

Neuromyelitis optica and neuromyelitis optica-IgG seropositivity in Saudis with demyelinating diseases of the central nervous system

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Abstract

Background and Objective: Neuromyelitis optica (NMO) shares certain features with multiple sclerosis (MS). Similar phenotypes, wide spectrum and the differential prevalence of NMO among ethnic backgrounds pose diagnostic challenges. NMO-IgG antibodies are specific biomarker for NMO and facilitate its differentiation from other demyelinating diseases. This study aimed to assess the frequency of NMO and NMO-IgG seropositivity in Saudi patients with demyelinating diseases of the central nervous system. **Methods:** One hundred and four patients from neurology database at King Abdulaziz Medical City, Riyadh underwent clinical and laboratory examination, neuroimaging and NMO-IgG antibodies screening. **Results:** The mean age at presentation was 32 (± 9) years and there was an excess of females (female:male – 3:1). The mean duration of illness was 4.6 (± 3.2) years. During the illness, 48.1% of patients had clinical evidence of spinal cord involvement, 29.8% had optic neuritis and 14.4% had both features. A large majority (75.8%) of brain lesions fulfilled MRI criteria for MS and 17% had lesions extending over ≥ 3 vertebral segments. NMO-IgG antibodies were present in only one patient – a frequency of 0.96% in our study cohort.

Conclusion: Prevalence of NMO and NMO-IgG seropositivity is rare in Saudis with demyelinating diseases of the central nervous system. Hence, routine NMO-IgG testing is likely to have a low diagnostic yield.

INTRODUCTION

Neuromyelitis optica (NMO; Devic's disease; ICD-10: G36.0) is an inflammatory demyelinating disease of the central nervous system (CNS) that predominantly targets the optic nerves and the spinal cord.¹⁻⁴ NMO is a relatively rare disorder with an estimated prevalence of less than 1 to 4.4 cases per 100,000 in the Western populations.⁵ NMO is clinically characterised by the presence of optic neuritis (ON) and transverse myelitis (TM). Presence of longitudinally extensive spinal cord lesions extending more than three vertebrae, seropositivity for NMO-IgG and the absence of typical Multiple Sclerosis (MS) like brain MRI lesions are also regarded as important diagnostic features of NMO.⁶ NMO shares certain clinical and neuroimaging features with the MS, and has long been considered a clinical subtype of MS. This has contributed to the diagnostic difficulties.⁷

The discovery of NMO-IgG (antiaquaporin-4 IgG) antibody, however, has facilitated the diagnosis of NMO and helps in its differentiation from MS.⁶ NMO-IgG is regarded as a specific serum biomarker for NMO with a sensitivity and specificity of 73% and 91% respectively.^{3,6,8}

Demyelinating diseases of the CNS behave differently in Caucasian and Asian populations.⁹⁻¹¹ Hence, diagnosing such diseases by employing Western population-based criteria in the Asian populations may be problematic. The nature of demyelinating diseases, especially NMO, in Saudis with Arab ethnic background is unknown. Therefore, we sought to investigate the frequency of NMO and NMO-IgG seropositivity in a cohort of Saudi patients at a tertiary care centre.

METHODS

Patients presenting with the symptoms and signs

indicative of demyelinating involvement of the CNS are registered in the neurology clinic's demyelinating diseases database at the King Abdulaziz Medical City, Riyadh (KAMC-R), which is a 900-bed university-affiliated tertiary care centre. Clinical, demographic and laboratory information on all patients who are referred to the neurology clinic are recorded in the database. One hundred and four consecutive patients from the database were screened between May 2008 and December 2011. This study was approved by the review board at King Abdullah International Medical Research Centre, Riyadh. Written informed consent was obtained from all participants or their next of kin where appropriate.

Patients were evaluated by consultant Neurologists with at least 3 years' experience in the management of demyelinating diseases. The demographic and clinical parameters for all patients were recorded or retrieved from the case records by using standardised form and included: age at the onset of demyelinating disease, gender, place of birth, marital status, disease duration, symptoms at onset, number of annual relapses, family history of demyelinating diseases, outcome of the visual evaluation, the use and type of disease modifying therapies, and the last Extended Disability Status Scale (EDSS) score. EDSS scores were divided into three categories: 0–3.0, corresponding to mild disability; 3.5–5.5, signifying moderate disability; and 6.0–10, highlighting severe disability. The attack (relapse) was defined as the subjective symptoms or objectively observed signs typical of an acute inflammatory CNS demyelinating event, current or historical, with duration of at least 24 hours, in the absence of fever or infection.¹²

Brain and spinal cord magnetic resonance imaging (MRI) scans were obtained within the first week of patient's presentation at the clinic. Brain MRI scans were classified as being normal, abnormal but not meeting Barkhof/Tintore' criteria for MS, or typical for MS (Barkhof/Tintore' criteria met).^{13,14} Spinal MRI scans were classified as normal, showing non-specific or short-segment spinal cord lesion, or showing longitudinally extensive transverse myelitis (LETM). LETM was defined as contiguous spinal cord lesions over at least three spinal segments.

Serum NMO-IgG was measured by commercially available kits utilising an indirect immunofluorescence test at the laboratory of Bioscientia, Ingelheim, Germany. Indirect immunofluorescence assay has a sensitivity of 86% and a specificity of 91%.¹⁵

Statistical analyses were performed using the SPSS 19.0 software (IBM, NY, USA). Continuous data were expressed as the mean \pm SD and categorical data were expressed as n, percentage.

RESULTS

Demographic and clinical characteristics of the patients

The demographic and clinical characteristics of the patients are shown in Table 1. Of the 104 patients enrolled in this study, 72 (69.2%) were women. The mean age at presentation was 32 years (range: 15–64 years). Twelve patients (11.5%) experienced their first episode below the age of 20 years. The mean duration of illness was 4.6 (\pm 3.2) years at the time of NMO-IgG antibodies testing. A total of 174 relapses were recorded from all patients with a mean of 1.7 (\pm 1.7). Ninety patients (86.5%) had up to 3 relapses at the time of enrollment in the study. The median EDSS at the last follow-up was 2 (range: 0.5-8), indicating mild disability.

Neuroimaging, neuroelectrophysiological, and laboratory findings

The extent and features of the brain and spine lesions on MRI are listed in Table 2. A large majority (75.8%) of brain lesions in the patients fulfilled the MRI criteria for MS, and only three patients had a normal scan. Among the 77 patients who underwent spine MRI, 70 (91%) had spinal cord lesions out of which 13 patients (17%) had lesions that extended over three or more vertebral segments. There were no significant gender differences for both brain and spine MRI findings (data not shown). Thirty seven percent patients had bilateral conduction disturbances in the optic nerve on visual evoked potential (VEP). Serum anti-nuclear antibody was positive in only eight patients.

NMO Diagnostic Criteria and NMO-IgG findings

NMO-IgG antibodies were checked for all 104 patients. The result was positive in only one patient, which accounted for 0.96% of the patients who underwent the test (Table 2). Diagnosing NMO, however, is still possible based on the clinical and radiological features regardless of patients' NMO-IgG status as proposed by Wingerchuk *et al.*⁶ and highlighted in Table 3. Of all the patients

Table 1: Demographic and clinical characteristics of study participants

Characteristic	Total n = 104
Age at presentation (years) (mean ± SD)	32.0 (± 9.9)
Females, n (%)	72 (69.2)
Marital status, n (%)	
Single	42 (40.4)
Ever married	62 (59.6)
Place of birth, n (%)	
Riyadh (capital)	67 (64.4)
Elsewhere	37 (35.6)
Family history of DD, n (%)	20 (19.2)
Clinical features at presentation, n (%)	
ON	31 (29.8)
TM	50 (48.1)
Both ON + TM	15 (14.4)
Mean number of relapses, (range)	1.7 (0-8)
Medications in use at the time of data collection	
Beta-Interferon	42 (40.4)
Rebiff	33 (31.7)
Avonex	6 (5.8)
Cladripine	1 (1.0)
Not on medication	22 (21.2)
EDSS at last follow-up visit	
Mild	85 (81.7)
Moderate	13 (12.5)
Severe	6 (5.8)

DD, demyelinating diseases; ON, optic neuritis; TM, transverse myelitis; EDSS, extended disability status scale

that had their brain and spinal cord MRI available, only one patient fulfilled the diagnostic criteria for NMO even without consideration of the NMO IgG seropositivity status. This was a 46 years old lady who experienced severe relapsing cervical and thoracic longitudinally extensive transverse myelitis in 2004 followed by bilateral optic neuritis a year after the initial spinal cord involvement. She had strongly positive antinuclear antibodies, anti-Ro/SSA and anti-La/SSB antibodies. She was initially diagnosed as Sjogren's syndrome, but the diagnosis was revised to NMO on account of her meeting the NMO diagnostic criteria. She was also positive for NMO-IgG antibodies.

Final diagnosis

In addition to the one case of NMO described above, 87 patients (84%) had relapsing remitting

MS, three had primary progressive MS, and ten were suffering from secondary progressive MS in our study cohort. One patient had idiopathic transverse myelitis and two had clinically isolated syndrome.

DISCUSSION

Neuromyelitis optica and MS share several clinical and radiological features resulting in difficulty in ascertaining the diagnosis particularly in certain ethnic backgrounds such as Asian and Latin Americans. Relapsing lesions involving the spinal cord and optic nerves are very common among the patients with demyelinating diseases particularly in the Asian countries (opticospinal phenotype).¹⁶ This selective phenotype alone is not very helpful in differentiating MS from NMO.¹⁷ Hence, NMO-IgG antibodies are now widely accepted as a

Table 2: Neuroimaging, neuroelectrophysiological and laboratory findings

Characteristic	Total n = 104
MRI Brain, n (% of those tested) ^a	
Normal	3 (3)
Abnormal but MS criteria not met	21 (21.2)
Abnormal and MS criteria met	75 (75.8)
Spine MRI, n (% of those tested) ^b	
Normal	7 (9)
Lesions <3 vertebral segments	57 (74)
Lesions ≥3 vertebral segments	13 (16.9)
VEP, n (% of those tested) ^c	
Normal	24 (38.7)
Bilaterally prolonged	23 (37.1)
Unilaterally prolonged (Rt or Lt eye)	15 (24.2)
ANA, n (% of those tested) ^d	
Negative	72 (69.2)
Positive	8 (7.7)
NMO-IgG positive, n (%)	1 (0.96)

VEP, visual evoked potential; ANA, Anti-nuclear antibody

^aTotal tested = 99; ^bTotal tested = 77; ^cTotal tested = 62; ^dTotal tested = 80

marker of NMO, assisting in its distinction from MS.^{6,16,18-22} and providing substantial insight into the pathogenesis of this disease.⁴ The diagnostic criteria for NMO as proposed by Wingerchuk *et al.*⁶ facilitate its distinction from MS.

Our study represents the first comprehensive attempt to provide an estimate of the frequency of NMO and NMO-IgG seropositivity in a defined Saudi population. We showed that NMO-IgG seropositivity is a rare entity in Saudi patients with a frequency of only 0.96%. This is in contrast to the findings from China, Japan, Thailand, and Taiwan that reported a high seroprevalence of NMO-IgG, 33.8%, 27.1%, 39.3%, 32.3% respectively, among patients with demyelinating diseases of CNS.^{16,23-25} Our findings, however, are somewhat similar to the studies from India²⁶ and Australia²⁷, which reported seropositivity of 4%

and 2%, respectively. Hence, the diagnostic yield of routine testing for NMO-IgG antibodies in our patients with demyelinating diseases of the CNS is low and might not be cost-effective.

A very low NMO-IgG seropositive rate in our patient cohort can be due to a number of factors other than the rarity of NMO in the Saudi population. First, it can be due to the technical limits of indirect immunofluorescence assays that were used to detect NMO-IgG antibodies in our study. At least three seronegative patients in our study had antibody titres just below the threshold of detection by these assays. This phenomenon has previously been described, especially for Asian populations, where the application of Western diagnostic criteria was found to be inappropriate.²⁸ In the light of this finding, we aim to employ other available

Table 3: Diagnostic criteria for Definite NMO*

Criteria
Optic neuritis
Acute myelitis
At least two of three supportive criteria:
1. Contiguous spinal cord MRI lesions extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

* Adapted from Wingerchuk *et al.*⁶

assays, like the cell-based and fluorescence-based immunoprecipitation²⁹, for the detection of NMO-IgG to validate our findings from this study. This will particularly be useful to confirm NMO diagnosis in patients with LETM. Second, active and long-running immunosuppression induced by the treatment, particularly beta-interferon, as was the case in our study might decrease the serum level of autoantibodies and lead to a negative test result.³⁰ In our cohort, the mean duration of illness was 4.6 years and 79% of patients were on disease modifying drugs at the time of NMO-IgG antibodies testing. Third, it is probable that, like in other autoimmune diseases, there may be involvement of more than one target antigen. A study using protein microarray identified three new autoantibodies that had a role in NMO pathogenesis.³¹ This pathogenetic mechanism may be relevant in our patients. Finally, cell-mediated autoimmunity instead of autoantibodies may have a predominant role in NMO pathogenesis^{1,4} and this mechanism may be more relevant in our patients.

In conclusion, we found that NMO has a low frequency and a low NMO-IgG seropositivity in a group of Saudi patients. Despite relatively higher rate of spinal cord involvement, majority of our patients presented with “conventional Western type” MS. However, these findings are preliminary, based on a relatively small sample, and need to be confirmed in independent studies in Saudi Arabia and other populations in the Arab region. Furthermore, validation and refinement of NMO-IgG assays, their application to individuals of different ethnic and racial backgrounds in different countries and clinical settings would be necessary steps to better understand, detect, and treat this debilitating disorder.

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DISCLOSURE

Conflict of interest: None

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