Neurological Spectrum Disorders Associated with Anti–MOG Antibody

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Abstract

Optic neuritis (ON) is an inflammatory disease of the optic nerve characterized by pain and visual loss and often associated with multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSD). Autoantibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been reported in patients with inflammatory central nervous system disorders including isolated optic neuritis (ON).

Objective: To investigate the differences of clinical features, cerebrospinal fluid (CSF), MRI findings and response to steroid therapies between patients with optic neuritis (ON) who have myelin oligodendrocyte glycoprotein (MOG) antibodies and seronegative group. This study was done in a period between June 2015 and July 2018, 65 patients were included in this study with ON who ophthalmologists had diagnosed as having or suspected to have ON with acute visual impairment and declined critical flicker frequency, abnormal findings of brain MRI, optical coherence tomography and fluorescein fundus angiography at their onset or recurrence. After exclusion of all patients who fulfilled the diagnostic criteria of neuromyelitis optica (NMO)/NMO spectrum disorders (NMOSD), MS McDonald's criteria, we defined 40 patients with idiopathic ON (12 males, 28 females, age range 15-60 years). Sera from patients were tested for antibodies to MOG and aquaporin-4 (AQP4) with a cell-based assay.

Results: 37.5% (15/40) were positive for MOG antibodies, 2.5% (1/40) were positive for AQP4 and 25 (62.5%) were seronegative. Among the 15 patients with MOG antibodies, four had optic pain (p=0.007) and five had prodromal infection (p=0.05). Two of the 15 MOG-positive patients showed significantly high CSF levels of myelin basic protein (p=0.05) and none were positive for oligoclonal band in CSF. On MRIs, five MOG-positive patients showed high signal intensity on optic nerve, four had a cerebral lesion and two had a spinal cord lesion. Six of the eight MOG-positive patients had a good response to steroid therapy.

Conclusions: The present results indicate that Patients with NMOSD and MOG positive antibodies have distinct clinical features, fewer attacks and better recovery than seronegative patients.

Keywords: *optic neuritis; myelin oligodendrocyte glycoprotein; autoantibodies; demyelinating diseases.*

Introduction

Optic neuritis (ON) is an inflammatory disease of the optic nerve characterized by pain and visual loss and often associated with multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSD). Recent evidence suggests that certain forms of ON are associated with anti–myelin oligodendrocyte glycoprotein (MOG) antibodies[1-4]. A distinct clinical subset of ON is characterized by multiple episodes that involve one or both optic nerves, occur within months or weeks and do not involve any other associated clinical or radiologic findings. This entity, defined as either recurrent optic neuritis (rON) or chronic relapsing inflammatory optic neuritis (CRION)[5], is typically corticosteroid-responsive and corticosteroid-

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dependent, often requiring immunosuppressive therapy for corticosteroid-sparing effect.

The MOG is a glycoprotein of 218 aminoacids expressed exclusively in the plasmatic membrane of the oligodendrocytes within the CNS. It is a minor compound of the myelin sheath but its localization on the outer surface made it accessible to reactive antibodies. It is belived that its extracellular domain induces cellular and humoral autoimmunity[5]. Antibodies directed against MOG (MOG-IgG) are mostly of the IgG1 subtype and are able to induce cytotoxicity and to fix complement[5].

The MOG-IgG is observed in several clinical syndromes, such as NMOSD, idiopathic recurrent or bilateral optic neuritis (ON), isolated myelitis, acute demyelinating encephalomyelitis and in pediatric MS. Although, it is not clear if the variable phenotypes that have been linked to MOG-IgG are a result of the technical limitations and lack of a standard detection method[5], or if they indicate certain heterogeneity in the immunological dysfunction that causes the production of these autoantibodies.

Patients and Method

Study Design: This is a cross-sectional study of patients with NMO or NMOSD that diagnosed according to revised criteria who visited the neurological department in Baghdad teaching hospital and AL yarmouk teaching hospital. The study extended from June 2015 and July 2018.

Study Sample: Sixty. five patients were enrolled in the study, from each a detailed medical history had been taken, thorough physical examination was done. We only included consecutive patients followed up in one of the 2 centers for whom information regarding the clinical attacks, brain and spinal cord MRIs and serum for antibody testing were available; 25 patients were excluded because of a lack of information. All patients seronegative for both AQP4 and MOG antibodies were fully investigated and alternative diagnoses were ruled out.

All serum samples were analyzed for AQP4 and MOG antibodies. The cell-based assay (CBA) for AQP4 antibody detected in living cells using HEK-293 cells. These samples were also analyzed for the presence of MOG antibodies using a CBA with live HEK-293 cells. The samples were tested for MOG antibodies at least twice at dilution of 1:100.

Statistical Analysis: This is descriptive study through which we determine the percentages of anti-NMO in blood and CSF and there relation to gender, relapse rate, EDSS and pattern of optic involvement. Statistical analysis was performed with the statistical package for social sciences (SPSS for windows version 16).

Results

Among the 40 patients with NMOSD, 37.5% (15/40) were positive for MOG antibodies and 2.5% (1/40) were positive for AQP4 antibodies. No patients were positive for both antibodies.

The mean age of patients with anti-MOG Ab was (23.9± 9) year old. Eleven (73.3%) were females and only four (26.7%) were male as shown in table (1)

None of the patients had encephalopathy or seizures. All 15 MOG-positive patients had at least one episode of ON and 9 of them fulfilled the criteria for rON/CRION (defined as ≥3 episodes of ON within a period of a few months to a year).

Table (1): The demographic characteristics of NMO positive patient

Patient Characteristic	Patients with anti-MOG+ve No.=15	Sero negative patients No.=25
Age/year (Mean±SD)	23.9±9	24.2±8
Sex Male	4 (26.7%)	8 (32%)
Female	11(73.3%)	17(68%)
Female to male ratio	2.7:1	2.1:1

Table (2): The clinical features of patients with anti-MOG Ab positive than seonegative group

Patients characteristic	Patients with anti-MOG+ve	Sero negative patients
Brain MRI at onset:		
Normal	11	5
Non specific lesion	4	4
CSF		
Cells, mean (SD)	3 (8)	44
Positive OGB	2	5
Chronic treatment	4	6
No. of relapse mean (range)	2(1-8)	3 (1-4)
Relapsing disease	11	6
No of total relapses	10	6
Titer of MOG-IgG (range)	100-600	

Anti-MOG +ve patients: eleven patients (73.3%) had a recurrent course and 2 of them (13.3%) presented features of corticosteroid-dependent chronic relapsing inflammatory ON. Bilateral simultaneous ON attack was observed in 8 patients (53.3%) and it was the presenting syndrome in three of the eight patients who had a monophasic course . In total, 10 patients (66.6%) were treated with chronic therapy . five patients (33.0%) had a severe visual disability and this outcome was associated with a relapsing course in patients with bilateral presentation .

Anti-MOG -ve patients: The female : male ratio 2.1:1.0 (17/25) in the seronegative group. The median (range) onset age was 24.2±8 (16–60) years ($p = 0.004$). In this group 12 patients with a single attack who presented initially with ON and myelitis, thus fulfilling the definitive NMO criteria in the first attack. In the group of patients with only LETM, 4 patients (26.6%) had MOG antibodies and 72% (18/25) were seronegative. Among the patients with bilateral simultaneous or recurrent ON, 6.5% (1/15) had MOG antibodies and 12% (3/25) were seronegative. In the group of patients with only LETM, 26.5% (4/15) had MOG antibodies and 38.5% (12/25) were seronegative. Among the patients with bilateral simultaneous or recurrent ON, 28% (7/15) had MOG antibodies and 52% (13/25) were seronegative. Painful tonic spasms were present in 6.6% (1/15) of the patients with MOG antibodies and 40% (10/25) of seronegative patients ($p = 0.008$). Among patients with ON attacks, we found that 19.8% (3/15) of the MOG antibody group and 32% (8/25) of the seronegative group had a visual acuity <20/200 ($p = 0.005$). One patient (6.6%) positive for MOG antibodies and 12.0% (3/25) of the seronegative patients had no light perception after an ON attack. Bilateral, simultaneous ON attacks were more common in patients with MOG antibodies than in those who were seronegative (60% (9/15) vs 24% (6/25), respectively; $p = 0.001$).

Table (3): comparison of clinical features between patients with anti-MOG Ab positive and seronegative

Characteristics	MOG Ab +ve	Seronegative	p-value
Phenotype n (%)			
NMO	2 (8%)	12 (48%)	0.001
NMOSD-LETM	4 (%)	18 (72%)	0.005
NMOSD-ON	11 (%)	8 (%)	0.05
Simultaneous ON+myelitis attack n (%)	1	3 (%)	0.007
No. of attacke median (range)	2 (1-6)	3 (2-9)	0.005
EDSS median (range)	2 (1-5)	3 (1-7)	0.005

An abnormal brain MRI was present in 37.5% (6/16) of patients with MOG antibodies and 56.7% (34/60) of seronegative patients..

Spinal cord lesions on MRI were present in 37.5% (5/15) and 71.7% () of patients with MOG antibodies and seronegative patients, respectively (table 3, table e-2). Lesions in patients with MOG antibodies were distributed more frequently in the thoracolumbar region. By contrast, patients with seronegative patients had more lesions distributed in the cervicothoracic region. All patients with MOG antibodies (6/6), all patients who were seronegative (43/43) patients had lesions covering 3 or more vertebral segments in the sagittal spinal cord MRI.

Discussion

Our study results suggest that patients with MOG antibodies fulfilling the definitive NMO criteria as recently reported[5] may actually be rare. The single NMO case in our study had a monophasic presentation with both ON and myelitis occurring during the same attack, similarly to the original description by Eugene Devic in 1894. In fact, some of these patients with MOG antibodies and single attack in the current studies may have a spatially limited form of acute demyelinating encephalomyelitis (ADEM) but without encephalopathy and typical brain lesions, which could mimic NMOSD. However, we also found recurrent patients with persistent MOG antibodies, which is not usually

observed in ADEM and precludes the generalization of this hypothesis to all patients.

The strong female predominance in patients with MOG antibodies was not found in the seronegative group and a lower female: male ratio was found in seronegative patients. A similar difference in the female: male ratio between the diseases (with MOG antibodies and seronegative group) was observed in previous smaller studies[5,6], We found a difference in the spatial distribution of spinal cord lesions on MRI between patients with MOG antibodies and seronegative group. Brainstem symptoms, such as persistent nausea/vomiting and hiccups, as previously reported in NMOSD[9,10], were more commonly found in the MOG antibody group than in seronegative groups.

Although MOG antibodies have been shown to be potentially pathogenic and to efficiently activate complement in vitro, these antibodies have been reported in a variety of demyelinating diseases such as ADEM and multiple sclerosis (MS)[12], especially in pediatric populations[13,14] and also in NMOSD[6]. It is possible that differences in antibody assays or cohort ascertainments have a role to play in the apparent non disease specificity of the MOG antibodies. One could argue that the presence of MOG antibodies in a number of distinct diseases may currently limit the use of the MOG antibody assay as a specific diagnostic biomarker and it is possible that other undiscovered autoantibodies may exist in the seronegative patients.

Because of the study design, patients with MOG antibodies who had received a diagnosis of ADEM and MS were not included in this study, so our study findings are currently limited to patients who received a diagnosis of NMOSD. MOG antibody-positive patients, regardless of whether they had a single attack or recurrent disease, had some distinct clinical presenting features, usually fewer attacks and a better recovery after an attack than seronegative patients. Further long-term prospective studies are required to investigate whether patients with a single attack and patients with recurrent MOG antibodies—with clinical diagnosis of ADEM, MS, or NMOSD—have a singular disease, but with some differences in the clinical phenotype, disease course and treatment response.

Conflict of Interest: None

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Ethical Clearance: Not required

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