

## Systemic Lupus Erythematosus with Neuromyelitis Optica

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### Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease that can have detrimental effects on many different systems in the body, including the central nervous system. Neuropsychiatric SLE (NPSLE) refers to several different neurological and/or behavioral clinical syndromes, and has been reported as having a prevalence rate of approximately 30–40%, while manifestation of myelitis or optic neuritis of NPSLE is rare (~1%). Myelitis and optic neuritis are easily identifiable since myelitis is frequently transverse, and manifests as severe disturbances in both motor and sensory pathways, while optic neuritis is often both bilateral and severe. At least 85% of patients experience relapses in the form of optic neuritis, transverse myelitis, or both. Furthermore, some cases of NPSLE with optic neuritis are often complicated by myelitis. Interestingly, the characteristics of myelitis or optic neuritis in NPSLE are quite similar to neuromyelitis optica (NMO), a disease characterized by bilateral optic neuropathy and transverse myelopathy. In fact, magnetic resonance imaging (MRI) of patients with NPSLE has demonstrated longitudinal spinal involvement showing cord swelling and hyperintense lesions in central regions. These findings are also typically observed in MRIs of patients with NMO. Additionally, anti-aquaporin 4 (AQP4) antibodies have been discovered in patients with NMO and with NPSLE with myelitis and/or optic neuritis. Therefore, complications that are often encountered with NMO should be considered when treating cases of NPSLE with myelitis and/or optic neuritis. Moreover, since the treatment of NMO closely resembles the therapeutic approaches taken for NPSLE, corticosteroids alone or in combination with immunosuppressants could prove effective in reducing incidents of relapse. Some patients, however, may be refractory to steroid therapy; in such cases, plasma exchange may have priority over other second-line therapeutic strategies, such as intravenous immunoglobulin and rituximab, because of treatment approaches typically employed in NMO. In this review, I will discuss pathological similarities between NPSLE with myelitis and/or optic neuritis and NMO with the aim of demonstrating that our knowledge of NMO should be considered when treating NPSLE with myelitis and/or optic neuritis.

**Keywords:** Neuropsychiatric lupus; Anti-aquaporin-4 antibody

### CNS Involvement in SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease that can have detrimental effects on the central nervous system (CNS). Neuropsychiatric SLE (NPSLE) refers to several different neurological and/or behavioral clinical syndromes such as stroke, seizures, myelopathy, mood disorders, and cognitive impairment [1] (Table 1), and a 30–40% prevalence rate of NPSLE has recently been reported [2]. In a 3-year prospective study of 370 patients with SLE and no history of CNS complication, 16/370 patients were reported to develop major CNS-related events including myelopathy (4/16), optic neuritis (1/16), and positive neuromyelitis optica (NMO)-IgG antibodies (2/16) [3]. It has been shown that antiphospholipid antibodies including anti-cardiolipin and lupus anti-coagulant are some of the strongest NPSLE-related factors expressed especially in relation to cerebrovascular disease [4,5]. One study also reported anti-ribosomal P antibodies as risk factors for SLE psychosis [6]; however, this is inconclusive since another report showed no relation between these antibodies and neuropsychiatric illness [7]. Moreover, anti-double stranded DNA antibodies (anti-dsDNA), which are the most represented autoantibodies in SLE, are reported to cross-react with NR2A and NR2B subunits of the N-methyl-D-aspartate receptor (NMDAR) [8,9]. Thus, anti-NMDAR antibodies seem to correlate

with CNS manifestation of NPSLE including cognitive impairment and depression [8,9]. Recently, anti-aquaporin-4 (AQP4) antibodies were discovered in patients with NMO [10] and in patients with NPSLE, especially with myelitis or optic neuritis [11-13]. The relevance of this antibody will be discussed in the following section.

### Neuromyelitis Optica

NMO first described by Devic in 1894 is a disease characterized by bilateral optic neuropathy and transverse myelopathy, which can be pathologically identified by severe demyelination and necrotic changes [14]. Approximately one century after Devic's initial report, neurologists in Western countries diagnosed severe opticomyelitis with NMO regardless of relapse status, while neurologists in Asian countries classified such cases as an opticospinal form of multiple sclerosis (OSMS) in cases of relapse and Devic's disease in cases where a monophasic pattern emerged [15,16]. However, the discovery of NMO-IgG by Lennon et al. in 2004 caused a paradigm shift in the diagnosis and treatment of NMO [17]. In 2006, both United States and Japanese groups reported that cases of Japanese OSMS were very similar to NMO [15], and the diagnostic criteria for NMO were revised that same year [18]. Lennon et al. also found that NMO-IgG binds to a dominant water channel expressed on the foot process of astrocytes called aquaporin-4 (AQP4) [10,19,20]. As discussed, anti-AQP4 antibodies have been discovered both in patients with NMO and with NPSLE.

S.No	Manifestations
1	Common (5–15% cumulative incidence)
2	Cerebrovascular disease
3	Seizure
4	Relatively uncommon (1–5%)
5	Cognitive dysfunction
6	Major depression
7	Acute confused state
8	Peripheral nervous disorders
9	Rare (<1%)
10	Psychosis
11	Myelitis
12	Chorea
13	Cranial neuropathies (including optic neuropathy)
14	Aseptic meningitis

**Table 1:** Major manifestations of CNS lupus [3].

Optic neuritis in NMO is often both bilateral and severe [21,22] and patients of NMO with optic neuritis have a higher likelihood of permanent vision loss than patients with typical optic neuritis such as multiple sclerosis (MS) [23]. In contrast to optic neuritis, myelitis in NMO is frequently transverse, and manifests as severe disturbances in both motor and sensory pathways at the same time as the appearance of disruptions to bowel and bladder functions [24]. At least 85% of patients experience relapses in the form of optic neuritis, transverse myelitis, or both [24]. Moreover, over 50% of relapses occur in the first year, approximately 75% of relapses occur within 3 years, and 90% of relapses occur within 5 years [24]. One study investigated the spinal cord of patients with NMO using axial magnetic resonance imaging (MRI) and found that over 60% of lesions exhibited T2-hyperintense regions that comprised of more than 50% of the cord area, and that these regions were mainly located in the central grey matter [20]. In relation to other autoimmune diseases and auto-reactive antibodies, 70% of patients with NMO have at least one auto-reactive antibody (except for NMO-IgG), and thus it seems that systemic autoimmune diseases including SLE are fairly similar to NMO [25].

## NMO-related Manifestations in NPSLE

### Myelitis

About 1–2% of patients with SLE exhibit myelitis [26], and a retrospective study of 22 patients affected by NPSLE with myelitis reported that 20 of the 22 patients were female [27]. Interestingly, this rate is similar to the female/male ratio that has been found in cases of NMO [20]. Moreover, 50% of these patients presented with signs of impairments to gray matter as characterized by flaccidity and hyporeflexia indicating nucleus dysfunction, while the other 50% of patients presented with signs of white matter damage as characterized

by spasticity and hyperreflexia indicating pyramidal tract dysfunction [27]. The patients with impaired white matter regions had a history of optic neuritis and displayed higher levels of anti-AQP4 antibodies than patients with grey matter dysfunction; however, MRIs of both groups showed long cord lesions that spanned at least three vertebral segments, indicative of NMO. In total, 50% of the patients affected by NPSLE and myelitis in their study also satisfied criteria for the NMO spectrum of disorders [27].

### Optic neuritis

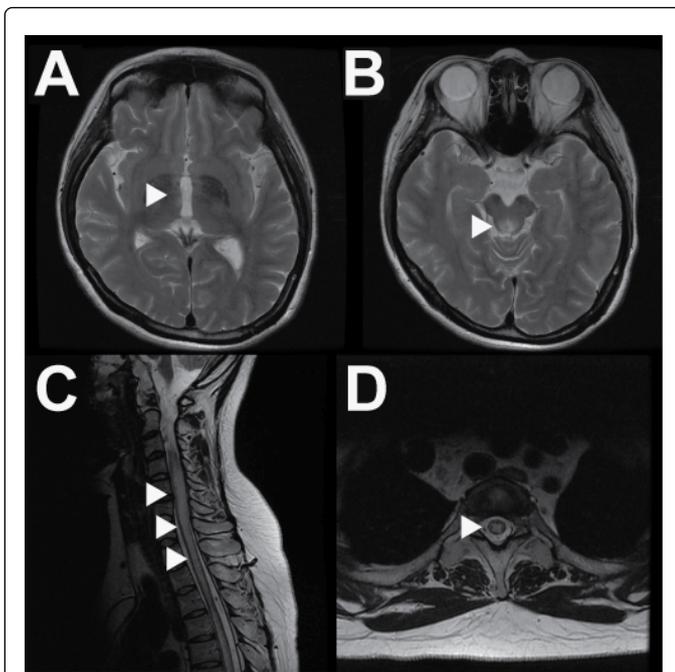
Optic neuropathy in NPSLE includes inflammatory optic neuritis and ischemic optic neuropathy [4]. Ischemic optic neuropathy is usually unilateral and occurs in patients with anti-phospholipid antibodies [4]. In contrast, optic neuritis is commonly bilateral in SLE [4], which results in a worse outcome compared to optic neuritis with MS. Interestingly, it has been suggested that bilateral optic neuritis and poor outcome are typically indicative of NMO. Therefore, characteristic manifestations of NPSLE also overlap with those of NMO.

### Syndrome of inappropriate antidiuretic hormone secretion

Seizures or acute states of confusion are canonical manifestations in NPSLE. In fact, a study in Thailand reported that about 6% of NPSLE cases presented with clinical manifestations of altered consciousness [28]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a hypothalamic-pituitary disease defined by hyponatremia and hypo-osmolality resulting from inappropriate continued secretion of the antidiuretic hormone despite increased plasma volume. Clinical symptoms mainly present as altered consciousness including confusion, disorientation, delirium, and generalized seizures. SLE-related SIADH is rarely reported [29] and, to our knowledge, no studies have been done to investigate the relationship between SIADH and anti-AQP4 antibodies. However, it has been reported that the hypothalamus is sometimes involved [30,31], which is an area of the brain that is known to have high levels of AQP4 expression [32] (Figure 1A and 1B).

### MRIs of NPSLE with Optic Neuritis or Myelitis

Representative MRIs of patients with NPSLE have reported such changes as cerebral atrophy, ischemic changes, intracranial hemorrhage, dural venous thrombosis, posterior reversible encephalopathy syndrome, rhombencephalitis (brainstem encephalitis), infections, and myelitis [33]. Small nonspecific T2-hyperintense lesions in deep white matter are usually seen in the brains of both patients with and without NPSLE. However, T2-hyperintense lesions larger than 10 mm are typically only reported in patients with NPSLE [34]. According to myelitis, MRIs of spinal cords in patients with NPSLE have been described in several case reports showing heterogeneous findings [35]. For example, Provenzale et al. reported eight episodes of transverse myelitis in four patients and consistently observed prolonged signals on T1- or T2-weighted MRIs as well as cord enlargement in 75% of the episodes [36]. Moreover, Deodhar et al. reported the first case of SLE with longitudinal myelitis in 1999 [37] and other groups have reported MRI findings of NPSLE with longitudinal spinal involvement [38,39] (Figure 1C), many of which showed T2-hyperintense lesions in central regions of the spinal cord and cord swelling, which are the typical MRI findings in NMO (Figure 1D).



**Figure 1: Typical MRIs of SLE with NMO.** (A) T2-weighted axial images indicate hyperintense lesions in the hypothalamus (B) and periaqueductal, which highly express the aquaporin 4 molecule. (C) A T2-weighted sagittal image of the spinal cord indicates the swelling and longitudinal lesion. (D) A T2-weighted axial image of the spinal cord indicates a hyperintense lesion in the central parts of the spinal cord.

### NPSLE and Anti-AQP4 Antibodies

It has been reported that anti-AQP4 antibodies can only be observed in patients with NMO spectrum disorders and not in patients with Sjögren syndrome/SLE with neurological manifestations but without optic neuritis or myelitis [11]. In fact, Závada et al. demonstrated that out of 76 serum samples obtained from patients with NPSLE only one sample derived from a patient with NPSLE and transverse myelitis was positive for anti-AQP4 antibodies [12]. On the other hand, in a case report by Kolfenbach, 1/7 patients with NPSLE and transverse myelitis tested positive for anti-AQP4 antibodies [13].

### Treatment

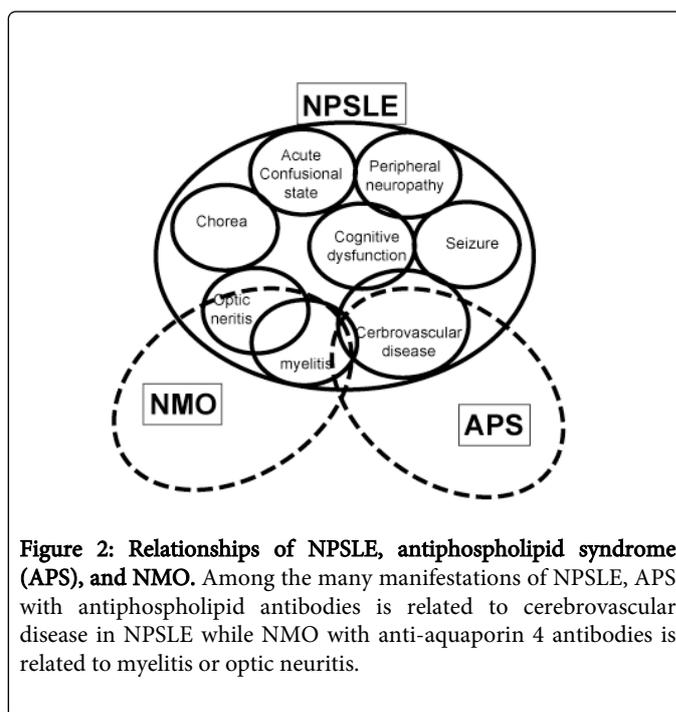
Steroid therapy such as high-dose intravenous methylprednisolone is often used to treat acute exacerbations of both NPSLE and NMO. However, some patients may be refractory to steroid therapy. In these cases, plasma exchange [40], intravenous immunoglobulin [41], and rituximab [42] have been used second-line therapeutic strategies. In cases where NMO is not responsive to steroids, plasma exchange therapy is typically selected [43-45]. Therefore, plasma exchange may have priority over other second-line therapeutic approaches in NPSLE with myelitis and/or optic neuritis. In instances of cerebrovascular disease where anti-phospholipid antibodies have been identified anticoagulation therapy is typically performed. Of note, immunomodulating agents that have been established as effective

treatments for MS may severely exacerbate both NMO [46,47] and SLE [48].

Therefore, corticosteroids alone or in combination with immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide) should prove effective in reducing incidence of relapse in both NMO [49-51] and NPSLE [4,52]. As described above, treatment of NMO is very similar to that of NPSLE, and this has been demonstrated in two patients with NMO and NPSLE who were successfully treated with high-dose corticosteroid therapy following plasmapheresis with azathioprine or cyclophosphamide [53].

### Conclusions

Manifestations of myelitis or optic neuritis in NPSLE are rare and display characteristic onsets. Myelitis is often transverse, recurrent, and longitudinal, while optic neuritis is usually bilateral and resistant to therapy with high-dose intravenous methylprednisolone alone or in combination with immunosuppressive agents [4]. Moreover, the patients with optic neuritis are often complicated by myelitis [4]. T2-weighted MRIs of spinal cords in patients with NPSLE and myelitis often exhibit cord swelling and hyperintense signals that are localized in the central part of the spinal cord. Interestingly, the way that NPSLE manifests and the pathology that is visualized on MRIs are quite similar to the characteristics of NMO. In fact, many NPSLE cases with myelitis and/or optic neuritis are often positive for anti-AQP4 antibodies (Figure 2). Taken together this suggests that complication often encountered with NMO should be considered when treating cases of NPSLE with myelitis and/or optic neuritis [54]. Furthermore, corticosteroids alone or in combination with immunosuppressants (azathioprine, mycophenolate mofetil, and cyclophosphamide) should prove effective in reducing incidents of relapse of both NMO and NPSLE.



**Figure 2: Relationships of NPSLE, antiphospholipid syndrome (APS), and NMO.** Among the many manifestations of NPSLE, APS with antiphospholipid antibodies is related to cerebrovascular disease in NPSLE while NMO with anti-aquaporin 4 antibodies is related to myelitis or optic neuritis.

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