# Deciphering the Footprints of Autoimmunity in CNS Demyelinating Disorders

Multiple sclerosis (MS) is a CNS (central nervous system) demyelinating autoimmune neurodegenerative disorder mediated by coordinated involvement of both T-cells and B-cells. The 2017 McDonald's criteria for MS emphasizes on the clinical and radiological features for the diagnosis of MS with an emphasis to exclude other alternative diagnosis or MS mimic. It is common practice to test for other systemic autoimmunity to exclude alternative diagnosis such as systemic lupus erythematosus (SLE) and Sjogren's syndrome and hence blood tests such as thyroid profile, B12, and ANA (anti-nuclear antibody) tests are performed. Diagnostic dilemma occurs when one of these autoimmune tests appear positive, whether it is a coincidental occurrence, epiphenomenon, alternative diagnosis, or MS mimic.

Many studies have tried to study the prevalence of these autoimmune disorders, autoantibodies, and their significance. There have been conflicting reports of association of MS with autoimmune thyroid disorders.[1,2] A questionnaire-based survey conducted in Canadian province among MS and general neurological disorders patients found high prevalence of Grave's disease and Hashimoto's disease in MS.[3] Epidemiological studies have shown clustering of autoimmune disease possibly due to genetic susceptibility or a common environmental trigger.[3,4] There are reports of shared risk and increased susceptibility for people with one autoimmune disorder to develop another autoimmune disorder suggesting genetic autoimmune predisposition.[5] Few genome-wide association studies have identified both classical Human leukocyte antigens (HLA) alleles and non-HLA genes in the contribution of autoimmune disorder susceptibility.[6] The peripheral blood mononuclear cell gene-expression levels of common candidate genes revealed common deregulated anti-inflammatory mechanisms in both MS and autoimmune thyroid disorders.[7]

In contrast to MS, autoimmune antibodies such as ANA, anti-Ro, anti-La have been more frequently associated in patients of AQP4-positive NMOSD (neuromyelitis optica spectrum disorders). Two university hospitals from South Korea tried to analyze the long-term prognostic value of ANA antibodies in AQP4-positive NMOSD. Nearly 43.2% patients had positive ANA with concurrent anti-SSA/Ro, anti-SSB/La, antiphospholipid, and anti-double stranded DNA antibodies. There were associated systemic diseases, namely SLE (12.5%) and Sjogren's (18.8%).[8] They did not find any difference between the clinical episodes, annual relapse rate, nor the lesion extent on MRI. This was contrary to few other studies[9] that showed ANA positivity was associated with more severe disease in AQP4 + ve NMOSD. A large Indian study[10] showed a high (33.6%) prevalence of abnormal autoimmune profile in AQP4-positive NMOSD and anti-Ro antibodies were more frequently (55.9%) found compared with ANA (8.8%).

This study[11] has been carried out from probably one of the first Demyelinating registry established in India under the aegis of Professor Lekha Pandit, who happens to be a pioneer in systematic, extensive evaluation of Demyelinating disorders in India. This is one of the first comprehensive study from India investigating the presence of two specific autoantibodies: ANA and anti-thyroid antibody (thyroid peroxidase: TPO-Ab, thyroglobulin: TG-Ab) and to detect the incidence of autoimmune disorders in a large cohort of patients with MS, AQP4-positive NMOSD, and MOGAD (myelin oligodendrocyte glycoprotein associated disorder).The salient features found in this study are [Table 1]: (i) Anti-thyroid antibodies were seen in: 20% to 26% of MS, AQP4, whereas the incidence was lower (9%–12%) in MOGAD and seronegative demyelination. (ii) Hypothyroidism was observed in 7% to 9% of MS, seronegative patients, while it was slightly higher (15%) in AQP4-positive NMOSD and MOGAD. (iii) ANA was in higher proportions in demyelinating patients compared with controls with frequency of 20% to 22% in MS, MOGAD, and seronegative patients and highest (42%) in AQP4-positive NMOSD. Hence, it is noteworthy to observe the higher incidence of ANA in AQP4-positive NMOSD patients which has been noticed in previous studies. Although this study evaluated only the anti-thyroid antibodies and ANA in a large cohort of demyelinating disorder patients, there were few lacunae as ANA positivity alone may not have significance to suggest existence of connective tissue disorders. Many studies

**Table 1: Frequency of thyroid antibodies and ANA positivity in the study population**

| | MS | AQP4 | MOG | SN | Controls |
|---|---|---|---|---|---|
| ATAb | 25.5% (26/102) | 20% (8/40) | 12.2% (5/41) | 9.1% (5/55) | 26% (12/41) |
| Thyroid dysfunction | 8% (9/111) | 15% (6/40) | 15% (6/41) | 9% (5/55) | 7% (4/41) |
| ANA | 20% (22/111) | 42% (17/40) | 22% (9/41) | 21% (15/71) | 4.3% (2/41) |
| ATAb+ANA | 3 | 0 | 0 | 0 | 0 |

*Abbreviations*: ANA: antinuclear antibodies; ATAb: Antithyoid antibodies; MS: Multiple sclerosis; AQP4: Aquaporin-4; MOG: Myelin oligodendrocyte glycoprotein; SN: Seronegative

have emphasized the presence of other antibodies especially in AQP4-positive NMOSD.

This raises the question as to whether we need to perform ANA testing in patients of CNS demyelination. What is the significance of ANA positivity in a patient with MS/AQP4? ANA test is sensitive but less specific for the diagnosis of SLE as ANA can be detected in many autoimmune conditions and healthy population.[12] Positive ANA tests showing speckled pattern at 1:160 titer and other patterns (homogeneous, peripheral, or centromeric) at low titers (</=1:40) is considered positive.[12] ANA positivity in a patient with MS is common suggesting immune dysregulation, but does not warrant routine screening. The diagnosis of MS should be based on the clinical symptomatology along with Revised 2017 McDonald's criteria and clinical exclusion of alternative diagnosis. Whereas, ANA positivity in patient with AQP4+ve NMOSD may require testing for other antibodies and search for associated SLE or Sjogren's syndrome. Positive ANA should always be interpreted by a specialist on the background of clinical context and available investigations.[12,13]

Several studies have tried to study the incidence of thyroid dysfunction in patients of MS and there have been conflicting reports.[14,15] A large systematic review observed that the most common autoimmune disorders in people with MS were thyroid disorders, psoriasis, uveitis, and inflammatory bowel disease.[16] Disease modifying agents such as interferon-β (IFN-β) and alemtuzumab have shown to increase the risk of development of thyroid dysfunction.[14] The absence of information regarding the disease modifying agents deserves particular mention in the Mangalore registry study. There definitely appears to be a possible trend for increased incidence of thyroid disorders in people with MS and this may increase with the usage of few disease modifying agents.

The clinical significance of detectable ANA in relation to MS fails to identify a clear association between their presence, disease activity, progression, or response to treatment, but may carry significance in AQP4-positive NMOSD. This suggests that routine ANA testing in patients with MS maybe unnecessary unless prompted by remarkable history or clinical finding but may be required in cases of AQP4-positive NMOSD. Although these antibodies are indicative of immune dysregulation, however, their presence may not be clinically meaningful or a cause of concern especially when clinical features are non-contributory. ANA relationship with MOGAD requires future studies and research. Thyroid disturbances may add to the comorbidity especially the neuropsychiatric aspects of demyelinating disorders, and a neurologist should be aware of precipitation of thyroid dysfunction with disease modifying agents. With the deepening research on autoantibodies and demyelinating disorders, lots of attention has been attracted on the relation between autoimmune antibodies, autoimmune disorders, and CNS demyelination especially in terms of the clinical significance and long-term prognosis that may require future studies with genome-wide association surveys and epidemiological data among different ethnic groups.

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