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Research article

Characteristics of cerebrospinal fluid oligoclonal band in anti-myelin oligodendrocyte glycoprotein (MOG) antibody associated disease

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ABSTRACT

Objective: To analyze the immune parameters of cerebrospinal fluid (CSF) and oligoclonal band (OCB) type in patients with anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated diseases (MOGAD).

Methods: Patients who were seropositive for MOG-IgG and diagnosed with MOGAD according to the diagnosis criteria in the Department of Neurology, Huashan Hospital, Fudan University from December 2020 to June 2022 were retrospectively included in this study. Complete clinical data, blood and cerebrospinal fluid samples were collected from all the participants. Paired serum and CSF MOG-IgG and autoimmune encephalitis antibody were assayed by Cell Based Assay (CBA) based on transfected target antigens. Paired serum and CSF albumin and IgG were detected by turbidimetric scattering method, and OCB was detected by standard operation procedure as described.

Results: A total of 86 patients (44 males and 42 females) with MOGAD were included in this study, with a median age of 30 years (range: 5–82 years). Among all the patients, 73 patients showed OCB type I, 12 patients showed OCB type II, and one patient showed OCB type III. The overall positive rate of CSF-OCB in MOGAD patients was 15.1 %. The 24-h intrathecal synthesis rate of CSF in the OCB-positive group (n = 13) was higher than that in the OCB-negative group [n = 73, 0.62 (0.26) vs 5.11 (13.67), $P = 0.003$]. Subgroup analysis revealed that the positive rates of CSF-OCB in the single MOG group (n = 61) and the group combined with other antibodies (n = 25) were 14.8 % and 16.0 %, respectively. The incidence of meningoencephalitis (13/61 vs 13/25, $P = 0.011$) was significantly different between the two groups. The proportion of patients with high (≥1:32) or low (≤1:10) CSF MOG-IgG also showed significant difference in the group combined with other antibodies ($P = 0.032$). Optic neuritis was more common in the relapse course group (n = 49) than the monophasic course group (n = 37, $P < 0.001$) No significant diferences of CSF immune parameters were found in the MOG-IgG$^{serum+/CSF-}$ group and the MOG-IgG$^{serum+/CSF+}$

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group, and the titer of MOG-IgG in the serum or CSF did not influence CSF immune parameters in different subgroups.
Conclusion: The overall positive rate of CSF-OCB in MOGAD patients was 15.1 %. The 24-h intrathecal synthesis rate of cerebrospinal fluid in the OCB-positive group was higher than that in the OCB-negative group. This study illustrated OCB characterization in MOGAD patients, and will shed light on the standardization of OCB test in the study of immune diseases.

1. Introduction

Anti-myelin oligodendrocyte glycoprotein-IgG (MOG-IgG) associated-disorders (MOGAD) is an immune-mediated inflammatory demyelinating disease of the central nervous system (CNS) targeting MOG, and its clinical phenotype is heterogenous and expanding [1,2]. Several studies have showed that MOGAD is a separate spectrum of disease from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) [1–4]. MOGAD can be manifested as encephalitis, meningoencephalitis, and brainstem encephalitis in addition to typical optic neuritis and transverse myelitis, and its clinical manifestations are often highly similar and overlapping with other demyelinating diseases (MS, NMOSD, ADEM, etc.) [1,2]。

Oligoclonal band (OCB) is a specific immunoglobulin performed for a discontinuous band generated by the activation of two or more B lymphocyte clones into plasma cells in the CNS [5–7]。In 1964, Laterre et al. found the presence of two or more unique gamma globulin zones in CSF electrophoresis, and named it CSF-OCB [7]. The presence of OCB in CSF has long been identified as a key immune diagnostic biomarker for MS [8,9].

Many studies have shown that CSF-OCB detection can provide evidence for the diagnosis and differential diagnosis of a variety of CNS inflammatory and non-inflammatory diseases. In addition to MS, positive CSF-OCB can also be seen in MOGAD [4,10], NMOSD [11,12], autoimmune glial fibrillary acid protein astrocytopathy, (GFAP-A) [11], autoimmune encephalitis (AIE) [13–15], other idiopathic inflammatory demyelinating diseases (IIDDs) [12,16], chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-barre syndrome (GBS), myelin-associated glycoprotein (MAG) antibody associated peripheral neuropathy and neurolupus [5,16,17]. The presence of specific OCB only in CSF instead of corresponding serum samples suggests abnormal immunoglobulin synthesis in the CNS, resulting from a persistent central inflammatory response. As an important biomarker in the diagnosis of MS, OCB has an extremely important and indispensable laboratory value in the clinical differentiation of MS from the diagnosis of MOGAD and NMOSD.

In this study, the paired samples of CSF and serum from 86 patients with MOGAD were enrolled and the characteristics of MOG-IgG titer, CSF IgG index, 24-h intrathecal synthesis rate, blood-CSF barrier (BCB), other immune parameters and CSF-OCB types were evaluated. This study provided support for the diagnosis and differential diagnosis of MOGAD.

2. Materials and methods

1 Participants

A total of 86 patients diagnosed with MOGAD in the Department of Neurology, Huashan Hospital Fudan University from December 2020 to June 2022 were retrospectively analyzed. This study was approved by the Ethics Committee of Shanghai Huashan Hospital. Clinical data, serum and CSF samples were collected for final analysis. According to the MOGAD guideline, the inclusion criteria were as follows: 1) Patients with one or more of the following types of symptoms: optic neuritis, meningoencephalitis, brainstem encephalitis, myelitis, and other special types; 2) Patients with demyelinating lesions corresponding to the symptoms on imaging; 3) Patients with positive MOG-IgG and 4) Ruling out other diseases.

2 Paired CSF and serum collection

All paired CSF/serum specimens were collected at the same time and stored at 2–8 °C until processing. 1～2 ml of CSF and 3～5 ml of venous blood was centrifuged at 3000 g/min for 4 min to collect serum/plasma.

3 Detection of MOG-IgG and autoimmune encephalitis antibodies in the paired CSF and serum

The MOG-IgG and autoimmune encephalitis antibodies of the paired CSF and serum were detected by Cell Based Assay (CBA). HEK-293 cells were used as living cells, subcultured and planted in 96-well plates. Different transfection systems based on live cell plasmids were established according to the antibodies to be tested: 1) MOG-IgG: pIRES-MOG-EGFP, 2) anti-NMDAR: pCDNA3.1-GRIN1-815R-GFP and pCDNA3.1-GRIN2A, 3) anti-AMPAR1: pCNDA3.1-GRIA1-GFP, 4) anti-AMPAR2: pCDNA3.1-GRIA2-GFP, 5) anti-Caspr2: pCDNA3.1-CNTNAP2-GFP, 6) anti-LGI1: pCDNA3.1-LGI1-Caspr2 transmembrance domain-GFP, 7) anti-GABARB1/2: pCDNA3.1-GABBR1-GFP and pCDNA3.1-GABBR2.

The autoimmune antibody in the sample bound to the target antigen on the transfection system. After incubation at 37 °C for 30 min, the unbound sample components were eluted by lotion. The binding antibody reacted specifically with the secondary antibody (anti-Human IgG-594, red). After incubation at 37 °C for 30 min, the excess secondary antibodies were eluted during the cleaning

process. Finally, 100 μL PBS was added to the 96-well plate for fluorescence microscope. The sample was considered positive according to the detection of both red and green fluorescence.

4 Detection and interpretation of immunological parameters and CSF-OCB [8,18,19]:

(1) The quantification of albumin (mg/dL) and IgG (mg/dL) in CSF and serum were detected by BNP automatic protein analyzer (Siemens Healthineers BNP or BN-II System protein analyzer and its supporting reagents).

(2) Albumin quotient (Q_{alb}) was calculated by the following formula: Q_{alb} = CSF albumin/serum albumin, to quantitatively assess BCB integrity. IgG quotient was calculated by the following formula: Q_{IgG} = CSF IgG/serum IgG.

(3) CSF IgG index was calculated by the following formula: IgG index = Q_{IgG}/Q_{alb}).

(4) 24-h intrathecal synthesis rate of CSF (mg/24h) was calculated using Tourtellotte's revised formula:

$$\text{24-h intrathecal IgG synthesis rate} = [(IgG_{CSF}\text{-}IgG_{serum}/K1) - (Alb_{CSF}\text{-}AlB_{serum}/K2) \times (IgG_{serum}/Alb_{serum}) \times 0.43] \times 5.$$

(5) The detection was performed according to the isoelectric Focusing (IEF) standard operation procedure (SOP) for detection of CSF-OCB (Sebia HYDRASYS 2 Isofocusing system PN1211, France) [8,17,20]. Based on IgG and albumin concentrations, agarose gel isoelectric focusing was performed according to the manufacturer's instructions, followed by immunofixation and qualitative evaluation of IgG OCB. Briefly, CSF and serum samples (10 μL each) from each patient were run in parallel at a concentration of 10–20 mg/L. After electrophoresis, the gel was incubated with peroxisase-labeled anti-IgG antibodies and the bands were displayed using appropriate chromogenic agents. The electrophoresis results were classified into the main OCB types (type I–V). Type I refers to normal serum (S) and normal CSF (C), with no intrathecal IgG synthesis. Type II was characterized by OCB only in CSF (with intrathecal IgG synthesis) and normal serum. Type III is OCB in both serum and CSF, but OCB (intrathecal IgG synthesis) bands are present in CSF that are not present in serum. Type IV refers to the presence of symmetrically separated OCB bands in the serum and CSF (symmetric pattern, no intrathecal IgG synthesis). V type is monoclonal band with symmetrical dense bands (no intrathecal IgG synthesis) in serum and CSF, respectively.

The electrophoresis results were interpreted independently by two inspectors (X.L and W·S) according to the key points of interpretation, including the presence, numbers and types of bands in the serum and CSF. According to the descriptive definition of CSF-OCB, CSF-OCB is positive for type II and III among the five types. If the result was inconsistent by the two inspectors, a third inspector (X.C.) will join the interpretation. The consistent results of at least two inspectors will serve as the laboratory's final report.

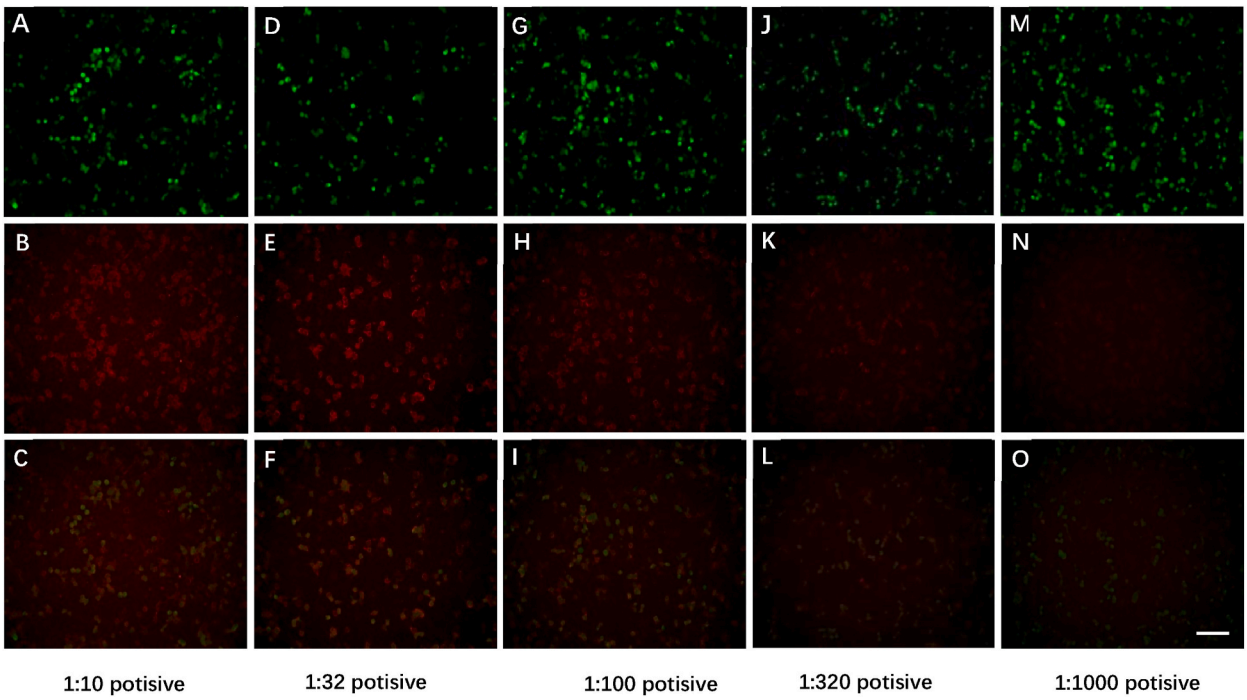

Fig. 1. Serum MOG-IgG was detected by CBA method. A-C, 1:10 positive,A (Green): HEK-293 cells transfected with pIRES-MOG-EGFP, B(Red): the result of 1:10 incubation were measured, C (Merge): the red fluorescence of B (secondary antibody) and the green fluorescence of A (transfection plasmid) overlapped and were identified as positive. D-F,1:32 positive; G-I, 1:100 positive; J-L, 1:320 positive; M – O,1:1000 positive. Scale bar = 200 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Statistical analysis

SPSS, 17.0 (IBM, USA) software was used for statistical analysis. The normality of continuous data was assessed by the Shapiro-Wilk test. Normally distributed continuous data were represented by mean ± standard deviation, and continuous variables not subject to normal distribution were represented by median (interquartile range, IQR). Student's *t*-test was applied to compare the continuous variables between groups. Comparisons of classification variables were performed by Chi-square test, adjusted Chi-square test or Fisher's exact probability test. $P < 0.05$ was considered as statistically significant.

4. Results

1. Identification of MOG-IgG by CBA method in living cells

The detection of MOG-IgG was carried out by laser confocal microscopy. The paired CSF and serum from the same patient were diluted in the following titers, 1) Serum: 1:10 positive (Fig. 1A–C), 1:32 positive (Fig. 1D–F), 1:100 positive (Fig. 1G–I), 1:320 positive (Fig. 1J-L) and 1:1000 positive (Fig. 1M − O); 2) CSF: 1:1 positive (Fig. 2A–C), 1:3.2 positive (Fig. 2D–F), 1:10 positive (Fig. 2G–I), 1:32 negative (Fig. 2J-L) and 1:100 negative (Fig. 2M − O).

2. The characteristics of CSF immune parameters and OCB types in MOGAD patients

Among the 86 patients with MOGAD, 44 were male and 42 were female, and the median age was 30 years old (age range 5–82 years). The clinical phenotypes mainly included optic neuritis (44.2 %), encephalitis (37.2 %), meningoencephalitis (30.2 %), brainstem encephalitis (20.9 %), myelitis (18.6 %), etc. Among all the patients, 73 patients showed OCB type I, 12 patients showed OCB type II, and one patient showed OCB type III (Fig. 3A). And the positive rate of CSF-OCB in MOGAD patients was 15.1 %. The blood-CSF barrier was damaged in 30 cases (34.9 %). The median CSF IgG index was 0.56 (0.13) and the median intrathecal synthesis rate of CSF was 2.78 (6.58) (Table 1).

The 24-h intrathecal synthesis rate of CSF in the OCB-positive group (n = 13) was higher than that in the OCB-negative group (n = 73) [0.62 (0.26) vs 5.11 (13.67), $P = 0.003$]. Other baseline data such as the incidence of prodromal symptoms, encephalitis, meningoencephalitis, brainstem encephalitis, myelitis, and other CSF immune parameters such as serum and CSF MOG-IgG titer, combination of other antibodies, BCB dysfunction, CSF IgG index showed no statistical difference (Table 1, Comparison group 1).

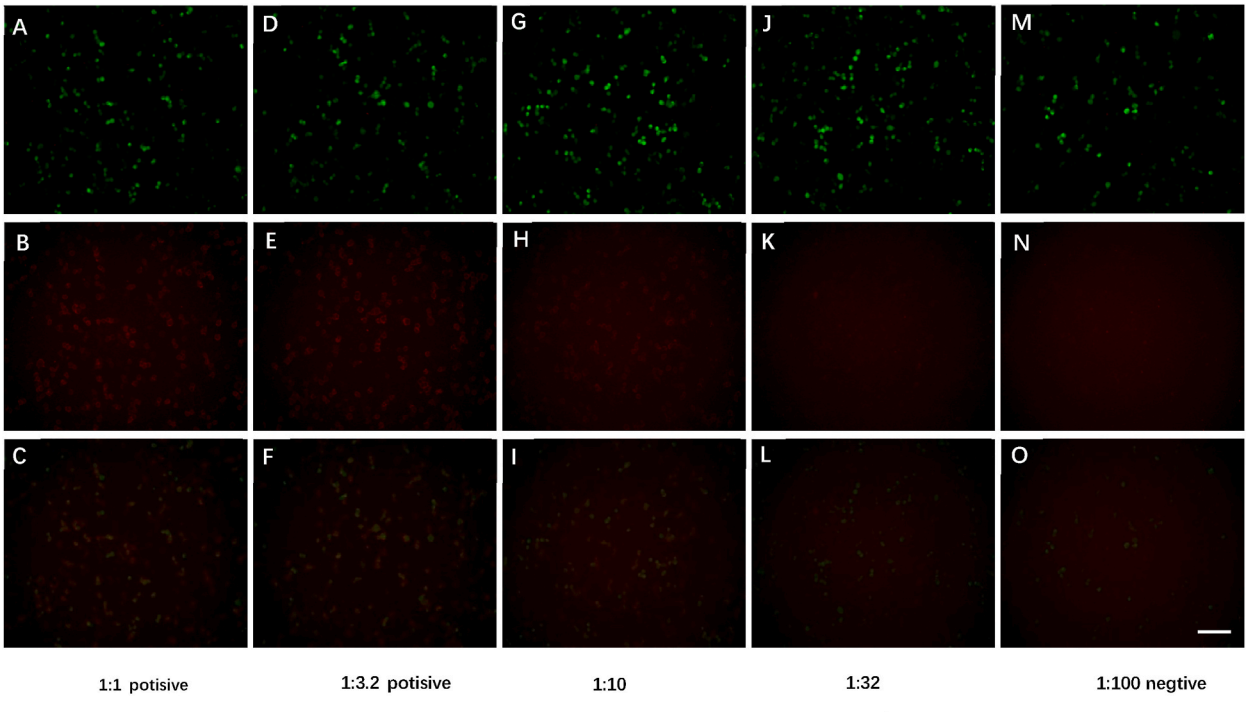

Fig. 2. CSF MOG-IgG was detected by CBA method. A–C, 1:1 positive, A (Green): HEK-293 cells transfected with pIRES-MOG-EGFP, B (Red): the result of 1:1 incubation were measured, C (Merge): the red fluorescence of B (secondary antibody) and the green fluorescence of A (transfection plasmid) overlapped and were identified as positive. D–F,1:3.2 positive; G–I, 1:10 positive; J–L, 1:32 negative; M–O,1:100 negtive. Scale bar = 200 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

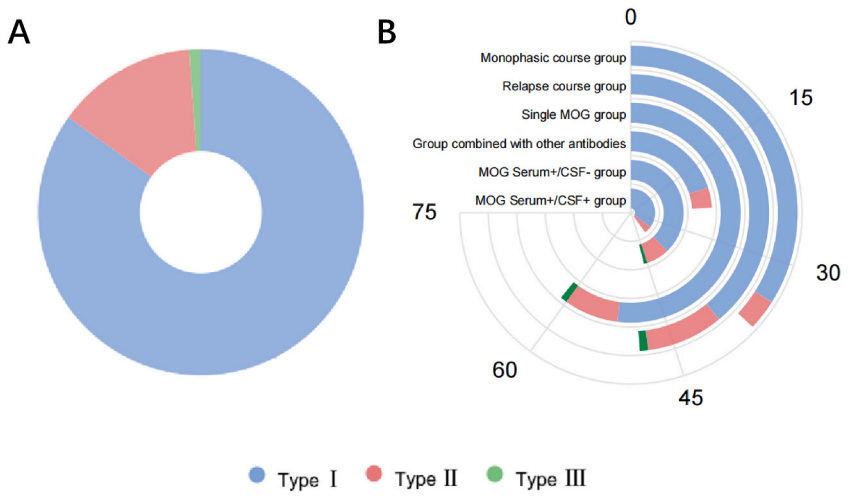

Fig. 3. Cerebrospinal fluid (CSF) oligoclonal band (OCB) types in anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated diseases (MOGAD). A: CSF-OCB types in 86 patients with positive MOG-IgG. B: The CSF-OCB types in the monophasic course group (n = 36) and the relapse course group (n = 49), the single MOG group (n = 61) and the group combined with other antibodies (n = 25), and the MOG-IgG$^{serum+/CSF-}$ group (n = 46) and the MOG-IgG$^{serum+/CSF+}$ group (n = 40).

3. The effect of disease course on CSF immune parameters and OCB types

Patients were divided into monophasic course group (n = 37) and relapse course group (n = 49) according to whether they had relapse in the course of disease. The positive rate of CSF-OCB was 8.3 % in the monophasic course group and 20.4 % in relapse course group (Fig. 3B and Table 1, Comparison group 2). The incidence of optic neuritis (8/37 vs 31/49, $P < 0.001$) was statistically significant between the two groups (Table 1, Comparison group 2).

4. The effect of combination with other antibodies on the CSF immune parameters and OCB types

Patients were divided into single MOG-IgG group (n = 61) and group combined with other antibodies (n = 25) (Table 1, Comparison group 3). Of the latter group, 19 cases were positive with anti-NMDAR, one case was positive with anti-NMDAR and anti-Caspr2, one case was positive with anti-NMDAR and anti-GABARb, one case was positive with anti-Caspr2, two cases were positive with anti-AQP4 and one case was positive with anti-Tr.

The positive rates of CSF-OCB in the single MOG group and the group combined with other antibodies were 14.8 % and 16.0 %, respectively (Fig. 3B and Table 1, Comparison group 3). The incidence of meningoencephalitis (13/61 vs 13/25, $P = 0.011$) was significantly different between the two groups. In the group combined with other antibodies, there was a statistically significant difference in the incidence of high (≥1:32) and low (≤1:10) CSF MOG-IgG ($P = 0.032$) (Table 1, Comparison group 3).

5. The effect of positive serum MOG-IgG and both serum and CSF MOG-IgG positive on CSF immune parameters and OCB types in patients with MOGAD

According to whether serum and CSF of the MOG-IgG were both positive in patients with MOGAD, they were divided into two groups: the MOG-IgG$^{serum+/CSF-}$ group (n = 46) and the MOG-IgG$^{serum+/CSF+}$ group (n = 40). The positive rates of CSF-OCB were 17.4 % and 12.5 % respectively in the MOG-IgG$^{serum+/CSF-}$ group and the MOG-IgG$^{serum+/CSF+}$ group (Fig. 3B and Table 2, Comparison group 1). There were no significant differences in the dysfunction of blood-CSF barrier, CSF-IgG index and 24-h intrathecal synthesis rate (Table 2, Comparison group 1).

6. The effect of MOG-IgG titer on immune parameters and OCB types

The distributions of MOG-IgG titers and CSF-OCB types in serum and CSF of 86 MOG-IgG positive patients were shown in Fig. 4. According to MOG-IgG titers (serum 1:10, 1:32, 1:100, 1:320, 1:1000; CSF: 1:1, 1:3.2, 1:10, 1:32, 1:100), patients were divided into serum MOG-IgG low titer (≤1:100) group (n = 55) and high titer (≥1:320) group (n = 31), CSF MOG-IgG low titer (≤1:10) group (n = 78) and high titer (≥1:32) group (n = 8) , respectively.

The positive rates of CSF-OCB in serum MOG-IgG low titer group (≤1:100) and high titer group (≥1:320) were 10.9 % and 22.6 %, respectively (Fig. 4A and Table 2, Comparison group 2). In the low (≤1:100) and high (≥1:32) CSF MOG-IgG groups, the positive rate of CSF-OCB was 14.1 % and 25.0 %, respectively (Fig. 4B and Table 2, Comparison group 3). There were no significant differences in the dysfunction of blood-CSF barrier, CSF-IgG index and 24-h intrathecal synthesis rate between the above comparison groups.

Table 1
Comparison of general data, CSF immune parameters and OCB types in MOGAD patients.

	MOGAD (total patients)	Comparison group 1			Comparison group 2			Comparison group 3		
		OCB positive group	OCB negative group	P value	The monophasic course group	The relapse course group	P value	The single MOG group	The group combined with other antibodies	P value
Total (n, %)	86 (100)	13 (15.1)	73 (84.9)	–	37 (43.0)	49 (57.0)	–	61 (70.9)	25 (29.1)	–
Age (Median, IQR)	30.0 (15.7)	30.0 (25.0)	30.0 (15.0)	0.591	31.0 (25.0)	28.0 (13.0)	0.381	30 (18.5)	30.0 (9.5)	0.693
Gender (male/female)	44/42	4/9	40/33	0.107	27/24	17/19	0.599	28/33	16/9	0.127
Prodromal symptom (n,%)	28 (32.6)	4 (30.8)	24 (32.9)	0.881	12 (32.4)	17 (34.5)	0.197	17 (27.9)	11 (44.0)	0.147
Optic neuritis (n,%)	38 (44.2)	7 (53.8)	31 (42.5)	0.870	8 (21.6)	31 (63.2)	0.000[a]	30 (49.2)	8 (32.0)	0.145
Encephalitis (n,%)	32 (37.2)	7 (53.8)	25 (34.2)	0.185	12 (32.4)	21 (42.3)	0.325	19 (31.1)	13 (52.0)	0.069
Meningoencephalitis (n,%)	26 (30.2)	4 (30.8)	22 (30.1)	0.964	8 (21.6)	18 (36.7)	0.127	13 (21.3)	13 (52.0)	0.005[a]
Brain stem encephalitis (n, %)	18 (20.9)	5 (38.5)	13 (17.8)	0.112	7 (18.9)	11 (22.4)	0.689	10 (16.4)	8 (32.0)	0.106
Myelitis (n,%)	16 (18.6)	1 (1.4)	15 (20.5)	0.232	7 (18.9)	10 (20.4)	0.863	13 (21.3)	3 (12.0)	0.316
Abnormal Cranial MRI (n, %)	64 (74.4)	12 (92.3)	52 (71.2)	0.076	24 (64.9)	40 (81.6)	0.079	44 (72.1)	20 (80.0)	0.450
Abnormal MRI of spinal cord (n,%)	20 (23.3)	4 (30.8)	16 (21.9)	0.498	9 (24.3)	11 (22.4)	0.839	14 (23.0)	6 (24.0)	0.917
Seurem MOG-IgG (≤1:100) (n,%)	56 (65.1)	7 (53.8)	49 (67.1)	0.362	26 (70.3)	30 (61.2)	0.384	38 (62.3)	18 (72.0)	0.386
Serum MOG-IgG (≥1:320) (n,%)	30 (34.9)	6 (46.2)	24 (32.9)	0.362	11 (29.7)	19 (38.8)	0.384	23 (37.7)	7 (28.0)	0.114
CSF MOG-IgG (≤1:10) (n, %)	77 (90.1)	11 (84.6)	66 (91.7)	0.549	33 (89.2)	44 (89.8)	0.928	57 (93.4)	20 (80.0)	0.078
CSF MOG-IgG (≥1:32) (n, %)	8 (9.4)	2 (15.4)	6 (8.3)	0.442	3 (8.1)	5 (10.2)	0.739	3 (4.9)	5 (20.0)	0.038[a]
Combined with other antibodies (n,%)	25 (29.1)	4 (30.8)	21 (28.8)	0.884	11 (29.7)	14 (28.6)	0.907	0	25 (29.1)	–
Anti-NMDAR	19	4	15	–	9	11	–	0	19	–
Anti-NMDAR&Caspr2	1	0	1	–	1	0	–	0	1	–
Anti-NMDAR&GABARb	1	0	1	–	1	0	–	0	1	–
Anti-Caspr2	1	0	1	–	0	1	–	0	1	–
Anti-AQP4	2	0	2	–	0	1	–	0	2	–
Anti-Tr antibody	1	0	1	–	0	1	–	0	1	–
OCB types										
Type I	73	0	73	–	34	39	–	52	20	–
Type II	12	12	0	–	3	9	–	8	4	–
Type III	1	1	0	–	0	1	–	1	0	–
OCB positive rate (%)	15.1	NA	NA	–	8.3	20.4	0.104	14.8	16.0	0.827
blood-CSF barrier dysfunction (n,%)	30 (34.9)	6 (46.2)	24 (32.8)	0.362	13 (36.1 %)	18 (36.7)	0.878	19 (31.1)	11 (45.0)	0.256
CSF IgG Index (Median, IQR)	0.56 (0.13)	0.56 (0.13)	1.97 (5.86)	0.160	0.62 (0.16)	0.57 (0.12)	0.346	0.56 (0.14)	0.57 (0.22)	0.219
24-h intrathecal IgG synthesis rate (Median, IQR)	2.78 (6.58)	0.62 (0.26)	5.11 (13.67)	0.003**	3.36 (8.02)	2.78 (4.98)	0.606	2.79 (5.02)	3.74 (10.13)	0.693

MOGAD: anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated diseases; CSF: cerebrospinal fluid; OCB: oligoclonal band.
[a] $P < 0.05$.

5. Discussion

MOG is expressed in the plasma membrane of oligodendrocytes of the CNS, located on the most surface of myelin sheath, and has been the focus of extensive research for more than 30 years [10,21]. With the introduction of the conception of culprit antibody, the pathogenicity of antibodies in different disease entities were re-evaluated, in which standardized laboratory tests play an important role in deciphering the significance of antibodies under different circumstances. Using the standardized protocol of CSF-OCB test constructed by our team previously [8], this study provided a detailed description of CSF-OCB and other immune parameters in MOGAD.

The presence of specific OCB only in CSF instead of corresponding serum samples suggests abnormal immunoglobulin synthesis in the CNS, resulting from a persistent central inflammatory response. Positive CSF-OCB has long been considered an important laboratory indicator of the diagnosis of MS, and can be detected in up to 95 % of clinically definite MS patients and 68–83 % of patients with clinically isolated syndrome through isoelectric focusing technique [22,23]. However, the specificity of CSF-OCB in MS diagnosis was not as high as the sensitivity, as positive OCB can also be detected in other neuroimmune diseases, including NMOSD [24], MOGAD [25], autoimmune encephalitis [26] and systemic autoimmune conditions [27]. Overall, our study found a 15.1 % positive rate in MOGAD patients, which was slightly lower than previous studies (up to 20 % positive rate) [1,2]. This may be explained by the

Table 2
The characteristics of serum and CSF MOG-IgG titer on immune parameters and OCB types.

OCB types	MOGAD (total patients, n = 86)	Comparison group 1			Comparison group 2			Comparison group 3		
		The MOG-IgG$^{serum+/CSF-}$ group (n = 46)	The MOG-IgG$^{serum+/CSF+}$ group (n = 40)	P value	The serum MOG-IgG low titer group (≤1:100) (n = 55)	The serum MOG-IgG high titer group (≥1:320) (n = 31)	P value	The CSF MOG-IgG low titer group (≤1:10) (n = 78)	The CSF MOG-IgG high titer group (≥1:32) (n = 8)	P value
Type I	73	38	35	–	49	24	–	67	6	–
Type II	12	7	5	–	6	6	–	10	2	–
Type III	1	1	0	–	0	1	–	1	0	–
OCB positive rate(%)	15.1	17.4	12.5	0.526	10.9	22.6	0.155	14.1	25.0	0.442
blood-CSF barrier dysfunction(n,%)	30(34.9)	15(32.6)	15(37.5)	0.635	23(41.8)	8(25.8)	0.074	26(33.3)	5(62.5)	0.110
IgG Index(Median, IQR)	0.56 (0.13)	0.54 (0.16)	0.57 (0.10)	0.609	0.57 (0.12)	0.56 (0.15)	0.350	0.56 (0.13)	0.58 (0.41)	0.364
24-h intrathecal IgG synthesis rate (Median, IQR)	2.78 (6.58)	2.75 (6.84)	2.85 (7.82)	0.536	2.78 (6.72)	2.92 (6.29)	0.786	2.74 (6.24)	4.02 (19.59)	0.513

MOGAD: anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated diseases; CSF: cerebrospinal fluid; OCB: oligoclonal band.

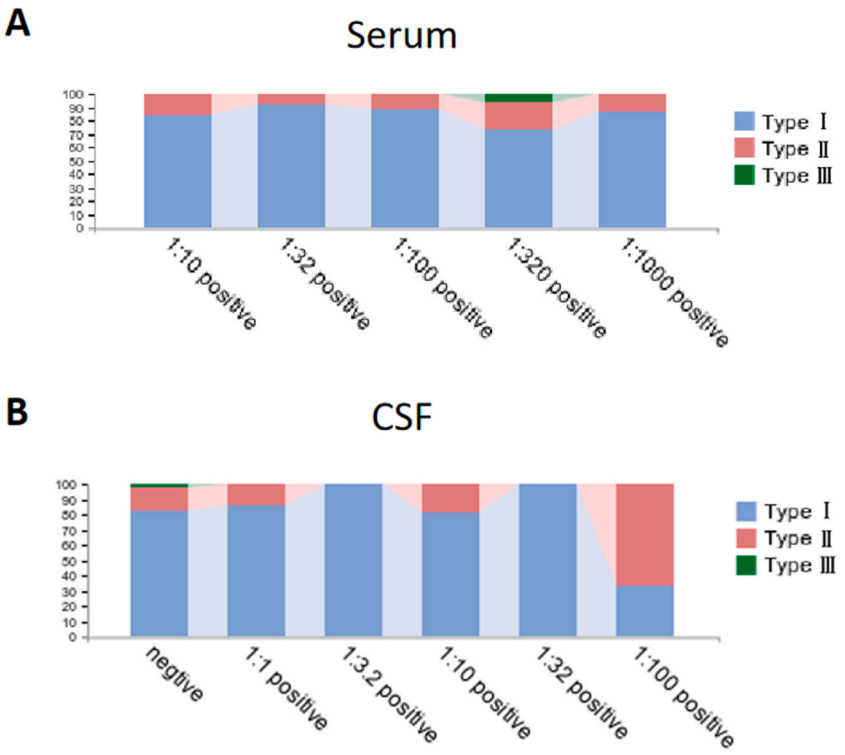

Fig. 4. The distribution of MOG-IgG titers and CSF-OCB types in serum and CSF of 86 MOG-IgG positive patients. A: The positive rates of CSF-OCB in serum MOG-IgG low titer group (≤1:100) and high titer group (≥1:320) were 10.9 % and 22.6 %, respectively. B: In the low (≤1:100) and high (≥1:32) CSF MOG-IgG groups, the positive rate of CSF-OCB was 14.1 % and 25.0 %, respectively.

different ethnicities and latitudes in different OCB analysis [23,28]. In this study, the paired samples of CSF and serum from 86 patients with MOGAD were enrolled and we evaluated the characteristics of MOG-IgG titer, CSF IgG index, 24-h intrathecal synthesis rate and other immune parameters and CSF-OCB types. Our study and previous studies indicated that caution should be taken in associating positive CSF-OCB with the diagnosis of MS in clinical practice, especially when other antibodies existed.

CBA method, which is widely used at present, can significantly improve the detection efficiency of pathogenic antibodies. The latest International MOGAD Expert Group recommended that serum MOG-IgG reports should include at least qualitative results (i.e., negative, weakly positive [low positive] and clear positive) and semi-quantitative results [1,29]. The expert group proposed criteria for clear positive and weak positive results of CBA based on fixed cells and living cells. For CBA in live somatic cells, it was recommended to define a clear positive as at least 2× dilution above the assay cutoff, or above the assay specific titer threshold. CBA positive in fixed cells was defined as titer ≥1:100. If the CBA assay in living cells is in the low range of the individual live cell assay or the CBA assay in fixed cells has a titer ≥1:10 but <1:100, the result is considered weakly positive [1]. In this study, the paired serum (1:10, 1:32, 1:100, 1:320, 1:100) and CSF (1:1, 1:3.2, 1:10, 1:32, 1:100) were diluted into different titers and MOG-IgG was detected by living cell CBA method.

According to whether CSF-OCB was positive or not, the patients were divided into OCB-positive group and negative group. The results showed that the 24-h intrathecal synthesis rate of CSF in the OCB-positive group was higher than that in the OCB-negative group. While other baseline data such as prodrome symptoms, encephalitis, meningoencephalitis, brainstem encephalitis, myelitis, and other CSF immunological parameters such as serum and CSF MOG-IgG titer, combination of other antibodies, blood-CSF barrier destruction, CSF IgG index showed no statistical difference. It is suggested that when OCB is positive in MOGAD, it is more likely to be combined with the increase of immunological parameters of CSF, which also provides a basis for the increase of intrathecal synthesis of CNS. CSF-OCB positive IgG index and 24-h intrathecal synthesis rate and other immunological parameters have always been important indicators for the diagnosis of MS [30]. Therefore, the detection of MOG-IgG is particularly important when CNS demyelination is suspected clinically in order to distinguish it from classic CNS demyelination diseases such as MS.

Our study found that different subgroups of MOGAD patients showed some differences in clinical characteristics and CSF immune parameters. Compared to the OCB-negative group, the 24-h intrathecal synthesis rate of CSF in the OCB-positive group was higher, suggesting that when OCB is positive in MOGAD, it is more likely to be combined with the increase of immune parameters of CSF, which also provides a basis for the increase of intrathecal synthesis of CNS. Our study also revealed that the incidence of meningoencephalitis was higher in the group combined with other antibodies compared to single MOG-IgG group. In addition, MOGAD patients combined with other antibodies seemed to have higher CSF MOG-IgG titer than the single antibody group. These results suggested that when MOG-IgG overlaps with other autoimmune encephalitis antibodies (such as NMDAR), it is more likely to combine with high titer of CSF MOG-IgG, and its clinical phenotype may overlap with that of corresponding antibody. This is consistent with previous studies

indicating that when MOG-IgG is combined with other encephalitis antibodies, the clinical phenotype of MOGAD overlaps with the corresponding clinical phenotype [13,31]. Therefore, the detection of MOG-IgG in the CSF, which may add evidence for its role as the culprit antibody, can improve the diagnostic accuracy of MOGAD in appropriate clinical settings [18,32].

Unlike MS and NMOSD, which are characterized by chronic recurrent clinical episodes, MOGAD usually presents a monophasic or relapse course [1,3,10,33]. In this study, the positive rate of CSF-OCB was 8.3 % in monophasic course group (n = 36) and 20.4 % in relapse course group (n = 49), and the incidence of optic neuritis was statistically significant. Studies have shown that the presence of CSF MOG-IgG enhances the diagnosis of MOGAD in the absence of an MS phenotype, and that intrathecal synthesis of MOG-IgG is associated with increased disability [32]. Although the diagnosis of MOGAD is based on positive serum MOG-IgG, the presence of MOG-IgG in CSF has been reported in patients, and paired positive serum and CSF MOG-IgG is common in MOGAD and is associated with more severe clinical manifestations [34]. In this study, the positive rates of CSF-OCB were 17.4 % and 12.5 % respectively in the MOG-IgG$^{serum+/CSF-}$ group and the MOG-IgG$^{serum+/CSF+}$ group. The positive rates of CSF-OCB in serum MOG-IgG low titer group ($\leq$1:100) and high titer group ($\geq$1:320) were 10.9 % and 22.6 %, respectively. In the low ($\leq$1:100) and high ($\geq$1:32) CSF MOG-IgG groups, the positive rate of CSF-OCB was 14.1 % and 25.0 %, respectively. There were no significant differences in the destruction of blood-brain barrier, CSF-IgG Index and 24-h intrathecal synthesis rate.

Studies have shown that the presence of CSF MOG-IgG enhances the diagnosis of MOGAD in the absence of an MS phenotype, and that intrathecal synthesis of MOG-IgG is associated with increased disability [32]. Although the diagnosis of MOGAD is based on positive serum MOG-IgG, the presence of MOG-IgG in CSF has been reported in several patients, and paired positive serum and CSF MOG-IgG is common in MOGAD and is associated with more severe clinical manifestations [29,34]. However, our study did not show differences in CSF immune parameters between the MOG-IgG$^{serum+/CSF-}$ group and the MOG-IgG$^{serum+/CSF+}$ group. Further analysis also found no differences between groups with different MOG-IgG titer in the serum or CSF. Although with no statistical significance, the positive rate of CSF-OCB showed a higher tendency in the groups with higher MOG-IgG titer in the serum or CSF, suggesting that higher MOG-IgG titer may be associated with higher incidence of CSF abnormalities, which should be tested in larger cohorts in the future.

The results of this study should be viewed in light of some limitations. First, the study was based on single-center data. Considering that the test results of some CSF immune parameters are influenced by geography and latitude [23,28], further multi-center study is warranted to compare the results affected by confounding factors. Second, the cohort in our study was relatively small, especially in subgroup analysis, which may reduce the inspection efficiency and increase the statistic error. Therefore, a larger prospective cohort based on standardized laboratory testing protocol is necessary for further validating the results of this study. Third, this study is of cross-sectional nature with no follow-up data. Further analysis of CSF immune parameters in MOGAD patients with their long-time prognosis will provide us with a more comprehensive understanding of the immunological characteristics of this group of disorders. Despite the above limitations, our study was morefocused on the CSF immune parameters of MOGAD patients in China based on published standardized laboratory processes [8].

In conclusion, we found that the overall positive rate of CSF-OCB in MOGAD patients was 15.1 %, and a series of other immune parameters of MOGAD were also characterized. Our study illustrated OCB characterization in MOGAD patients, and will shed light on the standardization of OCB test in the study of immune diseases.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of Huashan Hospital, Fudan University.

Consent for publication

All patients have signed the informed consent and agreed to sample collection and data publication in this study.

Author contributions

Wenjun Shao: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Xiaoni Liu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Jiatong Li:** Formalanalysis, Investigation, Methodology, Software, Writing – review & editing. **Tianyang Sheng:** Investigation, Methodology, Software, Visualization. **Yarong Li:** Data curation, Methodology. **Yuehua Gu:** Data curation, Methodology. **Bo Deng:** Data curation, Formal analysis, Validation. **Jingguo Wang:** Conceptualization, Data curation,Validation. **Wenbo Yang:** Data curation, Investigation, Validation. **Hai Yu:** Conceptualization, Formal analysis, Investigation, Validation. **Xiang Zhang:** Investigation, Validation, Writing – review & editing. **Xiangjun Chen:** Conceptualization, Funding acquisition, Project administration, Supervision, Visualization, Writing – review & editing.

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Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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