SHORT COMMUNICATION

Mycophenolate Mofetil as a Potential Therapeutic Option for Neuropsychiatric Lupus: A Case Report

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ABSTRACT

Neuropsychiatric lupus manifests clinically in a multitude of syndromes. The lack of specificity of serological and radiological tests make the confirmation of its diagnosis a challenge. The pathophysiology of neuropsychiatric lupus is not well understood and its evidence-based pharmacological treatment remains unestablished. We describe a patient who had bipolar affective disorder and angiographic evidence of cerebral arteritis that resolved with immunosuppressive therapy alone. Concomitantly, there was lupus-associated acute pancreatitis. Immunosuppressive therapy with high-dose corticosteroids had initiated control of active disease. Azathioprine, subsequently commenced as the steroid sparing agent, was discontinued because of adverse-effects. Disease-remission was later achieved and maintained with mycophenolate mofetil and low-dose prednisolone for 4 years. Though further studies are needed to confirm this observation, mycophenolate mofetil, a well-tolerated and established therapy for lupus nephritis and showing promise for the treatment of an increasing number of lupus-related pathologies, may be considered as a therapeutic option for neuropsychiatric lupus.

Keywords: Central nervous system, Mycophenolate mofetil, Neuropsychiatric, Pancreatitis, Systemic lupus erythematosus

INTRODUCTION

Neuropsychiatric systemic lupus erythematosus (NPSLE) and systemic lupus erythematosus (SLE)-related acute pancreatitis are poorly understood manifestations of SLE. Whilst high-dose corticosteroids can initiate disease-remission, a steroid sparing agent is often necessary for maintenance of disease remission. Thus far, disease-remission has been achieved and maintained with mycophenolate mofetil (MMF) and low-dose prednisolone for four years. This case report suggests that MMF may be a therapeutic option for NPSLE and lupus-associated acute pancreatitis.

CASE REPORT

A 32-year-old Indian lady, who had no past medical history, presented with increasing abdominal discomfort which started two days prior to hospital admission. She had a six-month history of fatigue and mild arthralgia. A few weeks before presentation, the patient became more talkative and hyperactive than usual, interspersed with abrupt brief episodes of severe low-moods. There was no history of thromboses or miscarriages. She did not have any other symptoms and did not take any prescribed or illicit drugs. There was no family history of illnesses.

On examination, she was afebrile and followed commands, but more hyperactive. Blood pressure was stable at 130/80 mm Hg. The abdomen was tender at the epigastric region with no rebound phenomenon. Apart from being talkative and fidgety, the neurological examination did not reveal any abnormality. The remainder of the examination was unremarkable.

The results of investigations were as follows (reference ranges are indicated in parenthesis): Haemoglobin was 10.5 g/dL (12–16 g/dL), leucocyte count 2.73×10^9/L ($4\text{-}10\times10^9$/L), platelet count 102×10^9/L ($140–440\times10^9$/L). Erythrocyte sedimentation rate (ESR) was 125 mm/hr (3–15 mm/hr), C-reactive protein 1.1 mg/L (0.2–8.8 mg/L). Complement C3 was 0.31 g/L (0.49–1.28 g/L) and C4 0.08 (0.20–0.72 g/L), serum amylase 255 U/L (44–161 U/L). Urea and electrolytes and thyroid biochemical profile were normal. Creatinine clearance was normal but there was significant proteinuria of 1.53 g/day (0.0–0.15 g/day). Anti-nuclear antibodies (ANA) was 1:800-speckled pattern with nuclear dots, anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody 72.3 IU/ml (<20 IU/ml) and tests for anti-Smith and anti-ribonucleoprotein antibodies were positive. Anticardiolipin immunoglobulin M (IgM) antibody titre was low-positive at 28 MPL but anticardiolipin IgG antibody and lupus anticoagulant tests were negative. The patient declined a lumbar puncture. Transthoracic echocardiography was unremarkable. The renal biopsy showed histological findings consistent with International Society of Nephrology and the Renal Pathology Society (ISN/RPS) class II lupus nephritis. Computed tomography (CT) scan of the abdomen showed textural alteration with generalised swelling of the pancreas indicative of acute pancreatitis. Magnetic resonance imaging (MRI) with angiography (MRA) of the brain revealed findings that were suggestive of an arteritis. There were multiple areas of stenoses and irregular patencies at the terminal internal carotid arteries and origins of bilateral middle cerebral arteries with beading of its branches consistent with a vasculitic process (Fig. 1).

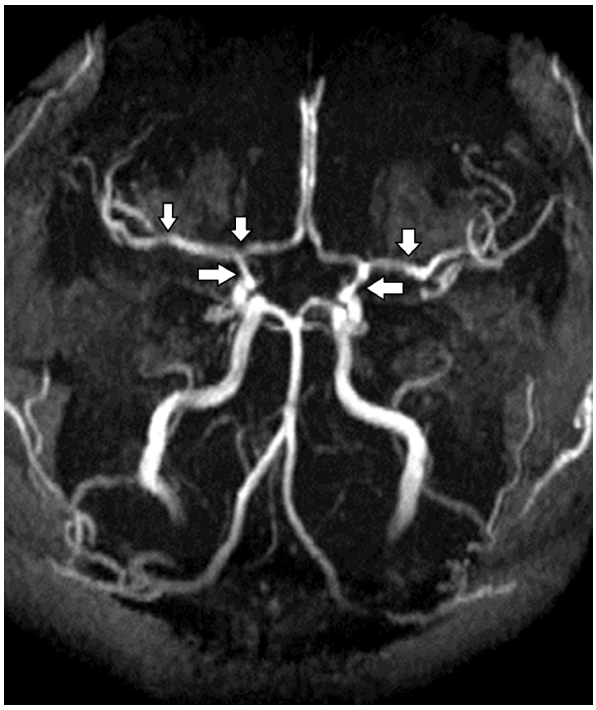

Fig. 1. Magnetic resonance angiography performed on admission that showed stenoses and irregular patencies at segments of bilateral terminal internal carotid arteries and middle cerebral arteries (white arrows) with beading-pattern of its branches consistent with arteritis.

A diagnosis of SLE with associated neuropsychiatric disease and acute pancreatitis was made. The pancytopenia and acute pancreatitis improved within one week of initiating intravenous hydrocortisone 100 mg every 6 hourly, and that corresponded with a reduction in ESR and rise of complements C3 and C4 levels. Azathioprine was initiated by the time the prednisolone was tapered to 0.5 mg/kg/day. However, the patient had intractable nausea and recurrent respiratory tract viral-illnesses. In addition, there was leucopenia (1.4×10^9/L) approximately two months after commencing azathioprine which recurred despite a lower starting and maintenance-dose of azathioprine. On both occasions of leucopenia, the clinical status of the patient and lupus-activity markers were not consistent with a flare of SLE. Azathioprine was therefore permanently discontinued.

Shortly after the discontinuation of azathioprine, a relapse of NPSLE, as evidenced by recurrence of manic-depressive symptoms and a corresponding fall in serum complements C3 and C4, rise in ESR and recurrence of pancytopenia, had occurred despite a very gradual taper of moderate-dose prednisolone that had been increased when azathioprine therapy ceased. Her pancreatitis did not recur. The flare of NPSLE was treated by increasing the daily dose of oral prednisolone to 1 mg/kg and at this point, MMF was introduced at 500 mg twice daily as the steroid-sparing agent.

The patient's psychiatric symptoms and pancytopenia completely resolved within six months of commencing immunosuppressive therapy. Thus far, after four years of treatment with MMF, the patient remains well on 1g twice daily. Prednisolone has been very gradually tapered to 2.5 mg daily. Low-dose risperidone, commenced on the advice of the psychiatric team upon diagnoses of NPSLE, was discontinued after one month because of resolution of the psychiatric symptoms. A follow-up MRI and MRA of the brain performed 18 months

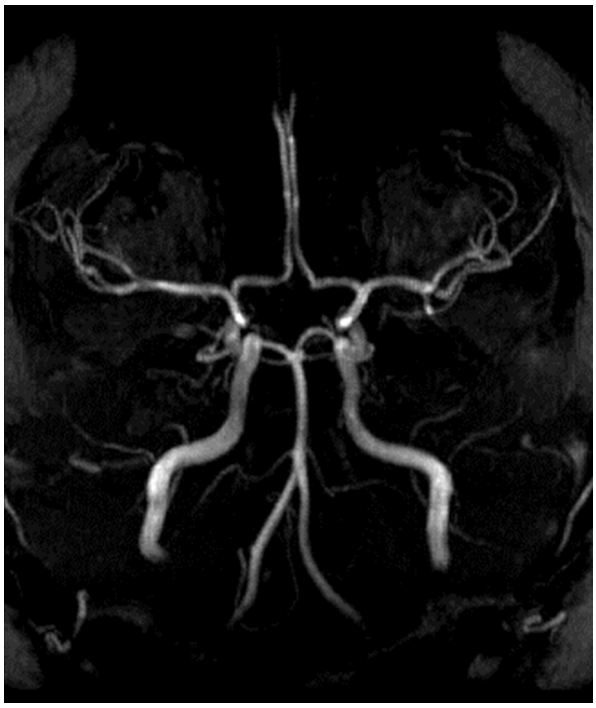

Fig. 2. Magnetic resonance angiography that showed reversibility of cerebral arteritis. This corresponded with resolution of neuropsychiatric lupus-disease with mycophenolate mofetil therapy

after diagnosis showed resolution of the cerebral arteritis (Fig. 2). Currently, repeated anti-dsDNA and anticardiolipin serology tests have been negative and complement C3 and C4 titre values are within normal limits.

DISCUSSION

The pathophysiology of NPSLE is not well understood, in part due to the difficulty in obtaining central nervous system tissue for analyses. Previously, proposed mechanisms involve immune-complex or autoantibody activation of endothelial cells, vessel wall thickening and stenosis, antiphospholipid antibody-mediated thromboses and breach of the blood-brain barrier (BBB)[1].

Establishing a diagnosis of NPSLE may be challenging because of several reasons. It has a multitude of clinical presentations and at present, there is a lack of a confirmatory test. The American College of Rheumatology (ACR) nomenclature facilitates research by standardising the types of NPSLE syndromes[2]. However, neither does it define more subtle psychiatric manifestations nor does it aid in situations such as differentiating NPSLE-related organic brain syndrome from primary psychiatric disorders. Another frequent diagnostic conundrum lies in determining whether the patient's psychiatric symptoms are corticosteroid therapy-induced or if they are indeed related to NPSLE-disease itself.

Several brain MRI scan findings such as multiple T2-weighted frontal-parietal lobe white matter lesions, premature global atrophy and vessel stenosis are found in patients with NPSLE but they are not specific to the disease[3]. Although there are no definitive imaging modalities that show characteristic findings of NPSLE, the combination of MRI and its advanced techniques such as magnetic resonance spectroscopy, magnetisation transfer imaging, diffusion-weighted imaging and diffusion-tensor imaging show potential in increasing diagnostic specificity for NPSLE[4].

Several autoantibody specificities such as anti-ribosomal P antibodies have been reported in patients with NPSLE. However, thus far, their diagnostic value may be limited due to the conflicting results of disease-association[5]. Further studies of known autoantibodies and especially novel brain-reactive autoantibodies associated with NPSLE are therefore warranted[6].

In this patient, a diagnosis of NPSLE was based on several findings. The patient had fulfilled the ACR classification criteria for SLE and had acute onset of symptoms of hypomania and endogenous depressive-illness as determined by psychiatric evaluation. Magnetic resonance imaging and MRA of the brain showed findings that were consistent with a vasculitic process rather than other pathology such as vasospasm. There were no other abnormalities such as metabolic and cardiovascular derangements that could account for the neuropsychiatric symptoms or the angiographic findings. It was unlikely that the patient had meningoencephalitis because, in the absence of the use of any antimicrobial treatment, an occult infective process would have likely manifested in a florid manner during the high-level immunosuppressive therapy.

Resolution of the patient's psychiatric syndrome that corresponded with marked improvement of inflammatory and serological markers of SLE and radiological demonstration of reversibility of cerebral arteritis with immunosuppressive therapy alone lends further evidence for a diagnosis of NPSLE. Systemic lupus erythrematosus-associated acute pancreatitis in this patient whom was steroid-naïve at presentation was diagnosed based on abdominal pain and tenderness, hyperamylasaemia

and CT scan findings. The patient did not receive any anti-platelet or anticoagulation treatment suggesting that the cerebral artery abnormalities were less likely to be thrombotic in nature.

Therapy for NPSLE involves a multidisciplinary team, which includes the psychiatrist, neuropsychologist and rheumatologist. The mainstay of therapy for NPSLE is immunosuppression if the neuropsychiatric manifestations are deemed to be due to autoimmune-mediated inflammatory injury[7,8], or anticoagulation if the neuropsychiatric manifestations are deemed to be due to a prothrombotic state secondary to anti-phospholipid antibodies[9]. The only randomised controlled trial in NPSLE demonstrated a better response to therapy with intravenous cyclophosphamide compared to intravenous methylprednisolone in 32 patients over two years[8]. An open-label study of 13 patients with NPSLE treated with oral cyclophosphamide 1–2mg/kg/day for six months followed by azathioprine 1–2 mg/kg/day also demonstrated clinical efficacy[7]. Anticonvulsants for seizures, antidepressants for mood disorders and antipsychotics for psychosis are useful adjuncts[10]. Pharmacologic therapy in cognitive impairment is uncertain[11]. Patients with NPSLE that participated in cognitive rehabilitation have reported better affect and quality of life, as well as memory self-efficacy[12].

The patient required treatment for SLE-related cerebral arteritis and acute pancreatitis. Therefore, azathioprine or cyclophosphamide was considered because of their proven efficacy for autoimmune vasculitides. However, cyclophosphamide was not commenced because of its serious toxicity profile, which includes reducing fertility. The patient was therefore commenced on azathioprine but it was withdrawn due to unacceptable adverse-effects. MMF was then initiated and able to further induce, and subsequently maintain disease-remission of SLE. Anticoagulation was not commenced in our patient as there was no previous thrombotic history or miscarriages, her antiphospholipid antibodies were not of moderate to high titre, and there were no thromboses noted on the MRA of the brain.

The improvement of this patient's cerebral arteritis was initially induced by corticosteroids. A steroid-sparing agent was necessary because a flare of disease had occurred despite tapering the moderate doses of daily prednisolone very gradually. The logic for using MMF as an immuno-suppressive agent in this patient with NPSLE was in part due to its efficacy in other immune-mediated central nervous system disorders such as multiple sclerosis[13,14], and its previous reported efficacy[15]. It is not known if either MMF or its active derivative crosses the BBB. However, it may be possible that its potent cytostatic effect on T and B-lymphocytes may cause immunomodulation outside of the BBB which consequently may down-regulate pathogenic NPSLE-related autoantibodies and cytokine activity at neuronal tissue-level.

B-cell depletion is an emerging targeted therapy for NPSLE. B cells are central to the pathogenesis of SLE, as they secrete proinflammatory cytokines; are precursors for plasma cells that secrete antibodies; and present antigens to T cells and other B cells[16]. Rituximab is an anti-CD20 monoclonal antibody, and it triggers B-cell death via at least three mechanisms: antibody-dependent cell-mediated cytotoxicity (ADCC); complement-dependent cytotoxicity (CDC); and direct induction of apoptosis[17]. Numerous case reports and open-label studies have described the efficacy of rituximab in NPSLE, with complete or partial therapeutic response being achieved in 85% of patients after one cycle of rituximab[18]. Belimumab is a fully humanised monoclonal antibody that binds to soluble B-lymphocyte stimulating factor (BLyS), a growth factor essential for B-cell survival, maturation and activation and immunoglobulin production by B cells, as well as development of B cells into plasma cells[19]. Following two large, phase 3, multicenter, prospective, randomised, controlled trials, BLISS-52[20] and BLISS-76[21], belimumab has been approved by the Food and Drug Administration (FDA) in 2011 for use in active, autoantibody-positive SLE in addition to standard therapy. The BLISS trials showed a clinically and statistically significant reduction in SLE disease activity and flare rates, steroid use, and prolonged time to lupus flare in patients. Overall improvement with belimumab treatment was seen in the small number of patients with baseline neurological involvement (n=45), with the most common abnormality involved being lupus headache (n=24). Improvement rates for headache with placebo and belimumab 1 and 10 mg/kg were 20.0%, 100% and 69.2%, respectively[22]. However, it is important to note that patients with severe active central nervous system involvement were excluded from the trials, and majority of the patients with

neurological involvement were of British Isles Lupus Assessment Group (BILAG) C category[22].

Mycophenolate mofetil is generally well-tolerated. It is less toxic than azathioprine and cyclophosphamide and is emerging as a promising therapeutic agent for an increasing number of SLE manifestations[23]. In order to determine the efficacy of MMF for NPSLE, analyses such as case-controlled studies or if feasible, randomised trials, would require a sufficient number of NPSLE patients who meet formulated and standardised classification criteria. Pending the results of those studies to confirm this observation, MMF may be considered as a therapeutic option for neuropsychiatric lupus.

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