

# Serum levels of anti-myelin antibodies in relapsing-remitting multiple sclerosis patients during different phases of disease activity and immunomodulatory therapy

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**Abstract.** Antibodies against myelin oligodendrocyte antigens have been found in the immunoreactive brain lesions of Multiple Sclerosis (MS) patients. Recently it has been proposed that these antibodies can be used as a prognostic marker in the course of disease. However, the serum levels of these autoantibodies during different phases of disease activity or after an immunomodulatory therapy have been poorly investigated. In this study the serum levels of anti-myelin oligodendrocyte glycoprotein (MOG) (directed against the epitopes 1–26 and 15–40) and anti-myelin basic protein (MBP) antibodies were sequentially measured in the same MS patient either in relapse or remission phases. We found that MS patients in the relapse phase had higher serum anti-MOG (peptides 1–26 and 15–40) and anti-MBP antibody levels than controls. In addition, the levels of anti-MOG 1–26 were also elevated during the relapse as compared with the remission phase but no significant changes were found in the levels of anti-MOG 15–40 or anti-MBP antibodies. We also evaluated the effect of interferon- $\beta$  therapy on anti-myelin antibodies. 1-year of interferon- $\beta$  treatment did not induce any changes in the levels of anti-MOG and anti-MBP antibodies. In conclusion, these data indicate that the use of peripheral levels of autoantibodies against MOG and MBP as marker of multiple sclerosis might be complicated by the phase of disease activity and by the epitope of the MOG protein used.

Keywords: MOG, MBP, multiple sclerosis, relapse, remission, antibodies

## 1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), characterized by infiltration of macrophages and lymphocytes into the CNS and subsequent immunologic destruction of myelin sheath. Pathophysiological studies in humans [12] and animal model [17] of the disease (the experimental autoimmune encephalomyelitis, EAE) underline mainly a T-cell basis for the induction of inflam-

matory process and the formation of sclerotic plaques. However, there is also evidence of a humoral immune activity in MS [27] because antibodies against myelin oligodendrocyte antigens have been found in the sites of lesion [23]. Several myelin-type proteins with specific antigenic epitopes are thought to be involved in myelin destruction. These include myelin basic protein (MBP), proteo-lipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG) [9].

Many studies report detectable levels of MBP autoantibodies [6,10] though other studies, using similar techniques, report their absence [3,15,41]. Similarly, the data regarding the detection of autoantibodies to MBP in the cerebrospinal fluid (CSF) of patients with MS vary widely [25].

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MOG is a minor component of myelin proteins [31] that is restricted to the CNS [2,5,19,24] and was identified as a candidate autoantigen in MS following the demonstration that MOG-induced EAE reproduced the immunopathology and clinical course of the human disease in rodents and primates [22,32,35]. MOG is located in the outermost region of the myelin sheath [5, 29,40] where it can be targeted by demyelinating autoantibody responses directed against its extracellular N-terminal Ig-like domain (amino acids 1–132) [28,36, 37]. A previous study has claimed that the most frequently recognised amino acid sequences are 1–26 and 63–87 in MS patients and 14–39 and 63–87 in healthy controls [14]. This concept was additionally supported by findings showing the presence of MOG-reactive antibodies associated with disintegrating vesicular myelin debris in acute demyelinating MS lesions [20,29]. A recent report also showed that MOG-antibodies can be used as a prognostic marker early in the course of disease [13].

Despite these evidences, it is not clear whether the presence of these antibodies points unequivocally to multiple sclerosis. In animal models, in contrast to what has been observed in major myelin protein knockout models [33], MOG<sup>-/-</sup> mice do not show any neurological symptom, and they have a normal life span and reproduction rate, suggesting that MOG is not essential in promoting and/or regulating the formation and maintenance of myelinated axons. Other studies in human have shown that elevated titers of these antibodies in serum and cerebrospinal fluid (CSF) can also occur in various neurological diseases, including non-immune-mediated disorders [1,11,38,39]. Moreover, many complicating aspects and issues in MS are still emerging. For example, it has been demonstrated that autoimmune reactions are not necessarily always detrimental; they may have benefits as well [8,16,26, 30].

These observations have raised a strong debate on the role of these antibodies in the pathogenesis and clinical course of MS. Interestingly, the relapsing-remitting (RR) course of MS is characterized by the switch from a phase of autoimmune activation to a phase of remission. This form of the disease has provided a model for investigating the role of these antibodies in the processes of autoimmune activation but the results of these studies were not consistent [23,34]. One possible explanation could be that since MS patients are characterized by a wide range of degree of autoimmune inflammation the selection of the appropriate and comparable experimental groups (either in relapse or remis-

sion) could be difficult. To avoid this problem we measured the serum levels of anti-MOG (directed against the epitopes 1–26 and 15–40) and anti-MBP antibodies in the same MS patient and evaluated whether the acute and the stable phase of disease are characterized by different titers of these antibodies. Moreover, to elucidate the question of whether myelin antibodies are deleterious or play a defensive role in MS, we tested the hypothesis that interferon-beta ( $\beta$ ) treatment induces significant changes in the circulating levels of these autoantibodies.

## 2. Materials and methods

### 2.1. Patients

Levels of anti-MOG and anti-MBP antibodies were determined in serum samples from 40 MS patients, both in relapse and in remission phase of disease, and 47 healthy controls. 33 MS patients started interferon- $\beta$  treatment and were also tested before and after 2, 6 and 12 months of therapy.

The patients underwent clinical examination and brain and spinal cord magnetic resonance imaging (MRI) in remission phase and at time of relapse. MRI data were acquired with high resolution 1.5 Tesla system (5-mm slice thickness). Scanning sessions included proton density (echo time [TE] 20/repetition time [TR] 2500), T2-weighted (TE 80/TR 2500) and T1-weighted (TE 17/TR 600) images. The T1-weighted images were acquired before and 10 minutes after an intravenous injection of gadolinium-diethylenetriaminepentaacetic acid (0.1 mmol/kg) (Gd-DTPA). Disease activity was evaluated by clinical examination and MRI. Patients were considered in relapse phase when they showed an episode of new neurological disturbance lasting at least 24 hours and/or Gd-DTPA enhancing lesions at MRI; in stable phase, when they had shown neither new neurological symptom nor enhancing lesions for three months [21]. Disability degree was assessed with the Expanded Disability Status Scale (EDSS). Informations about age, sex, clinical assessment of patients are shown in Table 1.

The study was approved by the Ethical Committee of our institution. Informed consent was obtained from all subjects volunteering for this study.

Table 1  
Clinical features of RRMS patients

Patients	Age (years)	Sex (male/female)	Disease duration (years)	Annual relapse rate (mean)	EDSS
40	28.8 ± 9.08	9M/31F	5.25 ± 6.09	1.5 ± 0.7	1.66 ± 1.54

Notes: Data are the mean ± SD. EDSS = Expanded Disability Status Scale; M = male; F = female.

### Serum levels of anti-MOG antibodies in relapsing-remitting MS patients and controls

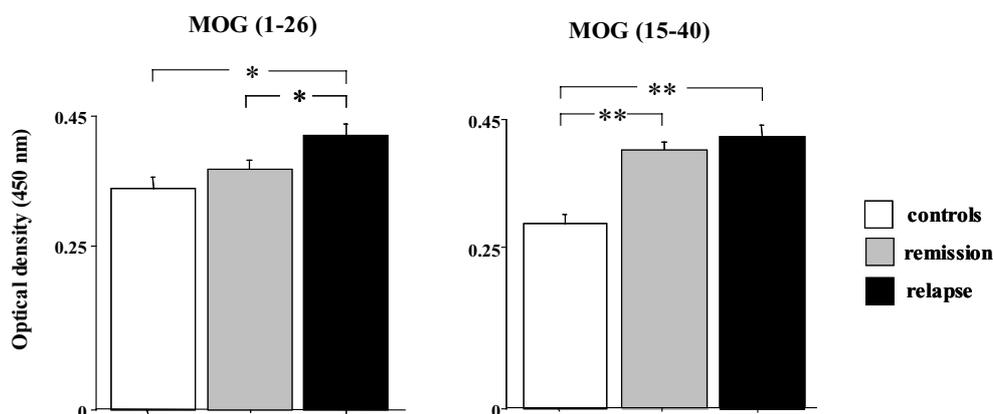


Fig. 1. Levels of antibodies against MOG (sequences 1–26 or 15–40) obtained from MS patients in relapse and remission phases and controls. Data are the mean ± SEM. Asterisks indicate statistical significances. \* $p < 0.05$ , \*\* $p < 0.01$ .

## 2.2. Antigens

Human MOG peptides, selected in the immunoglobulin-like domain of the MOG molecule, were synthesized and HPLC purified (more than 95% purity) by INBIOS (INBIOS srl, Italy). The specific peptide sequences is GQFRVIGPRHPIRALVGDEVELPCR1 corresponding to sequence 1–26 and LVGDEVELPCRISPGKNATGMEVGWY corresponding to sequence 15–40. Human MBP was purchased from Chemicon (CHEMICON Int., USA).

## 2.3. Blood sampling

Venous blood was collected in MS patients into sampling tubes. Samples were centrifuged within 20 min following sampling at  $2000 \times g$  for 20 min. Serum was then aliquoted and stored at  $-80^\circ\text{C}$  until assaying.

## 2.4. Antibody determination

Serum samples were tested for levels of anti-MOG and anti-MBP antibodies by a modified enzyme-linked immunosorbent assay, as previously reported by oth-

ers [30]. Briefly, 96-well microtiter plates (Nunc-Immuno plates; Nunc Als, Roskilde, Denmark) were coated with  $100 \mu\text{L}$  of a  $10\text{-}\mu\text{g/mL}$  antigen (recombinant human MOG peptides or MBP) solution in phosphate-buffered saline solution (PBS), pH 7.4, overnight at  $4^\circ\text{C}$ . Non-reactive sites were saturated with PBS with 1% bovine serum albumin [BSA] ( $200 \mu\text{L}$ ) for 2 hours at room temperature. A  $100\text{-}\mu\text{L}$  volume of plasma (diluted 1:5 diluted 1:200 in PBS with 1% BSA and 0.05% Tween-20) was added to each well, and the plates were kept at room temperature for 1 hour. After washing, goat biotinylated antihuman IgG anti-Fab ( $100 \mu\text{L}$ ), diluted 1:4000 in PBS and 3% BSA were added to each well of the tested plasma samples, and the plates were incubated for an additional 2 hours at room temperature. The plates were washed again, then peroxidase ( $100 \mu\text{L}$ ) that was conjugated to streptavidin and diluted 1:2000 in PBS and 1% BSA was added to each well, and the plates were incubated for 30 minutes at  $37^\circ\text{C}$ . Afterward, all plates were washed and a 3,3',5,5'-tetramethylbenzidine (TMB; Sigma-Aldrich Corp, St Louis, Mo) liquid substrate was added. The developing colour was stopped with  $100 \mu\text{L}$  HCl 1 M and read as an optical density at 405 nm ( $\text{OD}_{405}$ ). Each

### Serum levels of anti-MBP antibodies in relapsing-remitting MS patients and controls

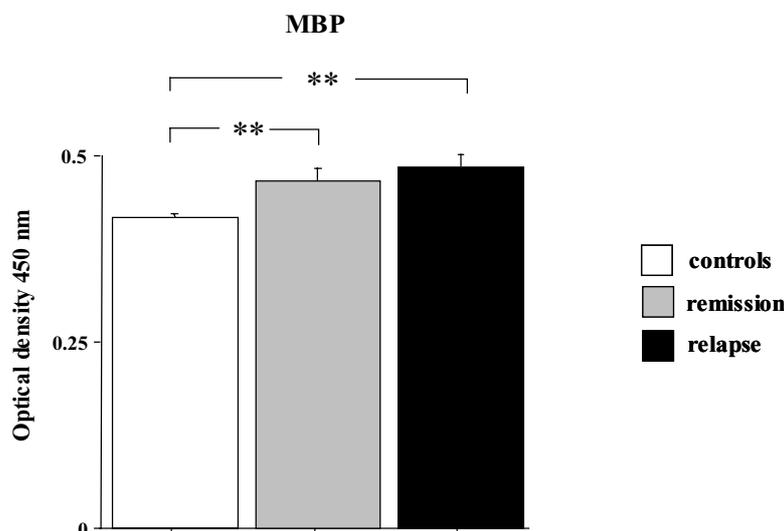


Fig. 2. Levels of antibodies against MBP obtained from MS patients in relapse and remission phases and controls. Data are the mean  $\pm$  SEM. Asterisks indicate statistical significances. \*\* $p < 0.01$ .

plasma sample was tested in duplicate, so the results for every specimen express the average value of the OD readings. The within-assay variation was less than 15%. Specimens were considered positive if their average OD reading was higher than the mean OD<sub>405</sub> level +2 standard deviations (SDs) of controls.

#### 2.5. Statistical analysis

Differences in variables between MS patients and healthy subjects were tested by analysis of variance (ANOVA) and comparisons between values obtained from the same patients in different phase of disease (relapse vs remission) or time of interferon- $\beta$  treatment (baseline vs 2-, 6-, 12-months) were performed by using the paired t test (all values were normally distributed). Results are expressed as mean  $\pm$  SE. P-values = 0.05 were considered statistically significant.

### 3. Results

#### 3.1. Levels of anti-MOG and anti-MBP antibodies measured in the same MS patients at different phases of disease (relapse vs remission)

We found that levels of anti-MOG 1–26 (Fig. 1) were significantly higher in MS patients in relapse phase than

Table 2

Number of patients positive for autoantibodies against the myelin proteins MOG and MBP

	Anti-MBP	Anti-MOG (1–26)	Anti-MOG (15–40)
Relapse	18/40**	0/40	9/40*
Remission	16/40**	0/40	8/40*
Controls	0/47	3/47	0/47

Notes: Values are the numbers of positive patients/total number of patients. Patients were considered positive to autoantibodies if their average OD reading was higher than the mean OD<sub>405</sub> level +2 standard deviations of controls. \* $p < 0.01$ , \*\* $p < 0.001$ , as measured with Fisher's exact P-value vs controls.

in remission ( $p < 0.05$ ). There were no significant differences in anti-MOG 15–40 (Fig. 1) and anti-MBP (Fig. 2) antibody levels between relapse and remission phases.

#### 3.2. Levels of anti-MOG and anti-MBP antibodies in serum from relapsing-remitting MS patients versus controls

Levels of anti-MOG 1–26 antibodies of MS patients in relapse phase were significantly higher than controls ( $p < 0.05$ ) (Fig. 1). The levels of anti-MOG 15–40 (Fig. 1) and anti-MBP (Fig. 2) antibodies were elevated in MS patients both in relapse ( $p$ 's  $< 0.01$ ) and remission ( $p$ 's  $< 0.01$ ) phases as compared with controls.

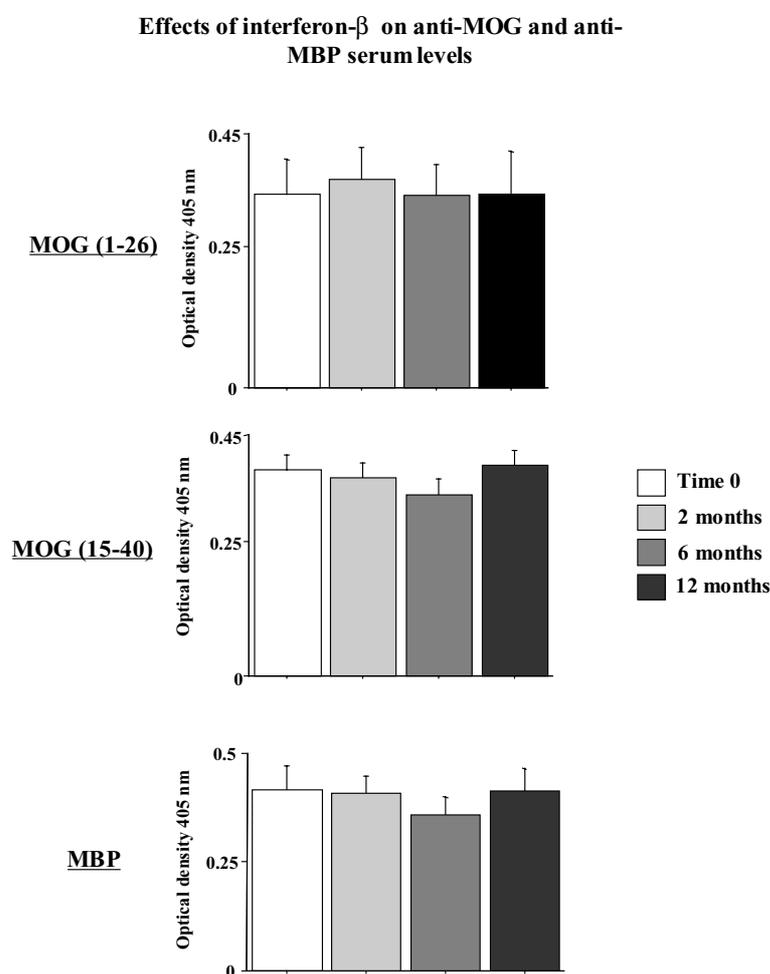


Fig. 3. Levels of antibodies against MOG (sequences 1–26 or 15–40) and MBP at baseline and after 2, 6, and 12 months of interferon- $\beta$  treatment in RRMS patients. Data are the mean  $\pm$  SEM.

### 3.3. Frequency of patients who were positive for the anti-MOG antibodies and the anti-MBP antibody

The cut-off value above which patients were considered positive for antibodies was set as the mean value for controls +2 SDs: 0.563 OD<sub>405</sub> for the anti-MOG 1–26 antibody, 0.481 OD<sub>405</sub> for the anti-MOG 15–40 antibody, and 0.516 OD<sub>405</sub> for the anti-MBP antibody. As shown in Table 2, in MS patients (both in relapse and remission phases) the frequency of positive values for the anti-MOG antibody 15–40 and the anti-MBP antibody was significantly higher as compared to controls ( $p$ 's > 0.05). There were no significant differences in percentage of anti-MOG 1–26 positive values between relapsing-remitting MS patients and controls.

### 3.4. Effects of interferon- $\beta$ on anti-MOG and anti-MBP serum levels

In 33 patients we measured the levels of anti-MOG and anti-MBP antibodies at baseline and after 2, 6, and 12 months of treatment with interferon- $\beta$ . As shown in Fig. 3, there were no differences between the levels of these autoantibodies measured before and after interferon- $\beta$  treatment.

## 4. Discussion

This study demonstrates that MS patients in the relapse phase had higher serum anti-MOG (peptides 1–26 and 15–40) and anti-MBP antibody levels than healthy subjects. In addition, the levels of anti-MOG 1–26

were also elevated during relapse as compared with the remission phase. We also observed that 1-year of interferon- $\beta$  treatment did not induce any changes in the levels of anti-MOG and anti-MBP antibodies.

The peculiarity of this study was the measurement of anti-MOG and anti-MBP antibodies serum levels in the same MS patient during the relapse and remission phases. Our data suggest that increased level of the antibody against the epitope 1–26, rather than the epitope 15–40, of MOG protein is a potential marker of the relapse phase. This finding might be explained by the three-dimensional structure of the MOG extracellular domain [7, 18]. It is possible that one antibody against a specific peptide sequence is directly involved in myelin damage while the presence of antibodies against other regions of the MOG protein may represent a secondary phenomenon not necessarily related to the disease.

Another important question is whether these autoantibodies are relevant as diagnostic tool for MS, as recently suggested [3]. However, our data failed to demonstrate a specific association between MS and serum levels of anti-MOG 1–26 antibodies. The serum levels of anti-MOG 1–26 antibodies of MS patients were usually not higher than the cut-off value for controls. Instead the percentage of anti-MOG 15–40 and anti-MBP-positive patients was significantly higher in MS patients as compared with the frequency in healthy subjects. These data are not consistent with those reported in a previous study [13]. However, it should be stressed that these analyses conducted cumulating large cohorts of patients have mostly generated conflicting results and the frequency of positive values can also be influenced by the sensitivity of the method used.

These findings uphold the question of whether these antibodies are deleterious or play a defensive role against further autoimmune attack after myelin breakdown [4]. In order to elucidate this question we followed over 1-year period 33 patients treated with interferon- $\beta$  (a disease modulating drug) and investigated whether this drug significantly alters the serum levels of the myelin autoantibodies. Our data showed that interferon- $\beta$  did not induce any changes of anti-MOG and anti-MBP antibodies. These data however do not exclude the possibility that interferon- $\beta$ , by reducing blood brain barrier access of these antibodies may produce beneficial effects.

## 5. Conclusion

In conclusion, our results indicate that antibodies directed against different epitopes of anti-MOG may

produce conflicting results. While anti-MOG 15–40 and anti-MBP antibodies may serve as a diagnostic tool for MS versus healthy subjects, anti-MOG 1–26 antibodies may be useful in determining a relapse versus a remission phase.

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