Systemic Lupus Erythematous (SLE) Complicated by Neuromyelitis Optica (NMO – Devic’s Disease): Clinic-Pathological Report and Review of the Literature

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ABSTRACT: Neuromyelitis optica (NMO) is usually a relapsing demyelinating disease of the central nervous system associated with optic neuritis, transverse myelitis involving three or more contiguous spinal cord segments, and seropositivity for NMO-IgG antibody. NMO is often mistaken for multiple sclerosis and there are relatively sporadic publications about NMO and overlapping systemic or organ-specific autoimmune diseases, such as systemic lupus erythematosus (SLE). We described a unique case of a 25-year-old Arab young woman who was diagnosed with SLE, depending on clinical, laboratory investigations and after she had fulfilled the diagnostic criteria for SLE and had presented the following findings: constitutional findings (fatigue, fever, and arthralgia); dermatologic finding (photosensitivity and butterfly rash); chronic renal failure (proteinuria up to 400 mg in 24 hours); hematologic and antinuclear antibodies (positivity for antinuclear factor (ANF), anti-double-stranded DNA antibodies, direct Coombs, ANA and anti-DNA, low C4 and C3, aCL by IgG and IgM). Recently, she presented with several episodes of transverse myelitis and optic neuritis. Clinical, radiological, and laboratory findings especially seropositivity for NMO-IgG were compatible with NMO. Accurate diagnosis is critical to facilitate initiation of immunosuppressive therapy for attack prevention. This case illustrates that NMO may be associated with SLE.

KEYWORDS: NMO, systemic lupus erythematosus, NMO-IgG antibody

INTRODUCTION: Neuromyelitis optica (NMO) was described by Eugène Devic in 1894 and it is known since then as Devic’s NMO (Devic’s disease). It is uncommon heterogeneous inflammatory demyelinating neuro-immunological disease of the central nervous system (CNS) that can occur idiopathically or in conjunction with other systemic diseases. NMO diagnostic criteria are characterized by sequential or concomitant attacks of transverse myelitis and optic neuritis, with contiguous spinal cord MRI lesion extending over three or more vertebral segments, and seropositivity for NMO-IgG (anti-aquaporin-4 (anti-AQP4)), which has been recently described as a sensitive and specific marker for NMO.¹⁻⁸

NMO affects both genders with three to nine times more prevalent in women than in men, the age of onset ranges from childhood to late adulthood, with a median of 20 to 50 years among adults and 4.5 years among children. However, NMO frequency is more or less the same worldwide.⁹

Some population-based studies have reported an NMO prevalence of 0.5 per 100,000 in Cuba,¹⁰ 1.0 per 100,000 in Mexico,¹¹ 2.0 per 100,000 in the United Kingdom,¹² 1.4–2.8 per 100,000 in the United States,¹³ and 4.4 per 100,000 in Denmark.¹⁴
In the past, the mortality rate was roughly 33% and globally affecting less than an estimated five persons per million populations per year. However, newer cohorts have shown that the mortality rates seem to be lower probably owing to the increased awareness for the condition along with the broad availability of anti-aquaporin-4 (anti-AQP4, antibody testing). 

Although NMO is rarely described in patients with SLE, the first published report was that of a 21-year-old woman with a four-year history of paraparesis and incontinence who developed right-sided retrobulbar optic neuritis. In fact, pathophysiological link between SLE and NMO has not yet been established completely, some studies estimated that the chances of a patient having both SLE and NMO were 1 in 5,000,000.

Our study comes to shed light and strengthen the fact that link between SLE and NMO can happen early or late during the life span.

SLE is a multiorgan and multisystem autoimmune disorder and its pathophysiology may have protein effects on all components of the CNS. The CNS and peripheral nervous systems (PNS) may be involved in SLE. About 25% of SLE may begin in childhood, and SLE may present both steadily chronic and more episodic neurologic symptoms throughout the life span. The presentation of symptoms and clinical signs are a reflection of the location and type of pathophysiology of the disease in which there is chronic inflammation of varied degrees that may wax and wane.

SLE is a pattern of autoimmune disease characterized by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations. The main pathological findings in patients with SLE are those of inflammation, vasculitis, immune complex deposition, and vasculopathy. The precise pathoetiology of SLE remains subtle. An extremely complicated and multifactorial interaction among a variety of genetic and environmental factors are probably involved. Polygenes contribute to disease vulnerability. The interface of hormonal milieu, gender, and the hypothalamo–pituitary–adrenal axis changes this vulnerability and the clinical expression of the disease. Faulty immune mechanisms, such as the clearance of apoptotic cells and immune complexes, are significant contributors to the development of SLE. The underlying causes of the disease may be explained by the deficit of immune system and the presence of environmental risk factors that trigger the disease.

NMO may present a different spectrum of symptoms; generally, it is presented as an acute disease, with an onset in 30–50% of the cases preceded by a virus-like syndrome, with headache, sore throat, fever, and malaise; ascending myelitis resulting in pain, which may be severe; numbness; weakness or acute respiratory and gastrointestinal symptoms. Sometimes patients may experience vision impairment, hearing impairment, olfactory dysfunction, pain, and cognitive dysfunction and various degrees of paralysis, as well as incontinence. NMO is a distinct autoimmune condition that may co-occur with SLE or other autoimmune diseases such as acute demyelinating encephalomyelitis (ADEM) and Behcet’s disease.

It is well known that it is closely linked with other systemic diseases including autoimmune diseases, Sjögren, myasthenia gravis or Hashimoto thyroiditis, infection, autoimmune-mediated vitamin B12 deficiency, and toxic exposure, which made some scientists to suggest that these infections or autoimmune diseases are the trigger for the onset of NMO, but a real pathophysiological association or etiology of NMO remains unknown.

Indeed, if an isolated disease episode affecting the spinal cord and optic nerve occurs after an infection or common cold, it is considered a post-infectious ADEM rather than NMO.

A major breakthrough came in 2004 when a specific biomarker NMO-IgG was found for the disorder. NMO-IgG is an autoantibody that targets AQP4 (a protein that is responsible for water channel that plays an important role in the blood brain barrier and astrocytic function in cells). The identification of NMO-IgG as a biomarker for NMO allows the disease to be differentiated from other autoimmune diseases, i.e., myasthenia gravis, systemic lupus erythematosus (SLE), necrotizing myelopathy, paraneoplastic myelopathy. More importantly, it has allowed the creation of animal models and the study of the mechanisms of the disease.

NMO is a severely disabling autoimmune disorder of the CNS, which was considered a subtype of multiple sclerosis (MS) for many decades that is presented with relapsing optic neuritis followed by spastic weakness and sensory loss. However, recently, highly specific serum autoantibodies (termed NMO-IgG or AQP4 antibodies (AQP4-Ab)) have been deducted in 60–80% of patients with NMO. These antibodies were subsequently shown to be directly involved in the pathogenesis of the condition. AQP4-Ab-positive NMO is now considered an immunopathogenetically distinct disease, thus it is certain that NMO is a nosologic disorder different from MS rather than a subtype of MS.

**Differential Diagnosis between NMO and MS**

Demyelinating diseases are a group of disorders of the CNS with dissimilar etiologies, characterized by inflammatory lesions that are associated with loss of myelin and eventually axonal damage. In this group, the most studied ones are MS, NMO, and ADEM. The Cerebrospinal fluid (CSF) and neuroimaging are essential to differentiate between these different diseases.

1. A very important difference that one should keep in mind, especially in patients with a bilateral optic neuritis, is NMO. Patients with NMO and relapsing myelitis and NMO spectrum disorder (NMOSD) with brain involvement have extensive spinal cord lesions that are longitudinally contiguous or linear (extending over at least three vertebral segments) with T1-signal intensity and swelling and atrophy of the cord and often there are...
few T2-lesions in the brain; on the other hand, MS has a typical distribution of White matter lesions (WMLs). Nevertheless, the optical coherence tomography shows more severe alterations in NMO than in MS, because a thinner retinal cell layer indicates widespread axonal and neuronal loss.\textsuperscript{2,4,48–51} Myelin-bearing oligodendrocytes are the primary inflammatory target in MS, but astrocytes are lost first in NMO.

The properties for MS are the involvement of corpus callosum, U-fibers, temporal lobes, brainstem, cerebellum, and spinal cord, and it has a typical distribution of WMLs. As a consequence, there is an important role for MRI in the diagnosis of MS, since MRI can show multiple lesions (dissemination in space), some of which can be clinically occult, and MRI can show new lesions on follow-up scans (dissemination in time).\textsuperscript{49–52}

2. Unlike MS, in which the lesions are usually smaller and peripherally located, NMO axial images the lesions which often involve most of the spinal cord.

Longer cord lesions in MS patient were only seen if there was a more aggressive disease or later on in the course of the disease.\textsuperscript{53}

3. The discovery of the antibody to AQP4, named IgG-NMO, the most abundant astrocyte water channel in the CNS permitted the differential diagnosis between MS and NMO. In fact, CSF and seropositivity test for NMO-IgG/AQP4 antibodies was presented in almost 60–80% of NMO cases, this fact justifies that NMO is a nosologic entity different from MS.\textsuperscript{54}

4. MS is characterized by CSF-restricted oligoclonal IgG bands, which is a hallmark of MS, but in NMO patients, they are usually absent. CSF pleocytosis is present in around 50% of NMO cases, and frequently included neutrophils, eosinophils, activated lymphocytes, and/or plasma cells.

5. Disability of NMO patients is usually more severe than that in MS patients, due to the severity of relapses followed by less recovery.\textsuperscript{18,51,55}

NMO diagnosis is primarily clinical, but MRI evidence of long spinal cord lesions extending over three or more vertebral segments during an acute attack of myelitis is helpful in differentiating this disorder from MS. NMO and NMOSD sometimes show asymptomatic lesions on MRI at onset, and it is difficult to differentiate MS from NMOSD by the fulfillment of the MRI criteria for MS on brain MRI at onset. However, the characteristic features of brain lesions are highly important for the early differentiation of the two disorders.\textsuperscript{56}

It is worthy to mention that some patients with seronegativity test for NMO-IgG/AQP4 antibodies even fulfill MS diagnostic criteria and had brain lesions at early stages of the disease, but spinal lesions of seropositive patients are longer and show increased cord swelling at onset MRI scans. Hence, brain MRI morphology shows differences between seropositive and seronegative patients at the time of onset in NMO, but differences between groups are time dependent and vanish over time.\textsuperscript{57}

### Treatment Options

Today, the first-line therapy with azathioprine or rituximab for severe disease course of NMO calls for prompt initiation of immunosuppressive treatment once the diagnosis of NMO or AQP4-Ab-positive NMOSD has been confirmed. IVIg may be used as the first-line therapy for children or for patients with contraindication to immunosuppressive therapies. In patients with NMOSD who are AQP4-Ab negative, therapy initiation depends on the severity and remission of the first relapse and the clinical course.

Second-line therapy of NMO: In the case of side effects or poor response, treatment can be switched from azathioprine to rituximab or vice versa, or to mycophenolate mofetil, methotrexate, or mitoxantrone.

The third-line therapy for NMO should be applied if disease progression occurs, and if the above treatments fail, the newer agents such as tocilizumab should be given with combination therapy (combination of steroid plus cyclosporin-A or methotrexate or azathioprine; combination of immunosuppression plus intermittent plasma exchange (PE); or combination of rituximab with methotrexate or intravenous immunoglobulins (IVIg)).\textsuperscript{6}

In this context, it is worthy to mention that the medication cyclophosphamide is no longer the drug of choice and has no evident efficacy,\textsuperscript{18} also the interferons-beta which are typical MS medications,\textsuperscript{59} natalizumab,\textsuperscript{60–62} and fingolimod need to be avoided in NMO due to their detrimental effect.\textsuperscript{58,63}

Other newer therapies are tocilizumab and eculizumab: tocilizumab is a drug used in treatment of resistant NMO patients with highly active AQP4-seropositive NMO who failed numerous immunosuppressive interventions, including high-dose corticosteroids, mitoxantrone, rituximab (anti-CD20), alemtuzumab (anti-CD52), and PE.\textsuperscript{64,65}

The tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, approved for the treatment of rheumatoid arthritis that has also shown efficacy in other autoimmune diseases, such as Castleman disease and SLE.\textsuperscript{66}

Eculizumab is a new agent under experiment – a therapeutic monoclonal IgG that neutralizes the complement protein C5 – in NMOSDs. Research reported that complement activation after binding of an IgG autoantibody to AQP4 is thought to be a major determinant of CNS inflammation and astrocytic injury in NMO. In addition, eculizumab seems to be well tolerated, significantly reduce attack frequency, and stabilize or improve neurological disability measures in patients with aggressive NMOSDs. The apparent effects of eculizumab deserve further investigation in larger, randomized controlled studies.\textsuperscript{66–68}

Treatment goes beyond medicine to include occupational therapists, physiotherapists, and social service professionals in cases of complex disability.

In summary, for sufferers of NMO, effective treatments are becoming available. The recognition of a specific marker NMO-IgG has not only facilitated the diagnosis of...
the condition but also presented a rational approach to the cure of the condition. Not only there are therapies that can decrease the impact of relapsing attacks and prevent attacks, but a therapy may be also possible by reduced-dose myeloablative regimens and hematopoietic cell replacement. Moreover, with reduced-dose myeloablative regimens, the mortality rate is low and approaching 1%.

**Case presentation.** We report a case of a 25-year-old Arab young woman with 11-year history of SLE. Five years later, three events of optic neuritis and two events of transverse myelitis were reported. To the best of our knowledge, this is the first case that had been encountered in the Arab community countrywide. The patient was presented to our hospital with acute urinary retention, headache, cold cyanotic fingers with ischemic changes in the tips of two, and reduced vision in the right eye. Normal admission and extensive clinical investigations including complete blood count, creatinine, electrolytes, liver function tests, prothrombin time, activated partial prothrombin time, and C-reactive protein were performed.

The sequence of events was as follow: at age 14 the patient was diagnosed with SLE depending on clinical, laboratory investigations, and after she had fulfilled the diagnostic criteria for SLE and had presented with the following findings: constitutional findings (fatigue, fever, arthralgia, and weight changes); dermatologic finding (photosensitivity and butterfly rash); acute or chronic renal failure (proteinuria up to 400 mg in 24 hours); hematologic and antinuclear antibodies (positivity for antinuclear factor (ANF), anti-double-stranded DNA (anti-dsDNA) antibodies, positive direct Coombs, positive ANA and anti-DNA, low C4 and C3, positive aCL by IgG and IgM).

At age 14, the patient was treated with prednisone 50 mg/day and hydroxychloroquine sulfate (plaquenil 200 mg/day) with remarkable improvement. At age 17, she appeared with clinical picture of nephrotic syndrome (urine protein up to 5.3 g/day) and consequently kidney biopsy was done and revealed mesangial proliferative glomerulonephritis. On the light of these developments, the dosage of prednisone was elevated up to 1 mg/kg/day with hydroxychloroquine 400 mg/day. At age 18, the patient had begun with azathioprine due to the persistent proteinuria up to 400 g/day, and the indices of inflammation and serology still elevated (positivity for ANF, anti—dsDNA antibodies, direct Coombs, ANA and anti-DNA, aCL by IgG and IgM) while low complement levels were registered. It should be noted that arrays of recurrent episodes of optic neuritis were reported within these years, the first episode was at age 19, the second was at age 20, and the third was reported at age 21. The diagnosis of NMO associated with SLE was confirmed by MRI, which demonstrated inflammation of the optic pathways during acute optic neuritis and showed spinal cord lesions extending over three or more vertebral segments, which was best appreciated on sagittal T2-weighted images. The cervicothoracic spinal MRI showed on a sagittal 3-mm-thick T1-weighted image after administration of gadolinium, a strongly enhancing region (red arrow), edema (yellow arrows) of the medulla, and the T1 hypointensities (arrowheads) in the medulla (Figs. 1–3).

In addition, the axial 0.7-mm-thick T2-weighted image demonstrates the optic neuritis as a T2 hyperintense involvement of the right optic tract (yellow arrows). The left optic tract is normal (red arrows) (Fig. 4).

All the episodes of optic neuritis were treated by pulse therapy of methylprednisolone (Solu-Medrol 1 g/day for 5 days), i.v. immunoglobulin 0.8 mg/day and immunosuppressive agent CellCept (mycophenolate mofetil), while hydroxychloroquine sulfate (plaquenil) and azathioprine were discontinued. The patient condition improved significantly and she was discharged from the hospital.

Figure 1. Cervical–thoracic spinal MRI in an NMO patient, after administration of gadolinium, a strongly enhancing region (red arrows) can be seen.

Figure 2. MRI of the Cervical–thoracic spinal cord region was done in an NMO patient. MRI T1-weighted image showed a strongly enhancing region after administration of gadolinium.
At age 24, the patient was admitted for five days at our hospital, she complained of urine burning and dysuria (painful urination), urine culture was done for suspicion to urinary tract infection (UTI), and *Escherichia coli* was found and was treated successfully by ofloxacin (fluoroquinolone). Additional investigations were performed and demonstrated the patient difficulty giving urine, and Catheter showed urine retention with remainder of 1000 mL, and the attempts to remove Catheter were in vain. The patient had no fever, chest pain, and shortness of breath, difficulty swallowing disorders, gastrointestinal heartburn or eyes redness, but she had cushingoid appearance, with butterfly rash and macular pink arms rash. Limbs sensory were reserved with equal depressed reflexes in both limbs, without motor deficit. Laboratory tests showed Leukopenia, kidney test was normal, hematologic and antinuclear antibodies (ANA, anti-Sm, anti-RNP, anti-Ro (SSA) were all positive, but anti DNA, C3 and C4 were normal, the lupus anticoagulant (LAC) was negative, and AQP4-Ab (also termed NMO-IgG) was positive. EMG showed speed transport borderline amplitudes and kidneys ultrasound was normal. The CSF was abnormal with mildly elevated protein (65 mg/dL), glucose (45 mg/dL), and the presence of pleocytosis including polymorphonucleocytes (43 cells).

**Conclusion**

Demyelinating diseases are a group of disorders of the CNS with dissimilar etiologies, characterized by inflammatory lesions that are associated with loss of myelin and eventually axonal damage. In this group, the most studied ones are MS, ADEM, and NMO. NMO is also known as an uncommon neuro-immunological disease, with relapsing course, potentially causing early disability. NMO has a global distribution and estimated prevalence of five persons per million populations per year. NMO was first described as a severe, monophasic, necrotizing disease with pure neurological involvement of optic nerves and spinal cord. During the last two decades, understanding of the diagnosis, clinical presentation, and pathophysiology of NMO has changed significantly.

NMO diagnosis is primarily clinical, but MRI evidence of long spinal cord lesions extending over three or more vertebral segments during an acute attack of myelitis is helpful in differentiating this disorder from MS. NMO and NMOSD sometimes show asymptomatic lesions on MRI at onset, and it is difficult to differentiate MS from NMOSD by the fulfillment of the MRI criteria for MS on brain MRI at onset. However, the characteristic features of brain lesions are highly important for the early differentiation of the two disorders.

It is worthy to mention that some patients with seronegativity test for NMO-IgG/AQP4-Ab even fulfill MS diagnostic criteria and had brain lesions at early stages of the disease, but spinal lesions of seropositive patients are longer and show increased cord swelling at onset MRI scans. Hence, Brain MRI morphology show differences between seropositive and seronegative patients at time of onset in NMO, but differences between groups are time dependent and vanish over time.

With such improvements in diagnosis and early description of cases over the past decade, NMO is still considered a disabling disease of the CNS and future studies should be
planned for better management of relapses and prevention of disability.

In our unique case, we described a case of NMO, occurring in a 25-year-old Arab young woman with SLE. Five years later, neurological manifestations (three events of optic neuritis and two events of transverse Myelitis) were reported.

To the best of our knowledge, this study is the first case that had been encountered in the Arab community countrywide.

In fact, early differentiation between MS and NMO is important, the thing that can make treatment more successful. Recently, using indirect immunofluorescence analysis, a new serum autoantibody (NMO-IgG) has been detected in NMO patients. The binding sites of this autoantibody were reported to colocalize with AQP4 water channels. Thus, we assumed that AQP4 antibodies in fact characterize NMO patients.

Indeed, the discovery of highly specific NMO immunoglobulin G (NMO-IgG) in 2004 opened a new era in the classification and understanding of NMO pathogenesis. Although NMO is rarely described in patients with SLE, it can appear as a first manifestation of SLE.

In fact, it is a well-known phenomenon that these two conditions (NMO and SLE) coincide quite often. The association of SLE and NMO makes the research to differentiate between the two conditions necessary.

In SLE associated forms, anti-AQP4-Ab positivity can help differentiating between SLE nerve system manifestation and NMO. We believe that recognition of NMO as a separate diagnostic entity, but possibly associated with other autoimmune diseases, is important not only because of nosologic classification, but also because it augurs a paradigm shift in the way such that patients are evaluated and treated and may increase the familiarity of the disease. Increased familiarity with the NMO, as well as more widespread use of the NMO autoantibody, will lead in the end to increased diagnosis of NMO in patients otherwise diagnosed with uncharacterized lupus myelitis.

In conclusion, earlier testing for NMO-IgG autoantibodies in patients with SLE and myelitis enables predicting the development of NMO and will facilitate quick intervention with plasmapheresis or other B cell–targeted treatments before waiting for episodes of optic neuritis or recurrent episodes of myelitis. Therefore, it is crucial to develop diagnostic tools for NMO, also because NMO-IgG is not detectable in all patients.

**Author Contributions**

Conceived and designed the concepts: AB. Analyzed the data: AB, MA. Wrote the first draft of the manuscript: AB, MA. Contributed to the writing of the manuscript: AB, MA, BB. Agree with manuscript results and conclusions: AB, MA, BB. Jointly developed the structure and arguments for the paper: AB, MA, BB. Made critical revisions and approved final version: AB, MA, BB. All authors reviewed and approved of the final version.

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