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Anti-MOG antibodies are not rare in isolated optic neuritis and myelitis and induce complement mediated demyelination

Carla Tortorella[1], Vita Direnzo[1], Claudia Palazzo[1,2], Antonio Cibelli[2], Elena Luciannatelli[1], Mariangela Mastrapasqua[1], Damiano Paolicelli[1], Pietro Iaffaldano[1], Maddalena Ruggieri[1], Grazia Paola Nicchia[2], Antonio Frigeri[1] and Maria Trojano[1]

[1.] Department of Basic Medical Science,Neuroscience and Sense Organs, University of Bari "Aldo Moro"-Policlinico, Bari, Italy, bari, Italy;
[2.] Department of Biosciences, Biotecnologies and Biofarmaceutical, University of Bari "Aldo Moro", bari, Italy

Introduction Recent studies indicate Anti-Myelin Oligodendrocyte Glycoprotein antibodies (MOG-IgG) as new serum biomarker of some forms of demyelinating diseases distinct from both classical Multiple Sclerosis (MS) and AQP4-IgG-mediated Neuromyelitis Optica spectrum disorders (NMOSD).

Aims and methods. The aims of this study were:

1. to evaluate, by a Cell Based Assay on HEK-293 cells stably transfected with human MOG, the frequency of serum MOG-IgG in a cohort of 57 adult patients with a first monosymptomatic episode of idiopathic autoimmune Optic Neuritis (ON) or Myelitis
2. to compare baseline clinical, laboratory and MRI features of patients with and without serum MOG-IgG
3. to investigate the potential cytotoxic effect of MOG-IgG, obtained by immunoadsorption, on ex vivo rat optic nerve. Rat optic nerve was cultured on transwell porous supports for 24 h in CO2/O2-bubbled artificial cerebrospinal fluid with human complement (HC) and/or MOG-IgG

Results.

- Nineteen patients (33%) showed serum anti-MOG-IgG: 11 myelitis and 8 ON.
- MOG-IgG positive patients were older (p=0.001), had more severe disability at onset (p=0.0001), lower incidence of CSF IgG oligoclonal bands (31% vs 73%; p=0.003), lower number of brain MRI lesions (p=0.0001) and higher frequency of longer MRI spinal cord lesions (36% vs 5%; p=0.001) in comparison to MOG-IgG negative subjects [Table 1].
- All patients were prospectively followed for a median period of 3.3±3.2 years. At follow-up, 42% of MOG-IgG positive patients satisfied MRI criteria for MS diagnosis vs 65% of MOG-IgG negative (p=0.07). [Table 1].
- Rat optic nerve exposure to MOG-IgG and HC produced marked loss of myelin as a consequence of an oligodendrocytic damage, whereas astrocytes were not involved as demonstrated by normal GFAP and AQP4 expression levels. [Figure 2].
- No damages were seen in rat optic nerve cultured with either MOG-IgG or complement alone. [Figure 1]

Table 1.
Clinical, demographic, CSF and MRI features of our cohort

	Total	MOG -	MOG +	p
N. Pts (%)	57	38 (67%)	19 (33%)	
Sex (female)	29	22	7	ns
Age at onset (years)	36±11	33±9.3	40.6±12.7	**0.001**
Type of Onset				
Myelitis	24 (42%)	13 (54.2%)	11 (45.8%)	**0.046**
NO	33 (58%)	25 (75.8%)	8 (24.2%)	
EDSS at the onset	1.9±0.9	1.7±0.7	2.5±1	**<0.0001**
CSF white cells, n.x mm3	7±8,3	7,5±9,4	5.6±5.5	ns
CSF proteins, mg/dl	54,7±75.6	45,3±14	74.7±132.3	ns
Presence of CSF oligoclonal IgG synthesis, n. pts (%)	34	28 (73%)	6 (31%)	**0,003**
N. brain MRI lesions				
0-1	10	1	9	**<0.0001**
2-9	37	30	7	
>9	10	7	3	
MS-like brain MRI lesions [n. pts (%)]	37	30 (81%)	7 (19%)	**0.001**
Spinal MRI lesions [n. pts (%)]	28	17 (60.7%)	11 (39.2%)	ns
LEMT [n. pts (%)]	5	1(5%)	4 (36%)	**0.06**
MRI Follow-up	51	35	16	**0.05**
Stable	22	13 (59.1%)	9 (40.9%)	
New lesions	26	21 (80.7%)	5 (19.3%)	
Reduction of lesions	3	1 (33.3%)	2 (66.7%)	
EDSS at the last follow-up	1.8±0.8	1.7±0.7	2±1	ns
Follow-up (years)	3.3±3.2	3.5±3	3±3.8	ns
II clinical episode [n.pts]	25	17 (68%)	8 (32%)	ns
Time between I-II clinical episode, (months)	18± 21	15±12.3	24.4±32.9	ns
DIT[a] and DIS[b] MRI at FU [n.pts (%)]	33	25(65%)	8(42%)	**0.07**

[a] DIT: dissemination in time
[b] DIT: dissemination in space

MOG-IgG induces complement mediated cytotoxicity on optic nerve

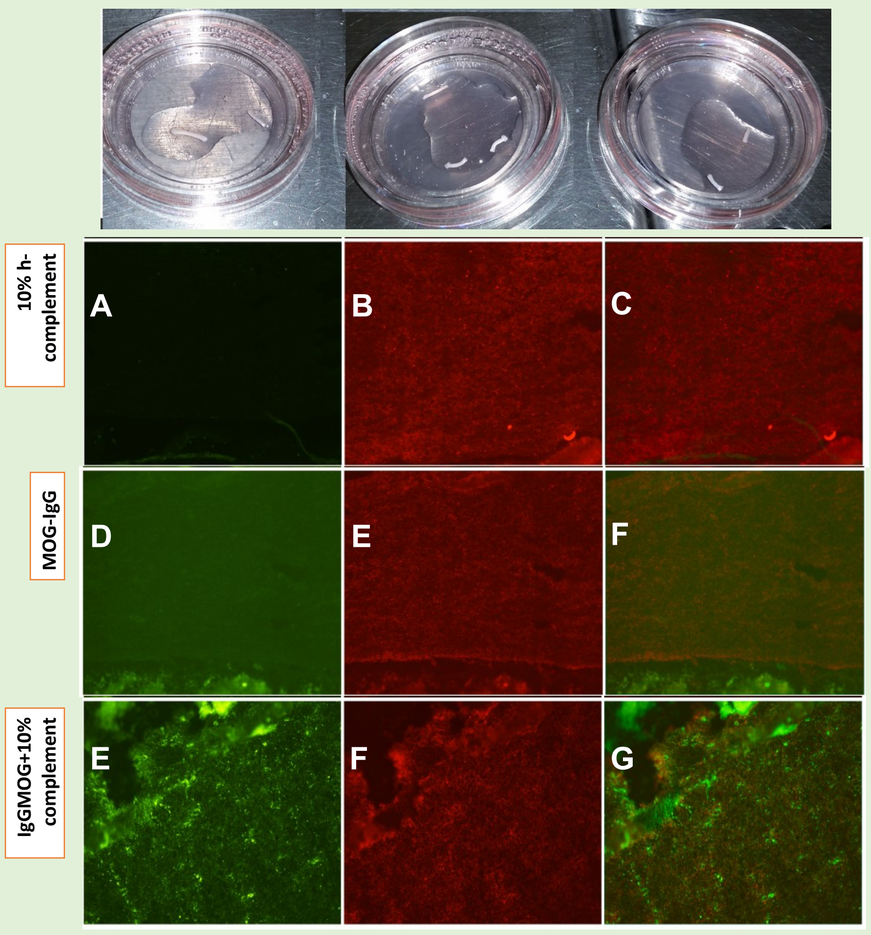

FIGURE 1.
The toxic effect of MOG-IgG antibodies was evaluated ex vivo in dissected rat optic nerves. The substrates were treated for 24 h with MOG-IgG in presence (E, F, G) or in the absence (D, E, F) of human complement. This allows to mimic the effect that may occur in patients with CNS demyelinating diseases.
Strong alteration of target tissue by MOG IgG is detectable by an anti human antibody only in the presence of active human complement.

MOG-IgG induces Oligodendrocitic damage and loss of myelin on Optic Nerve

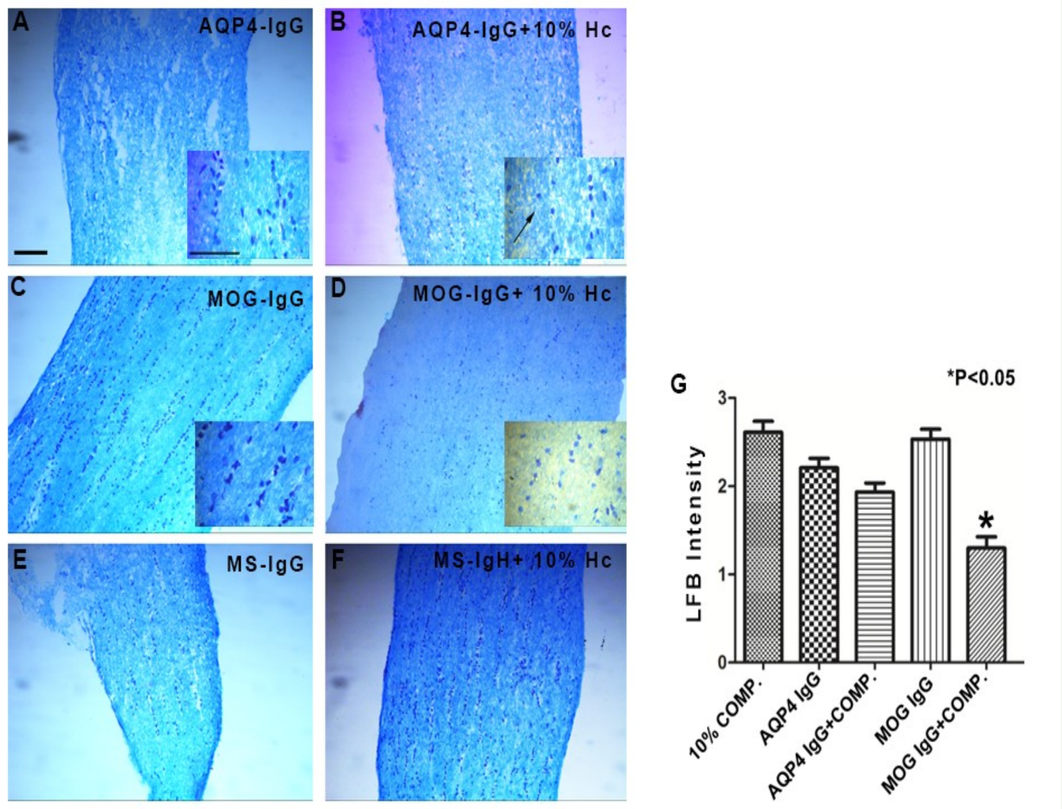

FIGURE 2. Luxol Fast Blue-Cresyl Violet myelin staining, showing the effect on Optic Nerve of AQP4-IgG (A,B) and MOG-IgG (C,D) in presence (B,D) and in absence of active human complement (A,C). MS serum was used as further negative control and shows no significant tissue alterations with or without Complement (E, F respectively). **Histogram showing the intensity of LFB staining (G) note that a considerable reduction is observable after 24 hours with MOG-IgG+ Hc. *p< 0.05**

CONCLUSIONS

The presence of serum anti-MOG antibodies is not a rare event at onset of ON or myelitis suggestive of CNS demyelinating syndrome The peculiar clinical and paraclinical characteristics of MOG-IgG positive patients and the demonstrated complement-mediated cytotoxic effect of MOG-IgG on rat optic nerve oligodendrocytes, suggest that MOG autoimmunity is associated to an oligodendrocytes-mediated disease more similar clinically to NMOSD and pathologically to a pattern II variant of MS. Such a hypothesis warrant therapeutical considerations.

References:
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