Diversity of Neuromyelitis Optica: Inner City Hospital Experience and Review of Literature

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Abstract

Neuromyelitis Optica (NMO) is a potentially devastating, complex autoimmune disease of the central nervous system that differs clinically and pathologically from the more common Multiple Sclerosis (MS). In this paper, we briefly describe our clinical experience with NMO patients treated in an inner city hospital in central Brooklyn, New York, and offer an up-to-date discussion of diagnosis, treatment, and prognosis of this rare condition.

Keywords: NMO; Pathology; Diagnosis; Treatment

Introduction

Neuromyelitis Optica (NMO) is an autoimmune disorder of the central nervous system usually associated with autoantibodies against Aquaporin 4 water channel (Anti-AQP4 Ab). The disease was traditionally defined as optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) [1]. However, within the last few years, a broader spectrum of presentations was identified and referred to as 'NMO spectrum disorders' (NOMOSD) [2]. NOMOSD are unified by the presence of the anti-Aquaporin 4 antibody and encompass the following syndromes: isolated or recurrent LETM; isolated, recurrent or bilateral ON; and cerebral syndromes with ‘NMO – typical’ brain lesions [3]. Although NMO was previously and usually considered to be a variant of MS, it is being increasingly recognized as a distinct clinical entity with a unique pathophysiology and differing epidemiology, genetics, treatment, and outcomes from MS [3].

Kings County Hospital Experience

In a three year span, we diagnosed and treated 12 inpatients with NMO in Kings County Hospital, Brooklyn, New York. Table 1 summarizes the demographic features, clinical presentations, antibody status, treatment, and outcomes of our 12 cases. All of our cases were positive for Anti-AQP4 Ab. Ten of the 12 cases were classified as full-fledged NMO [4], while two cases, including one pediatric patient, fell into the NMOSD category. Two of the patients presented to our institution after having multiple relapses and having been misdiagnosed with MS. The age of our patients ranged from seven to 53 years with a mean age of 34 (±15) years. All of our patients were women. Eighty-three percent of our patients were Afro-Caribbean. More than 50 percent of our patients had an extended disability status score (EDSS) 6.5 or higher at last follow-up (required bilateral assistance to walk, or worse). Seventy-five percent of our patients needed aid with their activities of daily living (ADLs). Three of our 12 patients had intractable vomiting, which was the presenting symptom in two patients and developed later in the course of the third.

Only three of our 12 patients responded to treatment with IV methylprednisolone for acute relapses, resulting in partial recovery of function. One patient (Patient 6 in the table) failed treatment with steroids, plasmapheresis, and intravenous immunoglobulin, and consequently became blind due to recurrent and devastating optic neuritis attacks. Two of our five patients treated with azathioprine prophylactically had mild disability and four of our patients were maintained on oral steroids alone. We encountered two pediatric cases, one of them presented with intractable vomiting, hiccups, and weight loss, which was attributed to vomiting and the other - with brainstem signs and symptoms.

The MRIs of our patients were consistent with NMO. Figures 1-6 show the most prominent radiologic findings in our patients.

Diagnostic Criteria

The two main sets of diagnostic criteria are the Mayo Clinic Diagnostic Criteria and the National Multiple Sclerosis Task Force Criteria [4], both of which require clinical events of optic neuritis and myelitis. The revised NMO criteria set forth by the Mayo Clinic require both transverse myelitis and ON. The supporting criteria, of which two must be met, include the following: brain MRI that is non-diagnostic for MS at initial presentation; spinal cord lesion on MRI that extends for three or more segments; and Anti-AQP4 Ab IgG seropositivity. The National Multiple Sclerosis Task Force requires all three of the following in an unspecified time interval: optic neuritis in one or both eyes; clinically complete or incomplete transverse myelitis extending over three vertebral segments on MRI; and no alternative inflammatory disease such as systemic lupus erythematosus, sarcoidosis, or Sjogren’s syndrome. The Mayo Clinic, however, recognizes that collagen vascular diseases and other autoimmune diseases can occur concurrently with NMO and should not preclude the diagnosis of NMO. One or two minor criteria must also be met per the National Multiple Sclerosis Task Force guidelines: either Anti-AQP4 Ab IgG seropositivity and/or supporting neuroimaging (a normal brain MRI; or a MRI which has the most prominent radiologic findings in our patients).

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as hypothalamic lesions or brainstem lesions extending upwards from spinal lesions.) [4].

Epidemiology

The worldwide prevalence of NMO varies from 0.52 to 4.4 in 100,000 [5]. It has a female preponderance, ranging from 2:1 to 10:1, depending on the case series. In our case series, all of our patients were women. Mean disease onset is around age 40, as is the case in our series (mean age of 39 years) [4]. Many of the earlier epidemiological studies were done in the Asian and Afro-Caribbean populations.. Although NMO is overrepresented in these populations relative to MS, most patients with NMO in the developed world are white [3]. In a multicenter French epidemiological study of 125 patients, 87 percent of the patients were white. Of the remaining non-white population, 45 percent originated from Sub-Saharan Africa, 37 percent from Asia, and 18 percent from Latin America [6].

The frequency of NMO in non-whites is quite high compared to MS. NMO is the cause of nearly 40 percent of the demyelinating diseases in Thailand [7], 20-30 percent in the Japanese, 27 percent among the West Indian population, and approximately 20 percent among Indians [3]. Cuban study of 89 patients with NMO showed equal prevalence among Cuban whites, Blacks, and mixed racial patients [8]. Another study among 178 Caribbean patients showed equal prevalence among Cuban whites, Blacks, and mixed racial ancestry. This probably reflects the demographics of our catchment area.

Clinical Findings

The classic NMO findings are optic neuritis and acute transverse myelitis, occurring either separately or together. However, the definition of NMO has expanded to include cerebral and neuroendocrine syndromes, even without optic neuritis or myelitis [2]. Optic neuritis may be unilateral or bilateral, sometimes affecting the chiasm, causing severe visual disability and even complete loss of vision. Usually, the optic neuritis attack is more severe in NMO than in MS and ocular coherence tomography demonstrates a greater loss of retinal nerve fiber layer, ganglion cell layer, and inner plexiform layer of the retina compared with MS [11]. Spinal cord attacks are also typically more frequent and severe than in MS. Typical symptoms of myelitis are bilateral sensory complaints, bowel or bladder dysfunction, paraparesis or paraplegia, and in some cases of cervical myelitis, quadriparesis or quadriplegia. Paralysis is rare in MS myelitis and should raise suspicion of NMO. Neuropathic pain and Lhermitte’s phenomenon (‘electric shock’-like paresthesias after neck flexion, suggestive of cervical spine pathology) [12,13] are frequently seen. Eight of our 12 patients had at some point in their disease course either symptoms of ON or LETM and two of the eight had both ON and LETM during their disease course. A recent case series of NMO patients recorded frequent, paroxysmal tonic spasms, or dystonia, mostly in a single limb, of short duration, occurring at any point in the disease course. All patients responded to treatment with carbamazepine [14]. In a retrospective study comparing 29 NMO patients with 66 MS patients, 85 percent of the NMO patients had more severe pain, needing multiple pain medications and reporting poorer quality of life [12]. In approximately 40-45 percent of patients with anti-aquaporin 4 antibodies, refractory

As illustrated in Table 1, Kings county patients.

### Table 1: Kings county patients.

| Patient | Age | Sex | Race/Country | Initial Presentation | Anti-AQP4 | EDSS | Preventative Treatment | Outcome |
|---------|-----|-----|--------------|----------------------|-----------|------|------------------------|---------|
| 1       | 49  | F   | Black/Haiti  | Paraparesis, bilateral ON, Urinary Retention. | +         | 6    | Oral steroids          | Wheelchair bound, legally blind and incontinent to urine. |
| 2       | 25  | F   | Hispanic/Dominican Republic | Unilateral ON and TM | +         | 2    | Mycophenolate Mophetyl (initially failed steroids and azathioprine) | Fully Functional, mild decrease in visual acuity. |
| 3       | 25  | F   | African American/US | Nausea, vomiting, hypnautremia, progressed to quadriaparesis. | +         | 4.5  | Azathioprine           | Requires some assistance with long distances but mostly functional |
| 4       | 41  | F   | Black/Haiti  | Severe TM with progressive quadriplegia | +         | 7    | Azathioprine           | wheelchair bound; requires assistance for most of her activities. Residual pseudoatrophia. |
| 5       | 19  | F   | Black/Haiti  | TM Paraparesis – sensory loss | +         | 7    | Oral Steroids after receiving IVIG and PLEX | Bilateral assistance for walking; requires assistance in most of her activities of daily living |
| 6       | 26  | F   | Black/Granada | ON | +         | 6.5  | Rituximab (failed repeat steroids and IVIG, PLEX, and azathioprine) | Bilateral support and some assistance with her self-care |
| 7       | 52  | F   | Black/Haiti  | Hiccup, vomiting, quadriaparesis | +         | 10   | NA | Patient died despite aggressive immune suppressive treatment in the acute phase |
| 8       | 46  | F   | Hispanic/Mexico | Recurrent paraparesis, Urinary Retention | +         | 7.5  | Azathioprine           | Wheelchair bound with some retention of self-care. |
| 9       | 36  | F   | Black/US     | Hemiparesis progressed to quadriaparesis | +         | 7.5  | Azathioprine           | quadriparetic, requiring assistance in most of her activities of daily living |
| 10      | 53  | F   | Black/Haiti  | Paraparesis, Urinary incontinence | +         | 4.0  | Oral Steroids          | Functional in most of his activities |
| 11      | 12  | F   | Black/Granada | Intractable vomiting, hiccups, quadriaparesis, diplopia, autonomic instability. | +         | 6.0  | Oral steroids+Azathioprine | Requires some assistance with ADLs |
| 12      | 7   | F   | African      | Diplopia, constipation | +         | 3.5  | Oral steroids          | Mostly fully functional |
nausea, vomiting, or hiccups occur, due to lesions in the brainstem affecting the area postrema [4], but only in 12 percent did they occur as the initial presentation [15]. In our series 25 percent of the patients had intractable nausea and vomiting. Extension of spinal lesions into the brainstem may cause neurogenic respiratory failure and death, as may have been the case in patient 7 of our series. Other uncommon presentations include endocrinopathies, due to hypothalamic lesions, exemplified by patient 3, who experienced central diabetes insipidus. Cerebral syndromes such as encephalopathy, and coma due to tumefactive lesions, have also been reported, and appear to be more common in children [4].

**Laboratory Studies**

The initial test to detect Anti-AQP4 Ab in serum was indirect immunofluorescence (IIF). IIF using tissue substrates had a sensitive of 54 to 73 percent and a specificity of 91 percent [16]. The cell-based assay using human embryonic kidney (HEK) cells has a sensitivity of 91 percent and a specificity of 100 percent [16]. A number of newer techniques that are available: radioimmunoprecipitation (RIPA), fluoroimmunoprecipitation (FIPA), enzyme-linked immunoabsorbent assays (ELISA), and cell based assays - reach specificity of 85-100 percent [16].

Cerebrospinal Fluid (CSF) studies may demonstrate mild pleocytosis (50-1000 × 10^6 with neutrophilic and eosinophilic predominance during acute relapse). Oligoclonal bands, commonly found in MS are absent in most NMO cases [17].
In a randomized study, plasma exchange demonstrated moderate to significant improvement in neurological disability compared to sham treatment in patients with acute demyelinating disease of the CNS [24]. Intravenous immunoglobulin (IVIG) can be considered as an alternative treatment of patients unresponsive to methylprednisolone and/or PLEX. A recent retrospective study of 10 patients with NMO, unresponsive to either IV methylprednisolone or PLEX, showed that 45.5 percent of patients improved after IVIG and the remaining were no worse after treatment [25]. Intravenous chemotheraphy, such as cyclophosphamide [26] or mitoxantrone should also be considered in severe cases [27].

Preventative therapy to prevent relapses is always required in NMOSD (unless there are strong contraindications). The commonly used drugs are azathioprine, mycophenolate mophetil, and rituximab, alone or in combination with oral steroids. Less commonly used are cyclophosphamide, mitoxantrone, and methotrexate. A consensus expert opinion on prophylactic treatment in NMO was recently published [28].

In a retrospective study of 99 patients with NMO, those treated with azathioprine had a 74 percent decrease in the annual relapse rate, regardless of concomitant prednisone treatment [29]. This drug takes three to six months to show effect. The authors recommended treating patients with at least 2.5mg/kg/day to have optimal benefit. It is also recommended to measure patients’ thiopurine methyltransferase (TPMT) levels prior to initiating therapy, as patients with deficient enzyme activity have a risk of toxicity and severe infections. Azathioprine carries a black box of warning of hematologic malignancies in patients on chronic treatment [30].

Rituximab is a chimeric anti-CD20 monoclonal antibody approved for the treatment of non-Hodgkin’s Lymphoma, rheumatoid arthritis, and other autoimmune diseases. Several open label studies showed that two doses of Rituximab 1 g every two weeks at six month intervals [31], not only decreased the number of relapses significantly but also considerably improved disability scores. A recent retrospective study analyzing five years of experience using Rituximab showed an 86 percent reduction in the annual relapse rate (ARR). Sixty percent of the treated patients were relapse-free during this period of time, and no serious adverse events leading to discontinuation were observed [32]. Mycophenolate mofetil 1 g twice a day was effective in some case series [33]. There is limited data with regard to the use of Mitoxantrone and Cyclophosphamide [30]. A small study of seven patients with chemotherapy refractory disease and considerable disability demonstrated that maintenance plasmaphereses not only improved disability, but stabilized disease over the course of seven years [33]. Two novel agents also have shown promise in treatment of recalcitrant cases of NMO: eculizumab, a monoclonal IgG that neutralises the complement protein C5 [34,35] and Tocilizumab, an inhibitor of IL-6 receptors [36].

Among emergent treatments, mention should be made of a non-pathogenic, recombinant monoclonal antibody against aquaporin 4, “aquaporumab,” that selectively blocks pathogenic NMO-IgG binding to AQP4. Thus, in the absence of effector function, aquaporumab lacks functionality for complement- and cell-mediated cytotoxicity. Aquaporumab was evaluated in vitro, ex vivo, and in vivo using cell cultures as well as mice [37]. There have been no human studies with this agent to date.

Interferon beta, commonly used to treat MS, should be avoided in NMO, in view of reports documenting worsening of disease activity in interferon beta-treated NMO patients, possibly due to the switching of...
the immune response to a more autoantibody-favoring Th2 dominated arm [38]. Natalizumab, an alpha-4 integrin antagonist and a potent MS drug, exacerbated NMO in a small study [39] as did another MS therapy, fingolimod [40]. These dramatic differences in response to treatment in MS and NMO highlight the absolute imperative of establishing a correct diagnosis at the earliest stage of the disease.

**Prognosis**

Earlier reports suggested that ninety percent of NMO patients have a relapsing course, and that the recovery from relapses is typically slow and incomplete [3]. Approximately 50 percent of patients in these original series were blind within five years [3]. Predictors of worse prognosis include number of attacks in the first two years; severity of the first attack; and presence of concurrent autoimmune disorders, such as systemic lupus erythematosus. [3] Seventy-five percent of the patients in our cohort had very high EDSS scores at the time of diagnosis and treatment initiation, consistent with a poor prognosis as previously reported. Our cohort also suggests that those treated in underprivileged hospitals rather than in tertiary care centers may have a worse prognosis, which may be due in part to delays in diagnosis and a suboptimal follow up. It is advisable to refer NMO patients to specialty MS clinics whenever possible.

Importantly, secondary progression, which is seen in 90 percent of untreated MS patients [41], is generally not part of the NMO course. An important clinical corollary of this observation is that aborting attacks results in disease remission [42]. In contrast, in MS, there is often disease progression without relapses [41].

**Conclusion**

As seen from our case series and a review of the literature, NMO is a potentially devastating disease that involves optic nerves, spinal cord, and the brain. Recovery from relapses is often disappointing, and the cumulative nervous system damage sustained during the attacks contributes heavily to long-term disability. Consequently, treatments, which can decrease the number of relapses, should be initiated as early as possible in the disease course, with the aim of reducing the chances of significant disability [4]. In a patient with an inflammatory disorder of the central nervous system, NMO should be considered in the differential, and timely treatment is likely to decrease morbidity and mortality.

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