How challenging can neuropsychiatric systemic lupus erythematous be? - experience from a tertiary care centre

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ACTA REUMATOL PORT. 2019;44:312-316

INTRODUCTION

Neuropsychiatric Systemic Lupus Erythematous (NPSLE) is a generic definition that includes a wide range of neurological and psychiatric manifestations of Systemic Lupus Erythematous (SLE). Its prevalence is highly variable (15 to 95%)[1] and strongly influenced by American College Rheumatology (ACR) nomenclature[2].

Early recognition of NPSLE manifestations is of extreme importance due to treatment and prognosis implications. Herein, we report four patients with NPSLE followed in Rheumatology and Neurology Departments of Hospital Garcia de Orta.

CASE SERIES

CASE 1

A 40-years-old male, with three-year history of SLE was admitted to hospital with sudden dysarthria, without any precipitating factor. He had documented hematological involvement and serositis, associated with antiphospholipid syndrome (APS; positive lupus anticoagulant, alveolar hemorrhage, mitral and aortic valves regurgitation with need for valve replacement and renal disease with thrombotic microangiopathy). Currently treated with hydroxychloroquine (HCQ), azathioprine (AZA; 2mg/kg/day) and warfarin. At hospital admission, only moderate dysarthria was noted. Cranium computed tomography (CT) was normal, but brain MRI demonstrated an acute ischemic stroke involving the ascending branches of the middle cerebral artery. Echocardiogram was unremarkable and laboratory showed infratherapeutic international normalized ratio (INR). The patient clinically improved was discharged under an increased dose of warfarin. He remained asymptomatic, without evidence of SLE activity, during four years, when he noted self-limited (less than 10 minutes) episodes of vertical binocular diplopia and holocranial, non-pulsatile headache, without any precipitating factor. He did not seek for medical observation until suddenly developing right central facial palsy and numbness of the right side of the body. At hospital admission, 45 minutes later, only discrete right central facial palsy persisted. INR was therapeutic and cranium CT had no acute alterations. Brain MRI showed no acute vascular lesions, but demonstrated white matter hyperintensities, microvascular in nature, and pallidum microbleeds. He completely recovered from facial palsy within the first 24 hours and was discharged under the same treatment. Nonetheless, one month later he suddenly developed gait instability with preferential deviation to the right, which spontaneously resolved within 10 minutes, and holocranial, pressure-type headache, without warning signs. Neurological examination was unremarkable. Laboratory showed slightly supratherapeutic INR. Cranium CT had no alterations, but brain MRI demonstrated an acute ischemic stroke at right postcentricity gyrus. Echocardiograms (transthoracic and transesophageal) and transcranial and carotid Doppler ultrasonography were unremarkable. In a patient with APS and recurrent thrombosis despite therapeutic anticoagulation, aspirin and rituximab (RTX; 1g twice, two weeks apart) were added, without new thrombotic events one year after first RTX cycle.

CASE 2

A 32-years-old female, with five-year history of SLE, was admitted with binocular, horizontal diplopia, associated with nausea, vomiting, vertigo and right hearing loss. One week before she reported fever and bilateral, frontal, pressure type headache. She had documented renal, articular, mucocutaneous and immunological involvement (negative antiphospholipid antibodies; aPL) and was under treatment with HCQ

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and AZA (2mg/kg/day). Neurological examination at hospital admission revealed limitation in left eye's abduction, suggesting left VI nerve palsy. Cranium CT was normal and brain MRI demonstrated focal pons' paramedian hypersignal in T2-weightened sequences and enhancement of left III and VI cranial nerve, after gadolinium administration. Audiogram revealed right, neurosensorial auditory acuity loss and laboratory showed decreased C3 and C4 complement fractions and increased anti-dsDNA antibodies and inflammatory markers. CSF disclosed 86 leucocytes/L (mainly polymorphonuclear), protein 63 mg/dL and normal glucose and septic meningitis was assumed and treated with ceftriaxone, ampicillin and acyclovir. Nonetheless, CSF turned out to be sterile and neurotropic virus research negative. NPSLE was eventually diagnosed and she started IV methylprednisolone (1g/day, 3 days), followed by prednisolone (PDN; 1mg/kg/day, in association with mycophenolate mofetil (MMF; dose titration to 2g/day). One month later, VI nerve palsy persisted and she referred onset of dysgraphia and motor discoordination during daily living activities. Neurological examination revealed left dysmetria and gait instability, without preferential lateral deviation. Brain MRI suggested cerebral vasculitis (Figure 1A and 1B) and new CSF disclosed 5 leucocytes/L, protein 29 mg/dL and normal glucose with 65 mg/dL. At this point RTX (1g, twice) was given in association with cyclophosphamide (CYC; 500mg), two weeks apart. Brain MRI one month after first RTX administration revealed improvement of vasculitic lesions (Figure 1C).

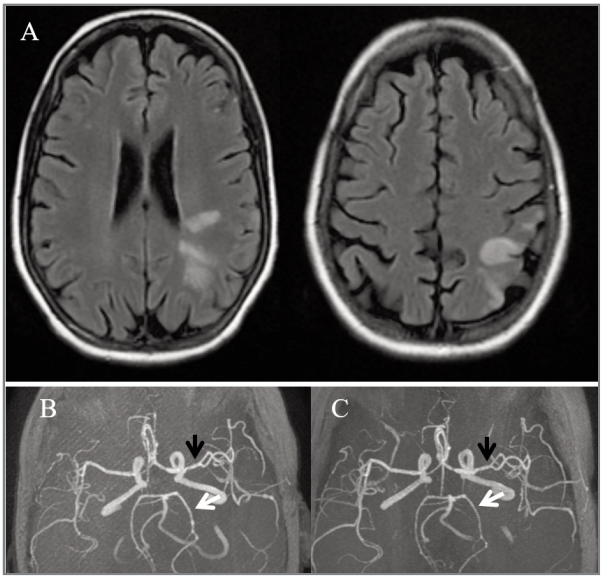

FIGURE 1. A (MRI in T2 FLAIR sequence) shows multiple ischemic lesions in different vascular territories, suggesting cerebral vasculitis. B (MRI in TOF sequence) shows segmental narrowing and irregularity of left middle (black arrow) and left posterior arteries (white arrow), with caliber improvement one month later (C), after treatment with cyclophosphamide and rituximab

CASE 3

A 39-year old female, with 13-year history of SLE with mucocutaneous, articular, lung, renal, haematological and immunological (triple positive aPL) involvement, under treatment with HCQ, PDN 10mg/day and MMF 1.5g/day, presented with holocranial, pressure type headache without warning signs, blurred vision and generalized tonic-clonic seizure. At admission she was markedly hypertensive (225/149 mmHg) and her neurological examination was unremarkable. Cranium CT and laboratory were normal. She was started on hypotensive treatment with complete recovery within 3 days and no complementary evaluation was performed.

Six months later she was readmitted with fever and holocranial, non-pulsatile headache. Laboratory showed haemolytic anaemia, thrombocytopenia, raised inflammatory markers, decreased C3 complement fraction, normal anti-dsDNA antibody and worsening proteinuria. Cranium CT was normal and CSF disclosed 230 leucocytes/L (mainly polymorphonuclear), protein 176 mg/dL and normal glucose with 60 mg/dL. Septic meningitis was assumed and she stopped MMF and started ceftriaxone, ampicillin and vancomycin. However, fever persisted (despite sterile CSF) and hyporeflexive paraparesis with total sensory loss below D10 developed. MRI demonstrated intradural-extramedullary hematoma D9-L3 secondary to traumatic lumbar puncture, which was successfully drained.

During postoperative period, she remained mildly hypertensive (medium blood pressure above 100-115 mmHg) and at the third day developed generalized tonic-clonic seizures. Brain MRI demonstrated asymmetric bilateral occipital cortical and subcortical white matter hyperintensities in T2-fluid attenuated inversion recovery sequence, suggesting posterior reversible encephalopathy syndrome (PRES). Electroencephalogram (EEG) showed teta slow wave activity located to right posterior temporal lobe, without epileptiform activity. Hypotensive treatment was readjusted and levetiracetam was added, with subsequent blood pres-

sure control and no seizure recurrence.

One month after surgery, despite intensive rehabilitation, motor and sensory alterations persisted, with onset of urinary retention. New MRI showed complete resolution of occipital oedema and holocord abnormal T2 hyperintense signal from conus medullaris into brainstem, with associated swelling, in relation to longitudinally extensive transverse myelitis (LETM; Figure 2A and 2B). Infectious and metabolic causes were excluded and anti-aquaporin-4 (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies were negative. NPSLE was assumed and she received methylprednisolone (1g/day, 3 days), followed by PDN (1mg/Kg/day) and intravenous human immunoglobulin (IVIg; 1g/kg/day for 2 days), due to persistent infection of open surgical scar. IVIg was kept monthly for 6 months, in association with HCQ and PDN 10mg/day, with resolution of MRI medullar findings and progressive neurological recovery, except for neurogenic bladder.

Twelve months after finishing IVIg she was readmitted with posterior, tension type headache, binocular horizontal diplopia and sudden loss of consciousness. At admission she was slightly hypertensive (156-75 mmHg), with neurological examination showing bilateral papilledema. Laboratory was unremarkable. Brain MRI suggested a new episode of PRES (Figure 2C).

PRES recurrence without immunosuppression or remarkable hypertension and LETM were considered NPSLE manifestations and she restarted monthly IVIg, due to recurrent cystitis in a patient with neurogenic bladder. After 5 months of IVIg no PRES recurrence occurred.

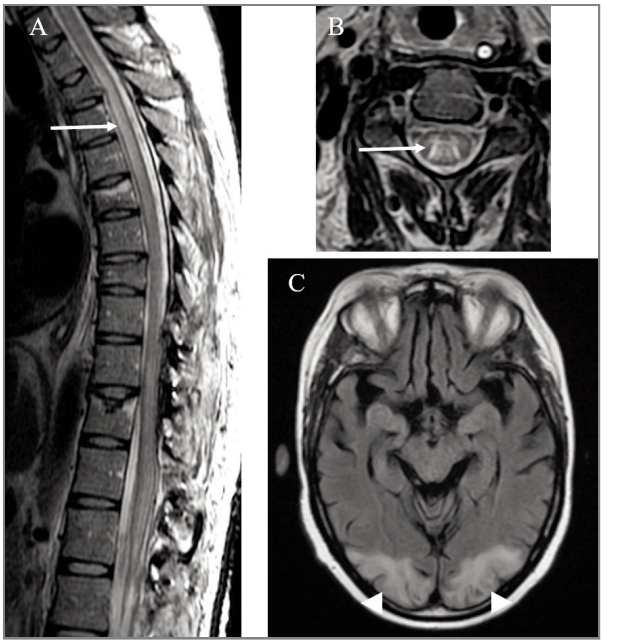

FIGURE 2. A and B (MRI in T2 FSE sequence) show abnormal hyperintense signal of spinal cord (arrow), at C4 axial level (A) and extending longitudinally through thoracic spinal cord (B). C (MRI in T2 FLAIR sequence) shows bilateral occipital cortical and subcortical white matter hyperintensities (arrowhead), compatible with posterior reversible encephalopathy syndrome

CASE 4

A previously healthy 36-years-old female with four-month history of vasculitic lesions of fingers and inflammatory poliarthralgias of hands, wrists and shoulders presented to a rheumatologist, who treated her with PDN 15mg/day and asked for complementary investigation. One week later, she suddenly developed auditory and visual hallucinations, delusional ideas of persecutory content, disorganized speech and motor agitation, which eventually led her to attempt suicide. At hospital admission, she was febrile, with psychomotor agitation and disorganized speech, but without meningeal signs. Cranium CT was normal and toxicological examination was negative. CSF disclosed 8 leucocytes/L, protein 35 mg/dL and normal glucose, with negative culture and neurotropic virus research. Brain MRI and EEG were normal. At the same time, complementary investigation showed decreased C3 and C4 complement fractions, positive antinuclear antibodies with positive anti-ds DNA and anti-ribosomal P protein (anti-Rib-P) antibodies, negative aPL, negative anti-AQP4, anti-MOG and anti-NMDA antibodies. NPSLE was assumed and the patient treated with IV methylprednisolone (1g/day, 3 days), followed by PDN (1mg/kg/day), in association with CYC (6 monthly pulses of 0.5-0.75 g/m^2 body surface) and antipsychotics, with complete neurologic recovery. Nine months after stopping CYC she remained asymptomatic, only under HCQ.

DISCUSSION

NPSLE is a complex entity, which comprise a wide range of neuropsychiatric signs/symptoms attributable to SLE. Risk factors associated with NPSLE include generalized SLE activity/cumulative damage, previous

or concurrent major NPSLE events and aPL[3].

In 1999, ACR developed a standard nomenclature and case definitions for 19 neuropsychiatric syndromes that are known to occur in SLE[2], including 12 central nervous system and 7 peripheral nervous system. However, these case definitions are not specific for SLE and other neurologic conditions reported in SLE patients, like NMO[4], PRES[5] and small fiber neuropathy[6], were excluded. More recently, Bortoluzzi et. al developed a new attribution model[7] that allowed a confident correct attribution of neuropsychiatric syndromes deemed as SLE.

Diagnostic approach of NPSLE should be similar for non-SLE patients presenting with the same manifestations [8] and mimickers like infections, drug-induced side effects, metabolic abnormalities (including alcohol-related) and malignancies have to be excluded. A general assessment of SLE activity may contribute to attribution to SLE [8].

Some autoantibodies have been implicated in specific NPSLE manifestations[9,] with aPL being largely recognized as risk factors for cerebrovascular ischemic events[10]. Nonetheless, they have also been associated with other NPSLE manifestations, such as chorea, movement disorders, cognitive dysfunction and myelopathy[11–14]. Psychosis has been associated with anti-Rib-P antibodies[15] and anti-endothelial cell antibodies[8]. Anti-glutamate receptor antibodies (ant-NMDA and anti-NR2) have been linked to cognitive dysfunction[16,17] and anti-AQP4 and anti-MOG antibodies to NMO[4].

Brain MRI remains the gold standard imaging exam in NPSLE [18], although position emission tomography can be useful in patients with neurological manifestations and normal MRI, by evaluating brain metabolic activity[19].

Management of patients with NPSLE includes symptomatic treatment and specific therapy dictated by the underlying pathophysiological process[3,20]. For instance, immune-mediated manifestations of patients with generalized lupus activity must be treated with steroids either alone or in association with other immunosuppressive drugs. Intravenous CYC associated with methylprednisolone demonstrated superiority compared to methylprednisolone alone[21] and is the drug recommended for severe NPSLE. Other immunosuppressants, like AZA and MMF, can be used as maintenance therapy after CYC or in cases of mild NPSLE[20,22,23]. In patients with severe refractory NPSLE, RTX, IVIg, plasma exchange and autologous hematopoietic stem cell transplantation can also be considered[3,20]. In case 2, cranial palsy was considered a mild NPSLE manifestation and therefore treated with MMF. However, as the patient developed one month later acute and severe cerebral vasculitis, we decided to switch treatment to CYC and RTX. In case 4, the severity of NPSLE manifestation, which was part of disease presentation, was responsible for the choice of CYC as the first treatment. IVIg might be particularly useful for patients with contraindication for standard immunosuppression, like infection, as in case 3.

Treatment of ischemic NPSLE includes control of cardiovascular risk factors, antiplatelet agents and/or anticoagulation[3,20]. Patients without aPL or who do not fulfill criteria for APS must receive aspirin as secondary thromboprophylaxis, while patients who fulfill criteria for APS must receive vitamin K antagonists[20]. In patients with APS and recurrent thrombosis, addition of aspirin[20] or treatment with high-intensity warfarin (INR 3-4) might be considered[24]. In patients with thrombotic recurrences despite adequate target INR, RTX has also demonstrated a beneficial effect[25], and was therefore added in case 1, after failure of therapeutic anticoagulation and aspirin.

In conclusion, NPLSE diagnosis can be extremely challenging and less specific manifestations, such as headache, cognitive dysfunction and mood disorders are the most commonly reported in literature[8]. Despite the small number of cases, this work is a single-centre experience, which presents some of the rarer NPSLE manifestations and in some cases with more than one manifestation in the same patient.

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