commonly occurring, impaired vision might indicate stroke episode.

According to the latest AHA Guidelines on ischemic stroke management, given the narrow therapeutic windows for treatment, timely ED diagnosis of ischemic stroke is paramount.[4] Thus, prompt patient evaluation in ED consists of initial examination carried out by emergency physician, collecting blood samples for laboratory tests, performing ECG and initiating stroke team. Door to head CT scan time shouldn't last longer than 20 minutes.

In this case however, history of renal hypertension, nephrotic syndrome, kidney transplantation and long-term treatment with cyclosporine and steroids were major risk factors indicating possibility of PRES occurrence. Taking under consideration short-lasting symptoms and possible causes of patients complaints other than stoke we decided to perform head MRI instead of standard CT scan.

The MRI revealed fingerlike zones of cerebral oedema in the occipital white matter (the bigger one on the left side) pressing against the brain ventricular system in the region of posterior horn of the lateral ventricle (Figure 1).

Based on radiological findings, neurological symptoms and numerous risk factors, patient was diagnosed with PRES. Since his blood pressure was normal, he required no emergency interventions and was transferred directly to the Clinical Neurology Department of the same hospital about an hour after admission to the ED.

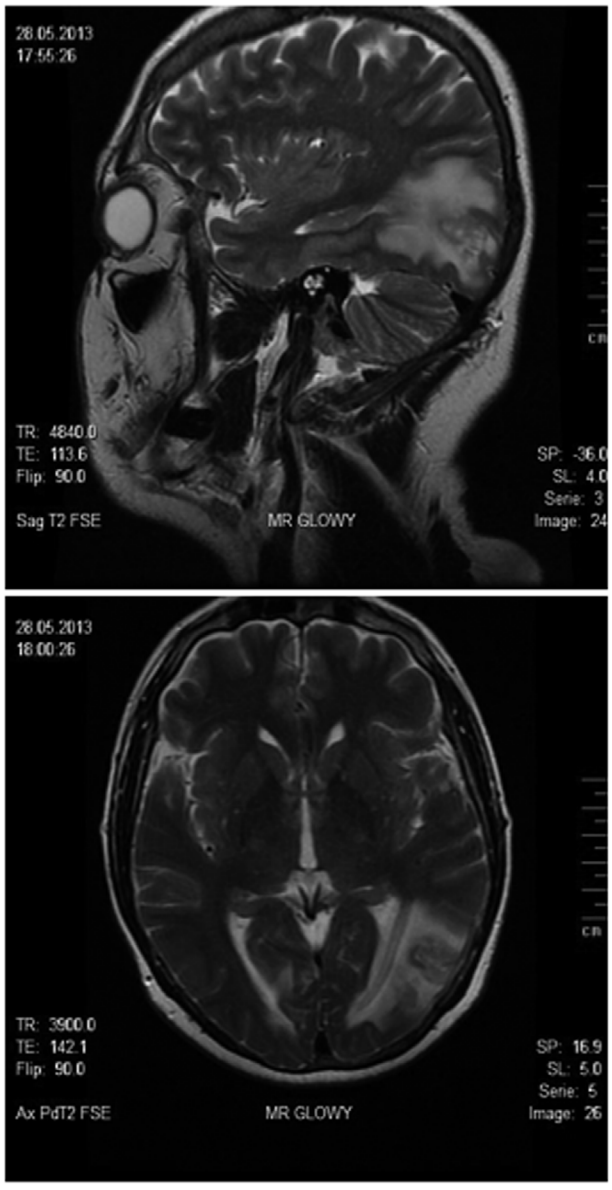

Figure 1. Patient's MRI performed on admission to the hospital. Visible white matter oedema in the occipital white matter.

4. RESULTS AND DISCUSSION

PRES was first described in 1996 by Judy Hinchey (initially as reversible posterior leukoencephalopathy syndrome – RPLS), who stated, based on a retrospective observation of 15 patients, that certain diseases and immunosuppressive therapy can result in neurological side-effects like disturbance of consciousness, vision disturbances, headaches and seizures related to white matter oedema. Among the potential causes of RPLS Hinchey enumerated immunosuppressive therapy, eclampsia or renal hypertension.[5]

Currently, there are several theories concerning the pathomechanisms of the development of PRES, however, none of them has found unequivocal confirmation. PRES most frequently occurs in hypertensive patients, with arterial hypertension playing a critical role in the pathogenesis of PRES.[6]

Normotensive patients develop compensatory mechanisms within the central nervous system to ensure constant cerebral blood flow despite blood pressure fluctuations. This phenomenon, known as autoregulation of cerebral blood flow, functions properly for mean arterial pressure (MAP) between 60 mm Hg and 120 mm Hg, preventing fluid leakage from the intravascular space to the interstitium. This autoregulatory mechanism remains under constant influence of metabolic and neurogenic factors, among which the leading role is played by sympathetic innervation of blood vessels, which induces vasoconstriction in response to increased MAP. Abnormal compensatory response, frequently occurring in patients with PRES, is related to increased permeability of blood vessels and culminates in vasogenic brain oedema. Due to poor sympathetic innervation of vasculature originating from the basilar artery, there is an apparent predisposition for oedema to occur in the parietal-occipital lobe region.[7] In patients with chronic arterial hypertension, especially if improperly controlled, the autoregulatory range of MAP values are shifted to the right. As a result of the said shift, normotensive patients present with symptoms of encephalopathy if the pressure suddenly raises above 160/100 mm Hg, while patients with chronic hypertension do not do so until the pressure rises to 220/110 mm Hg or greater.[8] Chronic hypertension is a relative protective factor in the development of PRES because, by causing cerebrovascular hypertrophy, it compromises permeability of the blood-brain barrier.

Apart from the mechanism of vasogenic cerebral oedema, there is also the theory of cytotoxic endothelial damage. The development of PRES is induced by both increased arterial pressure and all kinds of endothelial damage (e.g. in the course of diabetes, dyslipidaemia or nicotine addiction).[1] Both mechanisms are causing blood-brain barrier disturbances and resulting in oedema. Conditions like eclampsia, collagen diseases (systemic lupus erythematosus, multinodular arteritis),[9] sepsis, septic shock or status-post transplantation also predispose to the development of PRES.

There is also a wide variety of medicines which use increases the risk of PRES development. These include glucocorticoids and cytostatic drugs (e.g. cyclosporine, which effect on the development of PRES has been studied since the entity was first described in 1996).

Key role in the differential diagnosis of PRES is played by physical examination, the aim of which is to reveal PRES risk factors, and by neuroimaging: CT and MRI, of which the MRI seems more precise, because of the often occurring false negative results and difficulties to distinguish PRES from acute stroke in CT scans. The nuclear magnetic resonance (NMR) can reveal hyperintense lesions in occipital and parietal white matter in the time T2 FLAIR, DWI that are hypointense at time T1. Using the ADC is reported by some authors to be crucial in differentiating PRES with is-

chemic stroke (in PRES hyperintense, in stroke hypointense lesions). However, there are opinions negating this theory and pointing to the same image in both disease entities.[10]

Due to the clinical picture, it is essential to distinguish between PRES, ischaemic cerebral stroke, uremic encephalopathy, disequilibrium syndrome or cerebral venous sinus thrombosis.

One of the possible diagnoses in the case of aforementioned patient taken under consideration was sinus venous thrombosis since nephrotic syndrome and corticosteroid therapy are major risk factors of this entity. Symptoms such as headache, focal neurologic deficits, seizures and mental status disorders are common in both PRES and sinus venous thrombosis, however thrombosis is most frequently associated with increased intracranial pressure (ICP).[11] In this case however there was no evidence of coagulopathy in laboratory tests and no symptoms of increased ICP, yet differentiation based on clinical features is extremely difficult and final diagnosis had to be confirmed in neuroimaging. MRI in patients suffering from sinus venous thrombosis reveals thrombus in sinuses and, as a result from thrombosis, cerebral oedema with or without associated ischemic or haemorrhagic stroke.[11]

Patients with uremic encephalopathy sometimes show symmetrical changes within the region of basal ganglia, internal capsule and white matter, while patients with PRES present white matter oedema, especially in the occipital and parietal lobes.[12] Although usually typical, the location of oedemic lesions is not enough to make an unequivocal diagnosis, as the literature also describes cerebellar oedema, oedema of the frontal lobes or thalamus oedema in the course of PRES.[3]

The treatment of PRES involves elimination of the predisposing factor and arterial pressure reduction. Thus, it is crucial to properly differentiate ischemic stroke from PRES: in the course of PRES, arterial pressure should be intensely normalized, while in patients presenting with ischemic stroke, the process of reduction of arterial pressure should commence above 220/120 mm Hg or above 185/110 mm Hg – if thrombolysis is planned.[4] An early and accurate diagnosis, followed by appropriate causal and hypotensive treatment, leads to the subsidence of neurological symptoms and, subsequently, of radiological changes. On the other hand, improper or delayed treatment might cause preservation of stroke or PRES symptoms resulting in patient's disability and anxiety.[13]

In the case described, the predisposed patient developed full-blown PRES (chronic arterial hypertension, renal failure, status-post transplantation, chronic immunosuppressive treatment, cyclosporine and glycocorticosteroids), despite the appropriate values of arterial pressure. PRES in normotensive patients is rather rare, however literature describes similar cases.[2] The knowledge of the disease entity and the related symptomatology played the key diagnostic role in the case described and resulted in the appropriate selection of imaging methods (in Poland CT is preferred to MRI in emergency departments in the case of neurological disorders). Quick diagnosis and transfer of the described patient for further treatment in the neurological department led to full subsidence of the clinical symptoms within 24 hours following admission to the department.

5. CONCLUSIONS

Neurological emergencies are among the most frequent diagnoses of patients in hospital emergency departments. The leading cause of neurological disorders are cerebral strokes which, due to the variability of the location of ischemic or haemorrhagic focuses, are characterized by a wide spectre of neurological symptoms. PRES is characterized by symptoms resembling stroke which, when combined with its rare occurrence, makes the differential diagnosis difficult. Due to the differences in the management of ischemic stroke and PRES, as well as the time factor, which brings forward the preservation of neurological symptoms in both cases, a thorough, quick and accurate differential diagnosis followed by urgent implementation of therapeutic procedure in the hospital emergency department is essential. An accurate diagnosis can be put forward based on a thorough physical examination, performed taking into account the occurrence of predisposing factors, and based on radiological examinations. Introduction of the prompt and proper treatment leads to the subsidence of neurological deficit symptoms.

Conflict of interest

None declared.

References

1. Pedraza R, Marik PE, Varon J. Posterior reversible encephalopathy syndrome: A review. *Crit Care Shock*. 2009;12(4):135–143.
2. Yano Y, Kario K, Fukunaga T, Ohshita T, Himeji D, Yano M, et al. A case of reversible posterior leukoencephalopathy syndrome caused by transient hypercoagulable state induced by infection. *Hypertens Res*. 2005;28(7):619–623. https://doi.org/10.1291/hypres.28.619.
3. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR Am J Roentgenol*. 2007;189(4):904–912. https://doi.org/10.2214/AJR.07.2024.
4. Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2013;44(3):870–947. https://doi.org/10.1161/STR.0b013e318284056a.
5. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334(8):494–500. https://doi.org/10.1056/NEJM199602223340803.
6. Eguchi K, Kasahara K, Nagashima A, Mor T, Nii T, Ibaraki K, et al. Two cases of malignant hypertension with

reversible diffuse leukoencephalopathy exhibiting a reversible nocturnal blood pressure "riser" pattern. *Hypertens Res*. 2002;25(3):467−473. https://doi.org/10.1291/hypres.25.467.

7 Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL Jr. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol*. 1978;234(4):371–383. https://doi.org/10.1152/ajpheart.1978.234.4.H371.

8 Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet*. 2000;356(9227):411–417. https://doi.org/10.1016/S0140-6736(00)02539-3.

9 Primavera A, Audenino D, Mavillo N, Cocito L. Reversible posterior leucoencephalopathy syndrome in systemic lupus and vasculitis. *Ann Rheum Dis*. 2001;60(5):534–537. https://doi.org/10.1136/ard.60.5.534.

10 Legriel S, Pico F, Azoulay E. Understanding posterior reversible encephalopathy syndrome. In: Vincent JL, ed. *Annual Update in Intensive Care and Emergency Medicine*. Berlin: Springer; 2011:631–653. https://doi.org/10.1007/978-3-642-18081-1_56.

11 Rajewski P, Książkiewicz B. [Cerebral venous and sinus thrombosis]. 2010;12(1–2):47–50 [in Polish].

12 Lim MH, Kim DW, Cho HS, Lee HJ, Kim HJ, Park KJ, et al. Isolated cerebellar reversible leukoencephalopathy syndrome in a patient with end stage renal disease. *Intern Med*. 2008;47(1):43–45. https://doi.org/10.2169/internalmedicine.47.0461.

13 Abaraogu UO, Opara MC. Depression and dynamic balance recovery among stroke survivors: A preliminary investigation. *Pol Ann Med*. 2017;24(2):123–128. https://doi.org/10.1016/j.poamed.2016.05.001.