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Simultaneous screening for antibodies to myelin oligodendrocyte glycoprotein and aquaporin-4 in patients with optic neuritis using cell-based assay

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Neuromyelitis Optica; Optic Neuritis; Aquaporins; Myelin-Oligodendrocyte Glycoprotein; Cell-Based Assay

Abstract

Background: This study was aimed to test simultaneous detection of antibodies to myelin oligodendrocyte glycoprotein (MOG)/aquaporin-4 **(**AQP4) in serum samples of patients with clinically-diagnosed optic neuritis (ON), by fixed cell-based immunofluorescence assay (CBIFA).

Methods: The study involved 237 serum samples of patients with ON which were tested for MOG and AQP4 antibodies using fixed CBIFA kit which utilizes AQP4 or MOG protein transfected cells as a substrate.

Results: Of 237 serum samples, 22 (9%) were positive for AQP4, 66 (28%) were positive for MOG, and 138 (58%) were negative for both AQP4 and MOG antibodies. 11 (5%) patients with clinically-diagnosed multiple sclerosis (MS) were negative for both antibodies. None of the samples were positive for both AQP4 and MOG. Among 237, 132 women [18 (13.6%) and 37 (28%)] and 105 men [4 (3.8%) and 29 (27.6%)] were positive for AQP4/MOG antibodies and remaining percentage belonged to double negative and MS. Seropositivity rate was higher in women than men. Antibodies to MOG were significantly higher than AQP4 antibodies and evenly found in all age groups. There was no ambiguous result encountered in the study.

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Conclusion: In this study, the seropositivity for antibodies to MOG is more than AQP4 antibody in patients with ON. Fixed CBIFA is a useful tool for laboratory diagnosis of ON in the clinical setting of neuro-ophthalmology to plan the next line of treatment management effectively.

Introduction

Optic neuritis (ON) is inflammation of the optic nerve that can be due to demyelinating or non-demyelinating etiology. It is characterized by unilateral or bilateral acute visual loss usually associated with pain on eye movement, color defects, afferent pupillary defect, central scotoma, and abnormal visual-evoked response.[1] Associations of ON with sero-markers have revolutionized the management of ON. Mortality rates are high in neuromyelitis optica (NMO), most frequently secondary to neurogenic respiratory failure, which occurs with the extension of cervical lesions into the brainstem or from primary brainstem lesions.[2] Population-based studies from Europe and Southern Asian countries suggest that there is an increase in incidence and prevalence of NMO in ON.[3] More effective treatments combined with an earlier and more accurate diagnosis have led to improved outcomes by the differential diagnosis of NMO spectrum disorder (NMOSD) and multiple sclerosis (MS).

NMOSD is a demyelinating condition that selectively targets the spinal cord and optic nerves, resulting in transverse myelitis (TM) and ON. Aquaporin-4 (AQP4) is considered to be the target antigen of NMO-immunoglobulin G (NMO-IgG), which is a water channel protein highly concentrated in spinal cord gray matter. During the inflammatory condition, NMOSD antibodies mainly target astrocytes known to be AQP4 water channels, which leads to the dysfunction of astrocytes and the onset of clinical manifestations.[2,4,5] Recent studies have revealed that a proportion of these patients with AQP4 antibody-negative NMOSD have antibodies against myelin oligodendrocyte glycoprotein (MOG) localized on the outermost surface of the myelin sheath and oligodendrocyte in the central nervous system (CNS).[6-10] Autoantibodies against MOG are recurrently found in patients with the spectrum of inflammatory demyelinating diseases (IDDs) of the CNS, including acute disseminated encephalomyelitis (ADEM), MS, clinically isolated syndrome (CIS), NMOSD, and isolated ON or TM, predominantly in children.[11,12] MOG protein is believed to be marker antigen for the demyelinating disorder for over three decades based on the animal model study which induces experimental autoimmune encephalomyelitis (EAE).[13]

As per the 2015 International Panel for NMOSD Diagnosis (IPND) diagnostic criteria for NMOSD, cell-based assays (CBAs) for AQP4 are sensitive and highly specific, performing better than tissue-based assays and enzyme-linked immunosorbent assay (ELISA). A fixed CBA showed near-identical results to a live CBA.[14,15] The commercially available (Euroimmun, Germany) fixed cell-based indirect immunofluorescence assay (CIIFA) provides simultaneous detection of antibodies against AQP4/NMOSD-IgG and MOG. Double positivity is rare. In this pilot study, we utilized this commercially available kit for qualitative in vitro determination of human immunoglobulin G (IgG) antibodies for AQP4 and MOG protein in serum samples from consecutive patients with ON seen at a tertiary care center in India.

Materials and Methods

This was a retrospective study. The study period was 2 years (January 2018 to December 2019). Serum samples were collected after receiving duly filled consent forms from all 237 patients who were clinically diagnosed as ON and tested for both MOG and AQP4 antibodies. We applied a commercially available in vitro diagnostic test for the simultaneous detection of antibodies to AQP4 and MOG proteins, using the commercially available CIIFA. The patients enrolled in this study were based on the following inclusion and exclusion criteria.

Inclusion criteria: All patients with ON, with or without CNS demyelination, with or without previous history of ON who have undergone magnetic resonance imaging (MRI) brain and orbit and serum NMO and MOG antibody testing were included in the study.

Exclusion criteria: Optic neuropathies of infectious, granulomatous, ischemic, hereditary, infiltrative, toxic, and traumatic etiologies were exclusion criteria.

CIIFA-technique for detection of specific AQP4-IgG and MOG-IgG: CIIFA was performed on all serum samples for simultaneous detection of both MOG and AQP4 antibodies following the manufacturer's instructions. In brief, the biochip has transfected cells fixed on 3 squares (one first row square with negative control cells without the antigens and the second row with two squares, one

with AQP4 antigen coated cells and the second well with MOG antigen coated cells). The patient serum samples were diluted at 1:10 as per the manufacturer's instruction for qualitative evaluation. The fixed biochip was incubated at room temperature (RT) and was washed thoroughly with phosphate buffered saline with Tween 20 (PBST). Subsequently, the biochip was incubated with goat anti-human IgG fluorescein isothiocyanate (FITC)-conjugated with secondary antibody. After antibody labeling, the cells were again washed with PBST and embedded in a mounting medium and observed under a fluorescence microscope (Nikon Eclipse Ni-E Fluorescent Microscope) with a blue filter (wavelength of 450-490 nm).

Interpretation of results: If anti-AQP4 antibody was positive in the serum sample, the biochip well containing the AQP4 antigen showed a flat, smooth to fine-granular green fluorescence of the cell with some accentuation of the cell membrane whereas a flat, smooth to coarse-granular green fluorescence over the cell membrane was considered to be anti-MOG positive in the MOG antigen coated well. The negative control was just the substrate cells. To interpret the results, the negative control showed no specific fluorescence in contrast to the positive green fluorescence pattern (Figure 1) shown by the positive samples.

The collected data were analyzed and interpreted statistically. The percentage-wise distribution of patients in various age groups and gender-wise distribution of both AQP4 and MOG-positive mean and standard deviation (SD) values were analyzed. The Student's t-test and Fisher's exact test were used for parametric and nonparametric comparisons. All probability values were two-tailed and $P < 0.05$ and $P < 0.01$ were considered to be significant.

Results

Of 237 serum samples tested, 9% (22/237) sera were positive for AQP4 antibodies, 28% (66/237) for MOG antibodies and 58% (138/237) were negative for both AQP4 and MOG antibodies (Table 1). Besides, 5% (11/237) of patients diagnosed with MS were found to be negative for both antibodies. None of the samples was seropositive for both AQP4 and MOG antibodies. We did not encounter any nonspecific staining with ambiguous results avoiding repeat testing.

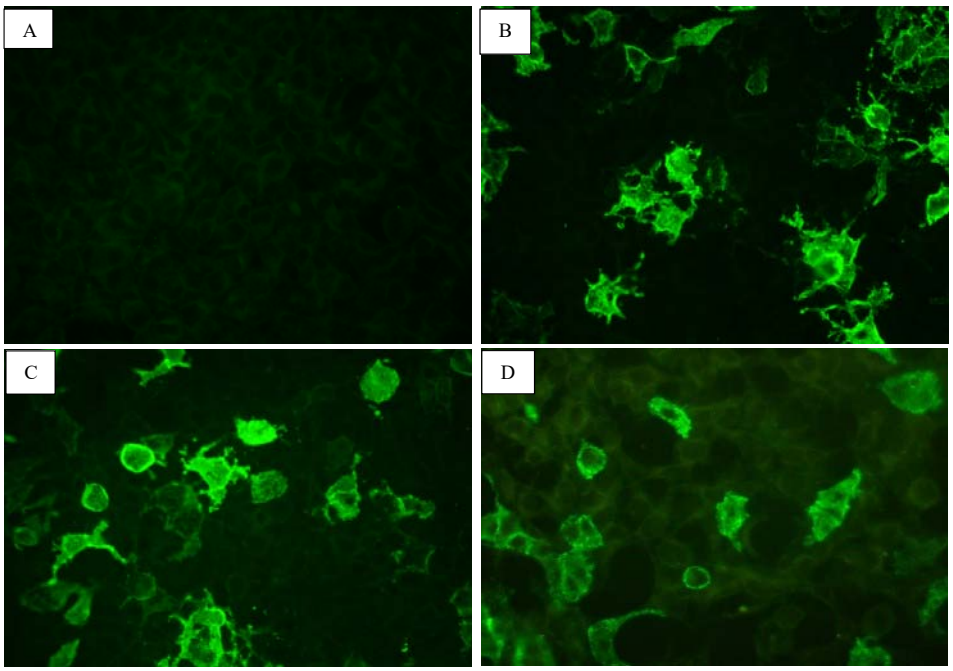

Figure 1. Representative staining pattern of cell-based indirect immunofluorescence assay (CIIFA) for aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibody
AQP4 positivity produces a flat, smooth to fine-granular fluorescence of the cell with some accentuation of the cell membrane. MOG positivity shows flat, smooth to coarse-granular fluorescence over the cell membrane. Negative control shows no specific fluorescence pattern. A: AQP4/MOG negative control; B: AQP4 positive control; C: Sample positive for AQP4; D: MOG positive control (40x magnifications) (imaging carried out in Nikon Eclipse Ni-E Fluorescent Microscope)

Table 1. Distribution of serum samples based on clinical spectrum

Characteristics	AQP4-IgG positive [n (%)]	MOG-IgG positive [n (%)]	Double negative [n (%)]	MS positive [n (%)]
Total (n = 237)	22 (9.0)	66 (28.0)	138 (58.0)	11 (5.0)
Women (n = 132)	18 (13.6)	37 (28.0)	69 (52.3)	8 (6.1)
Men (n = 105)	4 (3.8)	29 (27.6)	69 (65.7)	3 (2.9)

AQP4: Aquaporin 4; IgG: Immunoglobulin G; MOG: Myelin oligodendrocyte glycoprotein; MS: Multiple sclerosis

The gender-wise distribution showed that 55.7% (132/237) were women and 44.3% (105/237) were men. Among 132 women, 18 (13.6%) were positive for AQP4, 37 (28.0%) for MOG antibodies, 8 (6.1%) were MS, and 69 (52.3%) were double negative which were considered as seronegative for both AQP4 and MOG antibodies. In case of 105 men, 4 (3.8%) were positive for AQP4, 29 (27.6%) for MOG antibodies, 3 (2.9%) were MS, and 69 (65.7%) were double negative. AQP4 positivity was significantly higher in women (13.6% vs. 3.8%, P = 0.013) has a high female-to-male ratio, in contrast to the MOG with no gender-wise difference (28% vs. 27.6%, P = 0.390) (Figure 2A).

As per age-wise analysis, the age group from < 10 to 70 years evenly showed positivity to AQP4 and MOG. Antibodies to MOG were significantly higher in all age groups (P = 0.003). Antibodies to MOG were significantly higher in all age groups (P = 0.003) (Figure 2B).

Discussion

The advent of the CBA enabled native human MOG to be expressed on the cell surface as a target for this antibody.[16-18] As per the recent reports, live CIIFAs have become the gold standard, but not yet available in developing countries like India. They also have reported that both live and fixed CIIFA are considered to have excellent inter-assay reproducibility for the detection of human MOG-IgG antibodies.[17] Thus in this study, the CIIFA test was found to be user-friendly and easy to perform with a turnaround time of 75 minutes, and interpretation of the results is easier and clear-cut with positive or negative in comparison with the inbuilt negative control. The in vitro CIIFA kit claims to have clinical sensitivity of 75.0% and 99.9% specificity for AQP4 and 95.0% sensitivity and 98.1% specificity for MOG antibodies. In addition, none of the serum samples was positive for both AQP4 and MOG negative antibodies. It is important to consider that the double negative may contain unknown autoantibodies[7] or turn positive for AQP4 or MOG in later days. One of the retrospective cohort studies found dual positivity to both antibodies which is a rare coexistence; the patients had high titers of AQP4-IgG and low titers of MOG-IgG, which suggests that the disease phenotype may be more compatible with AQP4-IgG–positive NMOSD.[19]

As in the case of adult patients with the IDD, anti-MOG antibodies were found to be a disease-specific biomarker to those who have a disease distinct from NMOSD or MS; none had both antibodies with CIIFA.[20,21]

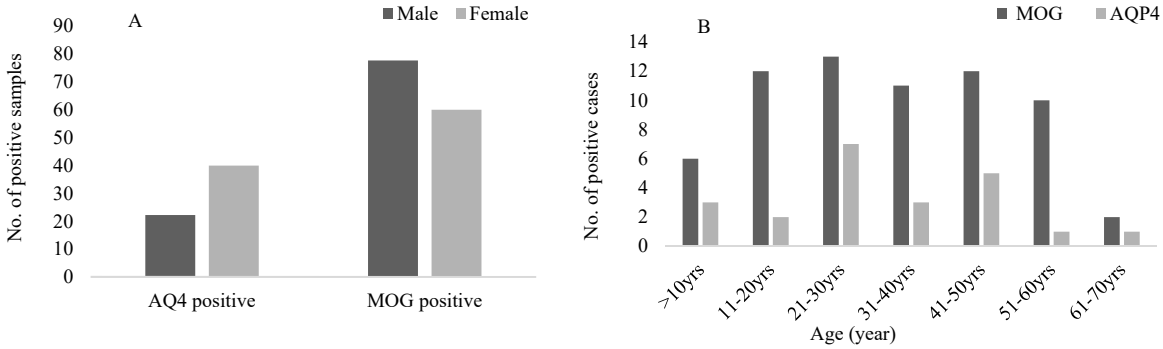

Figure 2. A: Distribution of antibodies to aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) according to age and sex. As per sex-wise analysis, AQP4 positivity was found higher in women (13.6% vs. 3.8%) and the female/male ratio was 9.0:2.0 (18/4) (statistically significant P = 0.013). MOG positivity (28.0% vs. 27.6%) shows no difference (P = 0.390); B: As per age-wise analysis, the age group range from < 10 to 70 years evenly showed positivity to AQP4 and MOG. Antibodies to MOG were significantly higher in all age groups (P = 0.003).

Detection of AQP4 and MOG antibody positivity in serum has an impact on the choice of the first line of therapy.[22] After the initial treatment with intravenous (IV) methylprednisolone therapy for ON, a maintenance treatment either immunomodulation with interferons or immunosuppressive (IMS) therapy would be planned depending on evidence of brain MRI lesion demyelinating or poor visual recovery. AQP4 antibody seropositive patients should not receive IMA like interferon (IFN) as the second line, as it can worsen the clinical condition. Patients' response to steroid treatment is different between the MOG group and the non-MOG group.[23] All adults with ON in the acute phase were treated with IV methylprednisolone over a period followed by oral prednisolone with variable durations, based on individual's clinician preference and ON subtype.[24]

A multicenter comparison study reported that both live cell-based methodologies had superior post-predicting value to the fixed cell assays suggesting positive results, and are more reliable indicators of MOG positivity than MOG-IgG ELISA.[18] Recently, another international multicenter comparative evaluation with MOG-IgG and MOG-IgM samples by comparing fixed immunofluorescence CBAs, flow cytometry live CBA, and ELISAs reported there is an excellent agreement (96%) between live CBAs for MOG-IgG for samples which were previously identified as clearly positive or negative for MOG from different national testing centres.[17] To overcome the conflicting results with western blot and ELISA, IPND recommends CBA as a universal method for MOG-antibody and AQP4 antibody detection.[14]

Based on antibody detection assay, MOG antibodies were initially identified as an important biomarker in children with demyelination. MRI is a critical tool used in the assessment of patients with possible demyelination. Zamvil and Slavin reported the presence of a subpopulation of AQP4 antibody-negative NMOSD patients who presented with serum MOG antibodies.[25] One of the retrospective etiological studies confirmed that MS was the leading cause of ON and MOG antibody was the second cause twice as common as ON with AQP4 antibody.[26]

NMOSD affects young adults ranging from 18-45 years of age with a mean age of 30-35 years in which women are affected predominantly.[3] According to another report, the median age of onset of NMOSD was 32 to 41 years ranging from children to older adults;[27] yet, in another study in 2015, a subpopulation of AQP4 antibody-negative NMOSD patients was found to be positive for MOG antibodies.[25] Recent reports suggested that the presence of MOG-antibodies strongly depended on the age at disease onset; similarly, MOG-antibodies frequently are found in children with ADEM and ON, also in adults with NMOSD and its limited forms.[28-30] This present study also showed that MOG antibodies were evenly distributed in children as well as in adult (31-60 years) age groups. The interesting finding in our study is that the number of AQP4 antibody positivity was more in women than men in agreement with the study reported during 2017.[31] In another study, more than 90% of patients with AQP4-ON were women, indicative of a strong female predominance in patients with AQP4-ON.[8] Similar findings about female/male ratio were also observed in AQP4 antibody-positive demyelinating disease.[7,32,33]

A possible limitation of our study is that being a tertiary care center, the study showed a higher percentage of atypical ON specifically in the Indian population. This is likely higher than the general populations when compared with other population-based studies.[34] In another study, AQP4-IgG and MOG-IgG accounted for 9% of ON[35] and one more study from the Netherlands showed that 7% of patients with the demyelinating disease were positive for MOG-IgG.[36] These studies suggest a lower percentage of MOG and AQP4. In another study on Sri Lankan population evaluating for suspected IDDs, MOG-IgG was detected in one of six (17%) patients and was 3.5 times more common than AQP4-IgG (5%), and there was no difference in the age-onset for MOG antibodies.[37]

Conclusion

The present study showed a higher incidence of antibodies to MOG than AQP4 in patients with ON. However, more number of serum samples need to be included to substantiate the results of this study.

Conflict of Interests

The authors declare no conflict of interest in this study.

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