

Reversible posterior leukoencephalopathy syndrome in a patient with thrombotic thrombocytopenic purpura

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Received: 21 February 2010 / Accepted: 24 November 2010
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Abstract Thrombotic thrombocytopenic purpura (TTP) is an autoimmune disorder characterised by fever, microangiopathic haemolytic anaemia, renal insufficiency, and thrombocytopenia. Neurological involvement, a prominent component of TTP, is characterised by a variety of brain lesions which include reversible cerebral oedema or magnetic resonance imaging (MRI) features of reversible posterior leukoencephalopathy syndrome (RPLS). TTP is frequently associated with deficiency of the von Willebrand factor-cleaving protease, ADAMTS13.

Here, we report a case of TTP with severe acute encephalopathy. Posterior leukoencephalopathy and brainstem oedema with triventricular hydrocephalus were observed on MRI. The low activity of ADAMTS13 was not observed and ADAMTS-13 antibodies were absent. Neurological symptoms and patient's condition were completely resolved by plasma exchange therapy in addition to high dose of methylprednisolone.

Keywords Reversible posterior leukoencephalopathy · Thrombotic thrombocytopenic purpura · ADAMTS-13 · Plasma exchange

Introduction

Posterior reversible leukoencephalopathy syndrome (RPLS) is a recently proposed clinico-neuroradiological entity presenting with a variety of neurological features [1]. These, although potentially devastating, are reversible on prompt diagnosis and appropriate treatment. Delayed diagnosis can lead to long-term neurological disability [2]. A relatively symmetrical pattern of involvement, typically in the subcortical white matter and occasionally in the cortex of the posterior circulation area of the brain is evident on magnetic resonance imaging (MRI) studies [1]. Common causes of RPLS are hypertensive encephalopathy, eclampsia, cyclosporin-A neurotoxicity, and uremic encephalopathy. Although the majority cases of RPLS are associated with hypertensive disorders, it has also been described in normotensive patients in association with thrombotic thrombocytopenic purpura (TTP) [3].

Case report

A previously healthy 53-year-old Caucasian man was admitted in an emergency department for the rapid onset of disturbances of gait, dizziness, urinary incontinence and lethargy. The pulse rate was 80 beats/min, temperature 38°C and blood pressure was 260/180 mmHg, partially decreased by administered nitroprusside, furosemide and clonidine.

White and red blood cells count and haemoglobin were normal ($7.5 \times 10^3/\mu\text{l}$, $5.55 \times 10^6/\mu\text{l}$, 15.7 g/dl). Platelet count ($86.0 \times 10^3/\mu\text{l}$), LDH (642 mg/dl), serum creatinine (1.90 mg/dl), and urea (53 mg/dl) were out of normal range. A brain CT scan showed an enlargement of the lateral and third ventricles. The day after, the patient

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started complaining weakness in lower limbs, mental confusion and impaired attention and because of worsening of symptoms he was admitted to our department. He was lethargic and neurological examination showed hyperreflexia and pathological reflexes in all four limbs. An electroencephalogram (EEG) was characterised by marked slowness in the left posterior hemisphere without evidence of epileptic activity.

MRI of the brain revealed abnormal signal bilaterally in the white matter of cerebral and cerebellar hemispheres with the involvement of midbrain and cerebellar peduncles (Fig. 1a). A triventricular hydrocephalus, presumably caused by brainstem oedema, was observed.

A lumbar puncture revealed a limp and uncoloured cerebrospinal fluid (CSF) with normal cell count ($0.8/\text{mm}^3$) and a barely elevated total protein concentration (77 mg/dl, normal value <40 mg/dl) with positive Pandy reaction. Polymerase chain reaction assay of Epstein–Barr virus (EBV)-DNA, Herpes simplex virus (HSV)-DNA,

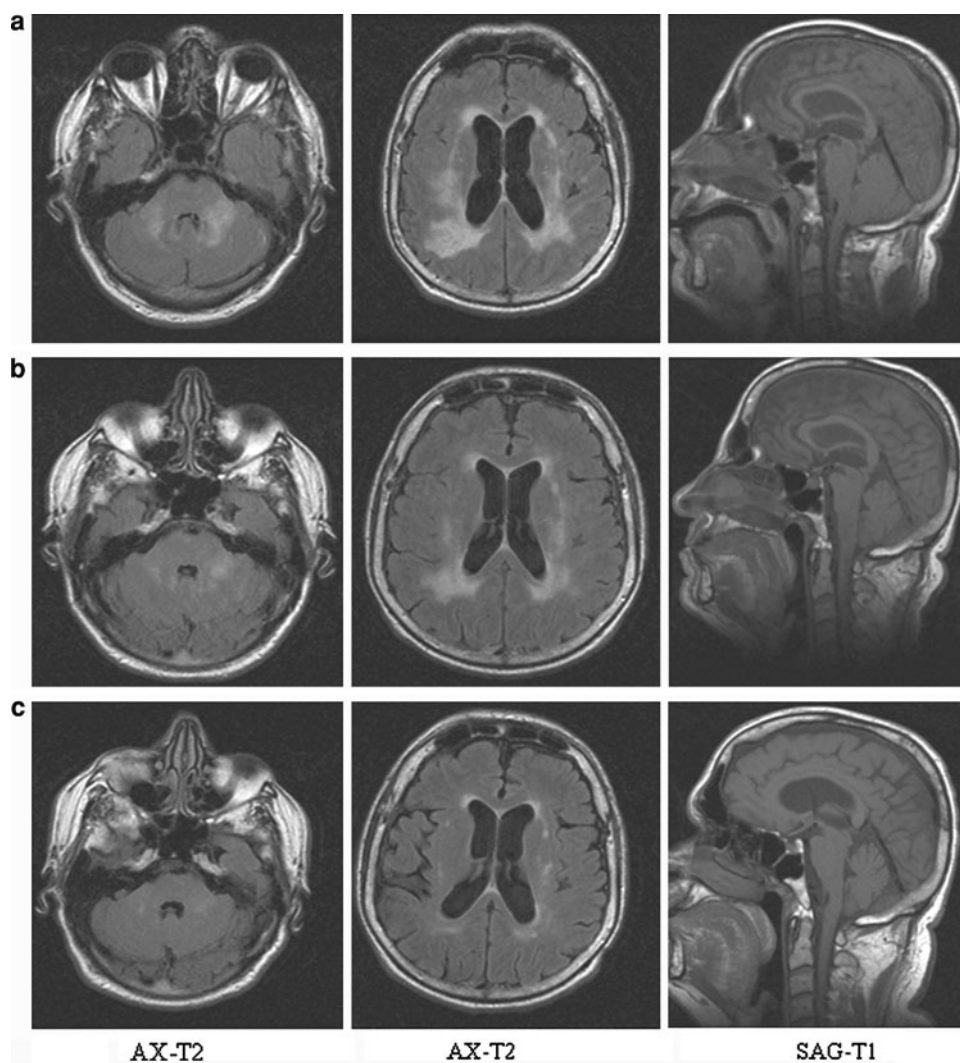
Cytomegalovirus (CMV)-DNA was negative. CSF cultures had no bacterial, viral and fungal growth.

After 2 days from admission, laboratory findings revealed a platelet count of $58.0 \times 10^3/\mu\text{l}$. Lactate dehydrogenase (LDH): 562 mg/dl (normal 200–480 mg/dl); serum creatinine: 3.04 mg/dl (normal 0.67–1.17 mg/dl); urea: 106 mg/dl (normal 10–50 mg/dl); bilirubin level: 1.42 mg/dl (normal 0.3–1.1 mg/dl); AST: 38 U/l (max. 37 U/l); GGT: 72 U/l (normal 8–61 U/l); rheumatoid factor: 106 IU/ml; coagulation profile, complement C3 and C4: normal.

The results of serological tests for acute infection with cytomegalovirus, Epstein–Barr virus, Herpes simplex virus, and Herpes zoster virus were negative. Serological tests of antibodies to hepatitis B and C virus and human immunodeficiency virus were also negative.

Tests for serum antibodies, including anticardiolipin, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), cytoplasmic anti-neutrophil cytoplasmic antibodies

Fig. 1 T2-weighted axial and T1-weighted sagittal section MRI. **a** Two days after the admission to our department: hyperintensity in the bilateral white matter of cerebral and cerebellar hemispheres with involvement of midbrain and cerebellar peduncles, **b** after 2 weeks, **c** 3 months later: almost complete resolution of abnormal signal on MRI



(cANCA), antinuclear antibody (ANA), anti-double stranded DNA antibody (dsDNA), anti-smooth muscle antibodies (anti-SM), anti-smooth muscle-ribonucleoprotein (anti-SM RNP), anti-Sjögren's syndrome A (anti-SSA) and anti-Sjögren's syndrome B (anti-SSB) were negative.

A 5-day regimen of high-dose intravenous administration of methylprednisolone (1 g/day) was started and within a week, an improvement of confusion and attentional difficulties was observed.

A diagnosis of RPLS in a patient with TTP was suggested by a second platelet count of $40.0 \times 10^3/\mu\text{l}$, the presence of schistocytes in the peripheral blood smear, in addition to acute renal failure, confusion and other neurological symptoms, and MRI features. A blood sample of the patient was sent to a reference laboratory for ADAMTS-13 assays. The patient was transferred to the haematology division. More details regarding clinical and therapeutic aspects of this recovery are reported elsewhere [4]. Briefly, a prompt plasma exchange therapy was started, with daily exchanges of one plasma volume while steroid therapy was continued. After eight daily plasma exchange without complete remission, an additional immunosuppressive treatment with rituximab (at a standard dosage of 375 mg/m^2) was administered weekly for 4 weeks. This treatment was continued despite ADAMTS-13 activity was 100% and no antibodies against ADAMTS-13 were detected. The platelet count was normalised and the neurological status improved progressively. The patient became totally normal after 3 months and a brain MRI showed nearly complete resolution of brainstem oedema and the T2 signal changes (Fig. 1c). Six months later, his neurological examination was normal. Twenty-four months later, no relapses have been observed and the patient is still healthy.

Discussion and conclusion

RPLS, also known as posterior reversible encephalopathy syndrome (PRES), is a clinical condition characterised by an acute or subacute onset of neurological symptoms (headache, altered mental status, confusion, and drowsiness), visual disturbance (hemianopsia, visual neglect, and cortical blindness), seizures associated with imaging findings of reversible cortical and subcortical vasogenic brain edema [5]. Eclampsia, hypertensive emergency, renal failure, autoimmune diseases and immunosuppressive therapy are common precipitating factors in RPLS [6].

The endothelial injury and the following release of factors promoting platelet activation and hyaline microthrombi formation in addition to blood–brain barrier injury are the most important pathophysiologic mechanisms for TTP-associated RPLS [3]. These factors could cause

hypoperfusion leading to stroke or, on the contrary, cerebral micro-haemorrhages due to thrombocytopenia and hypertension [7].

We present a patient with TTP, elevated blood pressure and posterior vasogenic oedema on MRI consistent with posterior leukoencephalopathy. The course of these MRI-featured lesions permitted us to define it as reversible.

Plasma exchange represents the first treatment of TTP patients with or without ADAMTS-13 deficiency. These two groups differ in the frequency of relapses. In fact, patients without ADAMTS-13 deficiency almost never relapse, on the contrary, about 50% of the patients with ADAMTS-13 deficiency suffer relapse within 2 years [8].

In our patient, in addition to the methylprednisolone, plasma exchange was started when the diagnosis of TTP was done, and as previously reported by other authors [9, 10], a rapid improvement of haemolysis and a normalization of platelet count were seen.

This case shows the importance of the recognition and prompt treatment of patient with TTP and further strengthens the evidence that, even if the demonstration of plasma level of ADAMTS-13 and its antibodies are diagnostic, the absence of this diagnostic test justify the beginning of therapy without waiting the test results.

Acknowledgments We thank the reviewers for their careful reading of the manuscript and helpful comments and Melanie Flynn for detailed and insightful corrections.

Conflict of interest The authors certify that there is no current or potential conflict of interest in relation to this article.

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