

# Rheumatologic profile in CNS demyelinating disorders

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## Abstract

**Background & Objectives:** Multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) are central demyelinating disorders that have an autoimmune inflammatory etiology. The aim of the present study is to assess the frequency of seropositivity for autoantibodies and other rheumatologic serum markers in patients with CNS demyelinating diseases and to determine whether the seropositivity for autoantibodies differs between MS, anti-AQP4 positive and anti-AQP4 negative NMOSD, and MOGAD within Indian population in Rajasthan. **Methods:** This is an analytical cross-sectional study that included all consecutive patients presenting with CNS demyelinating diseases during the period June 2021 to June 2023. The following information was collected from the patient: demographics; clinical syndrome of presentation, serum aquaporin-4 antibody, serum MOG antibody and CSF oligoclonal bands. Rheumatological profile including antinuclear antibody (ANA), rheumatoid factor (RF) antibodies, anti-dsDNA, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and anti neutrophil cytoplasmic antibody tests (both p & c ANCA) was investigated. Demographic and clinical characteristics were described in terms of absolute and relative frequencies. Rheumatologic profiles was compared across these diseases. **Results:** ANA and Anti dsDNA was significantly higher in NMOSD as compared to MS and MOGAD patients. Similarly, an insignificant increase in frequency of seropositivity for CRP, RA factor and ESR was noted in NMOSD.

**Conclusion:** Serum rheumatologic markers such as ANA, Anti dsDNA, ESR, CRP and RA factor are related to CNS demyelination. Further studies may be needed to determine the long term significance of these markers.

**Keywords:** Rheumatologic profile, multiple sclerosis, neuromyelitis optica, MOG antibody associated disease, ANA

## INTRODUCTION

The term demyelinating disorder refers to a group of diseases that share the common feature of myelin sheath loss with relative axonal preservation. This group includes multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD). Clinical and pathological aspects of these conditions suggest that they are inflammatory autoimmune diseases, which results in progressive deterioration of multiple body functions.<sup>1,2</sup>

Multiple sclerosis (MS) is one of the most

common autoimmune disease of the central nervous system (CNS). The diagnosis is based on the 2017 McDonald criteria; however, it is only made when there is no better explanation exists for the presenting symptoms.<sup>3</sup> The most common early sign and symptoms include pyramidal involvement (spasticity, hyperreflexia, Babinski sign, and clonus), ataxia, dysarthria, paraesthesia, faecal or urinary incontinence or retention and sexual dysfunction.<sup>4</sup>

NMOSD most commonly affects the optic nerves and spinal cord, leading to blindness and paralysis, but it often spares the brain, unlike multiple sclerosis (MS).<sup>5</sup> Among demyelinating

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disorders, neuromyelitis optica (NMO) affects up to 48% of patients in East Asia, up to 15% patients of African-Brazilians and around 1.5% of Europeans.<sup>6,7</sup> The serum IgG aquaporin 4 (AQP4) autoantibody, targeting the major water channel of the CNS localized in the astrocyte foot processes, is implicated in the pathogenesis of NMOSD.<sup>8</sup>

The autoimmunity surrounding patients with demyelinating diseases has been widely investigated. Recent studies show that patients with MS and NMO, as well as their families, are at greater risk of presenting, at some point, with an associated diagnosis of an autoimmune rheumatic disease.<sup>9,10</sup> Sloka *et al.* reported clustering of autoimmune diseases possibly due to genetic susceptibility or a common environmental trigger.<sup>11</sup> Similarly Anaya *et al.* suggested increased susceptibility for people with one autoimmune disorder to develop another autoimmune disorder, indicating genetic autoimmune predisposition.<sup>12</sup>

Against this background, the aim of the present study was to assess the frequency of seropositivity for autoantibodies, as well as other rheumatologic serum markers, in patients with CNS demyelinating diseases and to determine whether the seropositivity for autoantibodies differs between MS, anti-AQP4 positive and anti-AQP4 negative NMOSD and MOGAD within the Indian population.

## METHODS

This was an analytical cross-sectional study conducted at the Department of Neurology in North India over a two-year period from June 2021 to June 2023. The study received approval from the Institutional Human Ethics Committee (IHEC). It included all patients presenting with CNS demyelinating disease in in-patient or out-patient departments of Department of Neurology. Patients with MS were diagnosed according to McDonald's criteria, while patients with NMOSD were diagnosed using the International Panel for NMOS Diagnostic criteria 2015 (IPND).

The study used complete enumeration to enrol all eligible patients within the study period, adhering to prespecified inclusion and exclusion criteria. The following information was collected from each patient: demographics; clinical presentation syndrome, serum aquaporin-4 antibody, serum MOG antibody and CSF oligoclonal bands. Additionally, the patient's rheumatologic profiles, including

antinuclear antibody (ANA), rheumatoid factor (RF) antibodies, anti-dsDNA, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and anti neutrophil cytoplasmic antibody tests (both p & c ANCA) was investigated.

The data obtained was manually entered into Microsoft Excel and analysed using Software for Statistics and Data Science (Stata) v16. Descriptive analysis is presented using numbers and percentages for categorical variables; mean and standard deviation or median and interquartile range for continuous variables. Considering the continuous nature of outcome variable and data normality we used independent "t" tests (two-sided) to test for association of continuous variables and Chi square test (two sided) for categorical variables with 95% CI. Statistical significance was considered at  $p < 0.05$ .

## RESULTS

The present study included a total of 96 patients. The mean (SD) age of the patients included in the present study was 34.53 years (13.75); median (IQR) was 32.00 years (23.00 to 43.00) and ranging between 10.00 and 66.00 years. More than half (59.4%) were females. In the present study, 51.0% patients presented with optic nerve involvement, 85.4% with spinal cord involvement, and 49.0% with intracranial involvement. The rheumatologic profile of the patients showed that the mean (SD) ESR was 19.87 (16.41); with 9.4% CRP positive, 4.2% RA factor positive, 45.8% ANA positive, 34.4% anti ds DNA positive, 2.1 cANCA positive, and 1.0% pANCA positive. (Table 1), (Figure 1)

*Comparison between NMOSD patients and multiple sclerosis patients* (Table 2)

The results showed that patients with NMOSD and multiple sclerosis did not vary significantly by demographic characteristics, disease manifestation (except for cerebral lesions), and rheumatologic profile (except for ANA & anti ds DNA). Patients with multiple sclerosis had ten times increased chances of presenting with cerebral lesions compared to patients with NMOSD (OR 10.39, 95% CI 3.1 to 34.8) – a statistically significant association ( $p < 0.05$ ). Significantly ( $p < 0.05$ ) higher proportion of NMOSD patients (57.7%) had positive ANA compared to MS patients (34.6%) (OR 2.58, 95% CI 1.09 to 6.85); similarly a significantly ( $p < 0.05$ ) higher proportion of NMOSD patients (46.2%) had positive anti ds DNA in comparison

**Table 1: Comparison between NMOSD, MS and MOGAD**

| n (%) or Mean (SD)                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Anti-AQP4 antibody positive NMOSD (N = 44) | Anti-AQP4 antibody negative NMOSD (N=10) | Multiple sclerosis (N = 26) | MOG antibody associated disease (MOGAD) (N=18) |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------------------------|-----------------------------|------------------------------------------------|
|                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | n (%) or Mean (SD)                         | n (%) or Mean (SD)                       | n (%) or Mean (SD)          |                                                |
| <b>Demographic characteristics</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                            |                                          |                             |                                                |
| Age(in years)                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 35.43 (13.94)                              | 34.20 (18.18)                            | 34.85 (13.78)               | 31.39 (9.93)                                   |
| Gender                             | Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 28 (63.6)                                  | 4 (40.0)                                 | 15 (57.7)                   | 10 (55.6)                                      |
|                                    | Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 16 (36.4)                                  | 6 (60.0)                                 | 11 (42.3)                   | 8 (44.4)                                       |
| <b>Disease distribution</b>        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                            |                                          |                             |                                                |
| Optic nerve involvement            | Present                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 20 (45.5)                                  | 5 (50.0)                                 | 12 (46.2)                   | 12 (66.7)                                      |
|                                    | Absent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 24 (54.5)                                  | 5 (50.0)                                 | 14 (53.8)                   | 6 (33.3)                                       |
| Spinal cord involvement            | Present                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 39 (88.6)                                  | 8 (80.0)                                 | 23 (88.5)                   | 14 (77.8)                                      |
|                                    | Absent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 5 (11.4)                                   | 2 (20.0)                                 | 3 (11.5)                    | 4 (22.2)                                       |
| Intracranial involvement           | Absent                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 29 (65.9)                                  | 7 (70.0)                                 | 4 (15.4)                    | 11 (61.1)                                      |
|                                    | Present                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 15 (34.1)                                  | 3 (30.0)                                 | 22 (84.6)                   | 7 (38.9)                                       |
| <b>Rheumatologic profile</b>       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                            |                                          |                             |                                                |
| ESR                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 21.00 (16.03)                              | 22.88 (16.77)                            | 18.50 (15.53)               | 20.17 (18.96)                                  |
| CRP                                | Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 39 (88.6)                                  | 8 (80.0)                                 | 25 (96.2)                   | 17 (94.4)                                      |
|                                    | Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 5 (11.4)                                   | 2 (20.0)                                 | 1 (3.8)                     | 1 (5.6)                                        |
| RA factor                          | Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 43 (97.7)                                  | 9 (90.0)                                 | 26 (100)                    | 16 (88.9)                                      |
|                                    | Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1 (2.3)                                    | 1 (10.0)                                 | 0 (0.0)                     | 2 (11.1)                                       |
| ANA                                | Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 19 (43.2)                                  | 5 (50.0)                                 | 17 (65.4)                   | 13 (72.2)                                      |
|                                    | Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 25 (56.8)                                  | 5 (50.0)                                 | 9 (34.6)                    | 5 (27.8)                                       |
| Anti ds DNA                        | Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 22 (50.0)                                  | 8 (80.0)                                 | 20 (76.9)                   | 14 (77.8)                                      |
|                                    | Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 22 (50.0)                                  | 2 (20.0)                                 | 6 (23.1)                    | 4 (22.2)                                       |
| cANCA                              | Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 44 (100)                                   | 9 (90.0)                                 | 26 (100)                    | 17 (94.4)                                      |
|                                    | Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0 (0.0)                                    | 1 (10.0)                                 | 0 (0.0)                     | 1 (5.6)                                        |
| pANCA                              | Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 44 (100)                                   | 10 (100)                                 | 26 (100)                    | 17 (94.4)                                      |
|                                    | Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0 (0.0)                                    | 0 (0.0)                                  | 0 (0.0)                     | 1 (5.6)                                        |
|                                    | Anti-AQP4 Antibody positive NMOSD Antibodies to Neuromyelitis optica or aquaporin-4 (called NMO-IgG or AQP4-Ab) positive NMO spectrum disorder; Serum MOG Ab, Antibodies to Myelin oligodendrocyte glycoprotein; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; RA factor, Rheumatoid factor; ANA, Antinuclear antibody; Anti ds DNA, Anti-double-stranded deoxyribonucleic acid antibodies; cANCA, Antineutrophil Cytoplasmic Autoantibody, Cytoplasmic; pANCA, Perinuclear anti-neutrophil cytoplasmic antibodies |                                            |                                          |                             |                                                |

with multiple sclerosis patients (OR 2.86, 95% CI 1.09 to 8.27). 5 out of 52 (9.61%) patients with anti-AQP4 antibody positive NMOSD were subsequently diagnosed with systemic

lupus erythematosus (SLE) and 3 of 52 (5.76%) were subsequently diagnosed with Sjogren's syndrome. This was in comparison to none identified in the MS group.

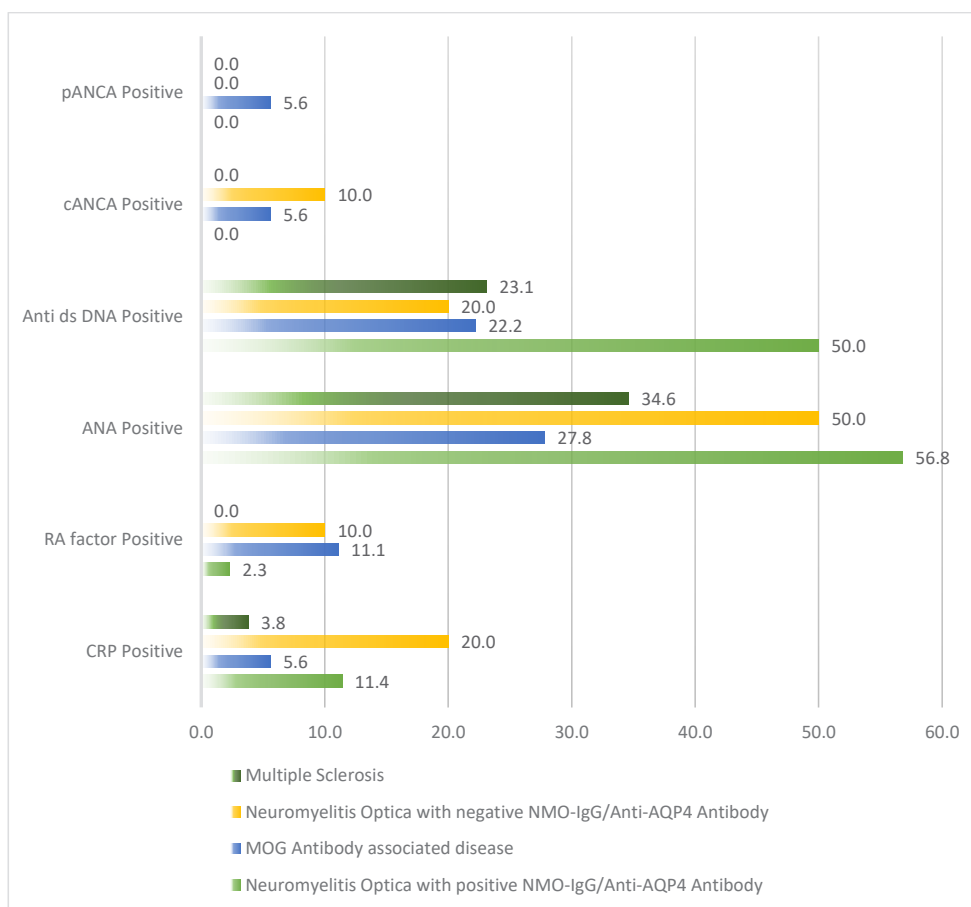


Figure 1. Seropositivity for rheumatologic markers in CNS demyelinating diseases

#### Comparison between other study groups and multiple sclerosis patients

In the comparison between anti-AQP4 antibody positive NMOSD and MS patients, it was found that 56.8% patients with anti-AQP4 antibody positive NMOSD had ANA positivity compared to 34.6% patients with multiple sclerosis – patients with anti-AQP4 antibody positive NMOSD had significantly increased chances (OR 2.49, 95% CI 1.09 to 6.79) of ANA positivity ( $p < 0.05$ ). Similarly, it was found that patients with anti-AQP4 antibody positive NMOSD had increased chances of anti ds DNA positivity (OR 3.33, 95% CI 1.12 to 9.88) and increased levels of CSF protein (MD 21.54, 95% CI 1.18 to 43.16) in comparison with multiple sclerosis patients ( $p < 0.05$ ). However, the chances of disease manifesting with cerebral lesions were increased with multiple sclerosis patients (OR 10.63, 95% CI 3.09 to 36.54).

The chances of cerebral lesions were much higher among multiple sclerosis patients (OR 12.83, 95% CI 2.29 to 71.79) when compared with anti-AQP4 antibody negative NMOSD patients ( $p < 0.05$ ).

The results showed that none of the demographic characteristics, disease manifestation (except cerebral lesions) and rheumatologic profile, varied significantly between MOGAD patients and multiple sclerosis patients ( $p > 0.05$ ). The chances of cerebral lesions were significantly higher (OR 12.83, 95% CI 2.29 to 71.79) with multiple sclerosis patients.

#### DISCUSSION

The present study aimed to assess the frequency of seropositivity for autoantibodies, as well as other rheumatologic markers in patients with CNS demyelinating diseases, and to determine whether the seropositivity for autoantibodies differs between MS, anti-AQP4 positive and

**Table 2: Comparison between NMOSD and multiple sclerosis**

| n (%) or Mean (SD)                                                                                                                                                                                                                                                                                                                                                                                                                                                              |          | NMOSD<br>(N = 52)     | Multiple sclerosis<br>(N = 26) | Total         | p value<br>OR (95% CI) or<br>MD (95% CI)   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------------|--------------------------------|---------------|--------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          | n (%) or Mean<br>(SD) | n (%) or Mean<br>(SD)          |               |                                            |
| Demographic characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                     |          |                       |                                |               |                                            |
| Age (in years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          | 35.79 (14.70)         | 34.19 (14.13)                  | 34.53 (13.75) | 0.892                                      |
| Gender                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Female   | 32 (61.5)             | 15 (57.7)                      | 47 (60.3)     | 0.744                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Male     | 20 (38.5)             | 11 (42.3)                      | 31 (39.7)     |                                            |
| Disease manifestation                                                                                                                                                                                                                                                                                                                                                                                                                                                           |          |                       |                                |               |                                            |
| Optic nerve involvement                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Present  | 25 (48.1)             | 12 (46.2)                      | 37 (47.4)     | 0.873                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Absent   | 27 (51.9)             | 14 (53.8)                      | 41 (52.6)     |                                            |
| Spinal cord involvement                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Present  | 46 (88.5)             | 23 (88.5)                      | 69 (88.5)     | 0.632                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Absent   | 6 (11.5)              | 3 (11.5)                       | 9 (11.5)      |                                            |
| Intracranial involvement                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Absent   | 34 (65.4)             | 4 (15.4)                       | 38 (48.7)     | <0.001*<br>OR 10.39, 95% CI<br>3.1 to 34.8 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Present  | 18 (34.6)             | 22 (84.6)                      | 40 (51.3)     |                                            |
| Rheumatologic profile                                                                                                                                                                                                                                                                                                                                                                                                                                                           |          |                       |                                |               |                                            |
| ESR                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |          | 20.60 (16.13)         | 18.50 (15.53)                  | 19.87 (16.41) | 0.618                                      |
| CRP                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Negative | 45 (86.5)             | 25 (96.2)                      | 70 (89.7)     | 0.187                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Positive | 7 (13.5)              | 1 (3.8)                        | 8 (10.3)      |                                            |
| RA factor                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Negative | 50 (96.2)             | 26 (100)                       | 76 (97.4)     | 0.311                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Positive | 2 (3.8)               | 0 (0.0)                        | 2 (2.6)       |                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Positive | 30 (57.7)             | 9 (34.6)                       | 39 (50.0)     |                                            |
| Anti ds DNA                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Negative | 28 (53.8)             | 20 (76.9)                      | 48 (61.5)     | 0.020*<br>OR 2.86, 95% CI<br>1.09 to 8.27  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Positive | 24 (46.2)             | 6 (23.1)                       | 30 (38.5)     |                                            |
| cANCA                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Negative | 51 (98.1)             | 26 (100)                       | 77 (98.7)     | 0.477                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Positive | 1 (1.9)               | 0 (0.0)                        | 1 (1.3)       |                                            |
| pANCA                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Negative | 52 (100)              | 26 (100)                       | 78 (100)      | —                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Positive | 0 (0.0)               | 0 (0.0)                        | 0 (0.0)       |                                            |
| *Statistically significant at p<0.05                                                                                                                                                                                                                                                                                                                                                                                                                                            |          |                       |                                |               |                                            |
| Serum NMO Ab, Antibodies to Neuromyelitis optica or aquaporin-4 (called NMO-IgG or AQP4-Ab); Serum MOG Ab, Antibodies to Myelin oligodendrocyte glycoprotein; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; RA factor, Rheumatoid factor; ANA, Antinuclear antibody; Anti ds DNA, Anti-double-stranded deoxyribonucleic acid antibodies; cANCA, Antineutrophil Cytoplasmic Autoantibody, Cytoplasmic; pANCA, Perinuclear anti-neutrophil cytoplasmic antibodies |          |                       |                                |               |                                            |

anti-AQP4 negative NMOSD and MOGAD within the Indian population.

The findings showed that females had a higher incidence of demyelinating diseases as compared to males. Patients with multiple sclerosis had a significantly increased chances of presenting with intracranial involvement as compared to

patients with NMOSD or MOGAD. These results were similar to those reported by Matthews *et al.* who described brain lesions distribution in seropositive NMOSD as compared to MS.<sup>13</sup>

ANA positivity was found in 57.7% patients with NMOSD compared to 34.6% of patients with MS. Only 27.8% of patients with MOGAD

had seropositive ANA, which was much lower. These results align with those reported from India by Netravathi *et al.*, who found ANA positivity in 20%, 42% and 22% patients with MS, NMOSD and MOGAD, respectively.<sup>14</sup> Ana Luzia *et al.* also obtained similar results in the paediatric population, reporting ANA seropositivity in 80% of NMOSD patients compared to 52.9% of patients with MS.<sup>15</sup> In their review of literature, Iyer A *et al.* identified 22 autoimmune conditions associated with NMOSD.<sup>16</sup>

Similarly, anti dsDNA was positive in 46.2% of NMOSD patients as compared to 23.1% of MS patients, which was statistically significant. In MOGAD, 22.2% of patients had seropositive anti dsDNA. Other rheumatologic markers, including ESR, CRP, RA factor and c ANCA was more frequently positive in NMOSD as compared to MS, although the differences were not statistically significant.

Anti AQP4 positive NMOSD patients had a higher seropositivity for ANA and anti dsDNA compared to anti AQP4 negative NMOSD patients, although these differences were not statistically significant. Similar to our results, a previous study showed that anti-AQP4 seropositive NMOSD differs clinically and epidemiologically from seronegative disease, with a strong predominance in women, more severe clinical attacks, a higher spinal cord lesion load, and a frequent association with coexisting autoimmunity.<sup>17</sup> We also observed a higher frequency of females and a higher frequency of spinal cord involvement in our study, although these findings were not statistically significant.

Similar findings were also reported by Lee *et al.*, who found that anti aquaporin-4 positive NMOSD with ANA positivity had a higher frequency of other auto antibodies, including anti ds DNA, anti SSA/Rho and Anti SSB/La. They also reported that those with ANA positivity had a higher incidence of systemic autoimmune diseases like systemic lupus erythematosus and Sjogren's syndrome.<sup>18</sup>

The reason why NMOSD patients have a higher rate of ANA seropositivity remains unclear. Multiple mechanisms for the co-association of AQP4 seropositivity and other autoimmune diseases, including SLE and SS, have been proposed, such as common genetic or environmental factors. Over 200 genetic loci have been associated with autoimmune diseases, some of which have associations with multiple diseases.<sup>19</sup> It has been speculated that

the coexistence of the two disorders in the same patient might reflect a general autoimmune predisposition involving the activation of both autoreactive Th1 cells (mainly linked to CNS lesions) and B cells via Th2 cells. The concept of coexisting independent, antibody-mediated autoimmune disorders in the same patient is further supported by the association of AQP4-antibody positive NMOSD with autoimmune conditions such as Grave's disease, myasthenia gravis, or coeliac disease, as observed in various studies.<sup>7,16</sup>

In their comprehensive systematic review on incidence and prevalence of autoimmune diseases in MS; Marrie *et al.* reported that fewer than 5% of individuals with MS suffered from most autoimmune conditions, with the possible exceptions of celiac disease, type I diabetes, thyroid disease, uveitis and psoriasis, for which at least one estimate was over 5%.<sup>10</sup>

The present study has some limitations. First, the study involves limited number of patients, hence a larger cohort may be needed to obtain results that are more generalizable. A longer follow up study may also provide better insights into the significance of this ANA seropositivity with the development of various systemic autoimmune diseases, as well as severity and prognosis of central demyelinating diseases.

In conclusion, patients with NMOSD present with a higher frequency of autoantibodies against cellular antigens. While a significant association was found only for increased seropositivity for ANA and anti dsDNA in NMOSD compared to MS, there was an insignificantly increased frequency of seropositivity for CRP, RA factor and ESR. The clinical significance of detectable ANA in MS fails to identify a clear association between their presence, disease activity, progression, or response to treatment, but it may carry some significance in NMOSD. Therefore, routine ANA testing in patients with NMOSD may be justified compared to in MS. The relationship between ANA and MOGAD requires further research. As research on autoantibodies and demyelinating disorders deepens, increasing attention is drawn to the relationship between autoimmune antibodies and CNS demyelination, especially regarding the clinical significance and long-term prognosis. This warrants future studies, including genome-wide association surveys and epidemiological data among different ethnic groups.

## DISCLOSURE

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Conflict of interest: None

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