A RARE NEUROLOGICAL COMPLICATION - POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND CLASS IV LUPUS NEPHRITIS

Anna Mirela Stroie, Mircea Nicolae Penescu
"Dr. Carol Davila" Teaching Hospital of Nephrology, Bucharest
Mailing address:
Anna Mirela Stroie
e-mail: annastroie@yahoo.com

Abstract

Posterior reversible encephalopathy syndrome is a rare manifestation of systemic lupus erythematosus, characterized by altered mental status, headache, convulsions, visual field impairment and posterior and reversible alterations on imaging scans[1,2]. The clinical picture develops over a few hours, presenting with rapidly progressive neurological symptoms[3]. It was first described in 1996. It is more frequent in patients with acute kidney injury or chronic kidney disease, thus in lupus patients with kidney disorders. It is associated with hypertension, other autoimmune diseases beside lupus, immunosuppressive therapies, especially antibody-based immunosuppressive therapy, and organ transplantation. It is clinically reversible within one week and imaging changes resolve within 2-4 weeks. It is treatable and has a good prognosis. We present the case of a young woman of 27 years, diagnosed with systemic lupus erythematosus who developed convulsive seizures, headache, visual impairment, being under immunosuppressive therapy with azathioprine. The kidney biopsy revealed class IV lupus nephritis and partial remission of the nephrotic syndrome. The other manifestations of SLE in this patient were cutaneous, immunological, articular and haematological. The patient had a good short, medium and long-term prognosis at 30 days and also at 6 months.

Keywords: *posterior reversible encephalopathy, seizures, lupus nephritis, reversible neurological lesions.*

Rezumat

Sindromul de encefalopatie posterioară reversibilă este o rară manifestare a lupusului eritematos sistemic, care se manifestă prin stare mentală alterată, conștiență alterată, cefalee, convulsii, alterări ale câmpului vizual și modificări posterioare și reversibile la nivel imagistic[1, 2]. Tabloul clinic se desfășoară pe parcursul câtorva ore, simptomele neurologice fiind rapid progresive[3]. A fost descris pentru prima oară în 1996. Este mai frecvent la pacienții cu injurie renală acută sau sau boală cronică de rinichi, deci la pacienții cu lupus care au și

afectare renală. Se asociază cu hipertensiune arterială, alte afecțiuni autoimune în afară de lupus, tratament imunosupresor, în special terapiile bazate pe anticorpi, trasplantul de organe fiind, de asemenea, un factor de risc. Sindromul este reversibil clinic într-o săptămână, iar modificările imagistice se remit în 2-4 săptămâni. Este o afecțiune tratabilă și care are un prognostic bun.

Prezentăm cazul unei tinere paciente de 27 de ani diagnosticată cu lupus eritematos sistemic, care a prezentat crize convulsive, cefalee, tulburări de câmp vizual, pacienta fiind pe tratament imunosupresor cu azathioprină. Biopsia renală a evidențiat nefrită lupică clasa a IVa și remisiune parțială a sindromului nefrotic. Celelalte manifestări ale LES la această pacientă au fost cutanate, imunologice, articulare și hematologice. Pacienta a avut un prognostic bun pe termen scurt, mediu și lung, la 30 de zile și 6 luni.

***Cuvinte cheie**: encefalopatie posterioară reversibila, convulsii, nefrită lupica, leziuni neurologice reversibile.*

Introduction

Posterior reversible encephalopathy syndrome is rare condition that is usually associated with autoimmune diseases, immunosuppressive therapy - especially based on antibodies, transplant patient and in acute or chronic kidney disorders. It is a rare manifestation of systemic lupus erythematosus, in which there is alteration of the mental functions, headache, seizures, visual impairment and transient and reversible changes at the level of the posterior cerebral fossa on neurologic scans[1,2], manifesting over a period of a few hours and presenting with rapidly progressive neurological symptomatology[3]. It was first described in 1996 by Hinchey and his fellows, presenting a series of 15 cases in that year[1]. This syndrome can include focal neurological deficits, status epilepticus or coma, but these situations are rare[4].

Using neuroimaging techniques, the reversible lesions are defined through by matter vasogenic cerebral oedema in the posterior areas of the cerebral hemispheres - the occipital, parietal lobes, rarely the bridge and cerebellum (practically, subcortical oedema with no infarction areas)[1]. It is assumed that the pathophysiological mechanisms include the capillary leakage (extravasation) and the blood-brain barrier rupture[5]. Multiple medical terms were used to describe this syndrome, mainly reversible

posterior leukoencephalopathy syndrome, reversible posterior cerebral oedema syndrome and reversible occipital parietal encephalopathy[6,7]. Other diagnosing imaging elements are haemorrhage, restrictive diffusion, contrast enhancement and vasoconstriction[8].

The global incidence of posterior reversible encephalopathy syndrome is unknown. Epidemiological data from retrospective studies, especially from the 1988-2008 period, that include patients with ages between 4-90, show a maximum incidence in young adults towards middle age, between 39-47 years old[9,11]. This syndrome is more frequent in female patients with associated chronic hypertension, chronic kidney disease, eclampsia, preeclampsia, bone marrow transplant or organ transplant or autoimmune diseases. In 35-40% of patients mechanical ventilation is necessary for at least 3-7 days[10,12]. Status epilepticus may require admission to the intensive care unit and can be seen in a small percentage of patients. In patients with lupus, the authors cite a percentage 0.69% of patients[7]. The real incidence is not fully known, because there are cases where neuroimaging and follow-ups are not available.

Definition

Posterior reversible encephalopathy syndrome is a rare neurological condition. Its frequency is rising in patients with lupus. It is a clinical imaging syndrome that includes visual perception impairment, seizures, headaches, visual field disorders and reversible imaging alterations at the posterior cerebral level and in the cerebellum, indicating lesions such as subcortical oedema, caused by capillary leakage (extravasation).

Pathophysiology

PRES (posterior reversible encephalopathy syndrome) is a neurotoxic condition accompanied by subcortical oedema in the parietal, occipital lobes and in the cerebellum. The pathophysiological mechanisms responsible for these alterations are the development of a subcortical vasogenic oedema in the mentioned areas. The mechanisms responsible for the development of this cerebral oedema are unknown.

There are two theories:

a. Severe hypertension that affects the self-regulation, followed by hypoperfusion and endothelial injury / vasogenic oedema.
b. Vasoconstriction and hypoperfusion lead to cerebral ischemia and vasogenic oedema, local immunological alterations and the activation of T lymphocytes and endothelial cells, this leading to leukocyte trafficking and cerebral/systemic vasoconstriction. The imaging results support the older theory of the vasoconstriction, combined with hypoperfusion as mechanism, hypertension causing the activation of the cerebral circulation self-regulation, ischemia and secondary cerebral oedema[13,14].

Differential diagnosis of the seizures

Most patients (3/4) have tonic-clonic seizures, most of them secondarily generalised. Status epilepticus is a rare condition[1]. It is important to take into consideration all of the possible causes of the seizures:

- Vascular causes: lupus vasculitis in immunobiologically active lupus (high levels of anti dc DNA antibodies, ANA, low C3, C4 levels), ischaemic stroke, cerebral venous thrombosis (typical cerebral imaging on a CT and MRI), thrombotic

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microangiopathy (schistocytes on peripheral blood smears, anaemia);

- Metabolic causes: hypoglycaemia, toxic substance consumption;
- Tumoral causes: glioblastoma (visible on CT and MRI);
- Neurological causes: generalised epilepsy (typical EEG pattern);
- Psychiatric causes: the patient mimics the seizures and doesn't respond to benzodiazepines;
- Cardiac causes: vasovagal syncope (the episodes last less than 15 seconds, with altered consciousness), cardiac arrythmias (visible on an EKG) - these possibly being caused by lupus myocarditis;
- Hypertensive encephalopathy: the seizures are reversible when blood pressure levels are controlled;
- Infectious causes: septic meningitis (CFS cultures, typical clinical signs - nuchal rigidity), multifocal encephalopathy caused by the JC virus;
- Secondary SLE neurological alterations: caused by the release of cytokines, anti-neuronal antibodies. High IL-6 levels are correlated with the relative risk of seizures and are present in PRES.

Treatment

The management of the posterior encephalopathy syndrome in lupus includes treating the acute hypertension, seizures and lupus activity and, if needed, admission to an intensive care unit.

Oral or iv antihypertension medication is used in most PRES episodes, diuretics and renal replacement therapy are used in case of oliguria and oedema unresponsive to diuretics.

The preferred treatment to control lupus are steroids, usually pulse therapy with methylprednisolone. Due to the fact that immunosuppressive medication is associated with PRES, a short interruption or reduction of the doses of the immunosuppressants is recommended (azathioprine, mofetil mycophenolate, calcineurin inhibitors, antibody-based immunosuppressive treatment), until the patient is stabilized, and afterwards reinitiated under strict medical supervision.

The treatment also includes antiepileptic medication.

The first line of antiepileptic drugs includes molecules such as: phenobarbital (discovered in 1912), phenytoin (used since 1938), pyrimidone (since 1954), ethosuximide (since 1906), valproic acid (used since 1967), carbamazepine (used since 1974), vigabatrin (1993), gabapentin (1993), lamotrigine (1995), topiramate (1996), oxcarbazepine (1998), levetiracetam (2000), pregabalin (2005), zonisamide (2007), lacosamide (2009), perampanel

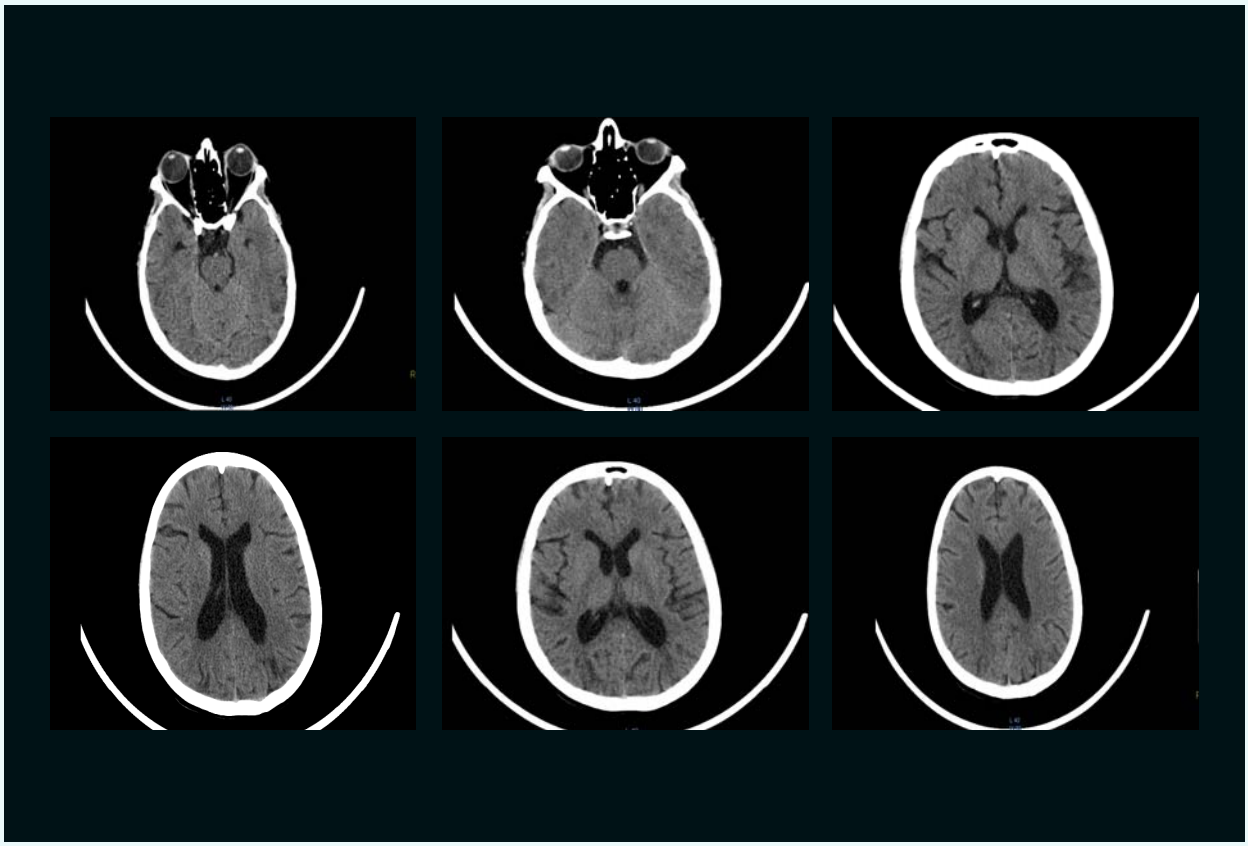

Figure 1. *The patient's cranial MRI, showing subcortical oedema, with no other brain lesions*

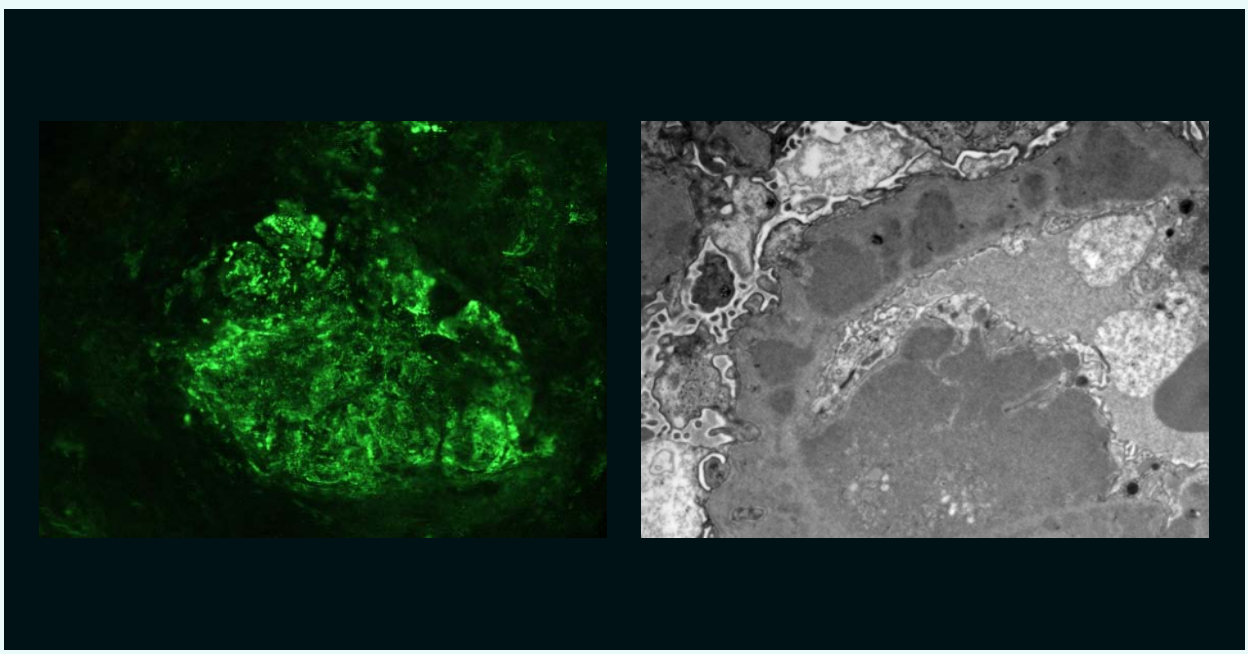

Figure 2. *The patient's kidney biopsy: on the right, aspect of anti C1q antibodies on immunofluorescence. On the left, dense deposits in electronic microscopy. Six glomeruli were examined, that presented mesangial expansion, lobulation accentuation and discreet extracapillary proliferation. Dense deposits frequently arranged like segments. Also present interstitial inflammation lesions. Discreet sclerosis - so, predominantly active lesions*

(2013). The duration of the anti-seizure treatment in PRES is not well established.

Case report

We present the case of a 27 year old patient, diagnosed with systemic lupus erythematosus since December 2009, with renal impairment, the biopsy indicating class III - IV lupus nephritis, with impure nephrotic syndrome at the time of diagnosis. The patient presented cutaneous, joint, immunological, haematological and renal manifestations.

The patient required temporary peritoneal dialysis in 2015 for an acute kidney injury, caused by a lupus flare, through lupus vasculitis, with subsequent partial regain of the kidney function, with a maximum serum creatinine of 4 mg/dL which, after the resolution of the episode, was stabilized at 2.2 mg/dL. The patient also presented iatrogenic Cushing disease after corticosteroid therapy, secondary osteoporosis, mixt dyslipidaemia, secondary hypertension (reno-parenchymal), the maximum BP being 190/110 mmHg, chronic anaemia secondary to systemic lupus erythematosus.

Throughout the course of the disease, the patient received 6 monthly pulses of cyclophosphamide for rapidly progressive renal failure since 2015, and, in February 2016, presented another episode of acute kidney injury caused by a prerenal ischemia, with maximum creatinine levels of 3.59 mg/dL, mild hypocomplementemia and received treatment with mofetil mycophenolate 1.5 grams/day. The patient presented a good immunological and renal response, but the anaemia worsened, as a result of the mycophenolate treatment. Considering these aspects, in December 2016 the mofetil mycophenolate was replaced with azathioprine 1mg/kg/day associated with 7.5 mg oral prednisone/day.

In February 2017 the patient presented generalised tonic-clonic seizures, with altered consciousness, mild coma, headache, visual field impairment. Clinically, the patient did not present any peripheral oedemas, had normal diuresis, BP 190/110 mmHg, generalised hyperreflexia and no nuchal rigidity. The lumbar puncture did not show any pathological changes of the cerebrospinal fluid. The EEG revealed dominant alpha waves in the posterior area, without any paroxysmal events and without interhemispheric electric discharges. The cerebral CT showed small subcortical hypodense areas in the bilateral occipital lobes, with normal cerebral ventricles. The MRI revealed areas of T2/FLAIR hyperintensity predominantly in the subcortical regions and borderline frontal, parietal, occipital lobes, symmetrical and in

the lower temporal lobe and upper cerebellum, with moderate distension of the cerebral ventricular system. The patient, up to this time, presented moderate kidney failure, classified as stage III B CKD, normal electrolyte levels and slight anaemia, with a small presence of schistocytes on peripheral blood smears. The patient was recommended anti-convulsant therapy with Levetiracetam 1g/day, a diuretic, antihypertensive medication with the resolution of the seizures.

The patient presented to the neurology department after three days, with bladder distension and secondary anuria. This episode was attributed to levetiracetam treatment and the dose was reduced from 1g/day to 500 mg/day over the course of 7 days, afterwards to 250 mg/day. There were few reported cases of urine retention in patients treated with levetiracetam[15], but after reducing the doses the patient regained urinary control within 20 days. The patient had a good neurological prognosis, without motor or sensory impairment. She was treated with levetiracetam 250 mg/day for maintenance for another month. After discontinuation of the anti-convulsant medication, the patient no longer needed a urinary catheter and had full control over her bladder.

Immunosuppressive treatment with azathioprine was discontinued and mofetil mycophenolate was prescribed in dose of 1.5 g/day plus oral prednisone 20 mg/day for 3 months, after which the prednisone dose was reduced to 10 mg/day, and after another 3 months, to 5 mg/day. Kidney function stabilised at creatinine 1.78 mg/dL, with partial remission of the nephrotic syndrome (proteinuria of 2.36 g/day), with normal serum blood count.

Discussions

Posterior reversible encephalopathy syndrome (PRES) is a rare condition in lupus patients, the risk factors for developing this pathology being the female sex, young age, high blood pressure, lupus activity and the presence of lupus nephritis in the context of visceral involvement of lupus [16,17, 18]. Levetiracetam is one of the first line anti-convulsant drugs, which our patient received. One of the adverse reactions of levetiracetam is bladder distension, that is reversible after treatment discontinuation[19]. Thus, we face a case study that presents two rare pathological entities: posterior reversible encephalopathy syndrome and bladder distension secondary to levetiracetam administration, showing the complexity of the clinical activity and the fact that the patients' uniqueness determines surprising evolutions, combining frequent manifestations with rare clinical presentations, in a unique and fascinating mosaic.

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