# NeuromyelitisOptica (NMO) e NeuroMyelitisOptica Spectrum Disorder (NMOSD): a joint study by two centres

*F. Bortolon, **C.Zuliani

*Multiple Sclerosis S.Bortolo Hospital – Vicenza
**Operative Unit of Neurology – Mirano (Ve)

## Introduction:

- NeuromyelitisOptic (NMO) is an immune-mediated disease, which is histopathologically characterized by astrocytic damage, demyelination, neuronal loss and often pronounced necrosis in the Central Nervous System (CNS).
- It mainly affects the optic nerves and spinal cord.
- The major progress in the diagnosis of NMO is tied to the discovery (in 2004) of the antibodies to channel aquaporin-4 (AQP4), which are highly specific and have a pathogenetic role.
- Some patients affected by NMO and NeuromyelitisOptica-Spectrum Disorder (NMOSD), AQP4-negative, present anti-MOG antibodies in the serum.
- Long considered a clinical variant of Multiple Sclerosis (MS), actually the disease is clearly distinguished form MS: 1) it affects females more than males with a 9:1 ratio (MS 2.5:1), and the age of onset is 10 years later than MS; 2) Optic Neuritis (ON) causes a more severe visual loss; 3) myelitis can be complete, associated with paraplegia or quadriplegia, caracterized by poor or no recovery; 4) Imaging tipically shows longitudinally extensive lesions spanning three or more vertebral segments (see also Fig. 1 and Tab 1).
- Recently the International Panel for NMO Diagnosis (IPND) has revisited NMO diagnostic criteria (Tab 2).
- A curative treatment for NMO does note exist to date. Instead, the main treatment goals are: 1) remission and improvement of relapse-associated symptoms; 2) long-term stabilization of disease course by means of relapse prevention; 3) symptomatic therapy of residual symptoms (see Fig. 2).

- ***In this study we conducted a two centres retrospective analysis of a series of patients with NMO/NMOSD***

| | Devic's disease | Multiple sclerosis |
|---|---|---|
| Distribution of symptoms and signs | Restricted to the optic nerves and spinal cord | Any white-matter track |
| Attack severity | Usually severe | Usually mild |
| Head MRI | Usually normal/non-specific changes | Multiple periventricular white-matter lesions |
| Cord MRI | Longitudinally extensive central necrotic lesions | Multiple small peripheral lesions |
| CSF cells | Pleocytosis during attacks | Rarely > 25 white cells |
| Oligoclonal bands | Usually absent | Usually present |
| Permanent disability | Usually attack-related | Usually in late progressive phase |
| Female patients | 80 – 90% | 60-70% |
| Coexisting autoimmunity | Frequent (30-40%) | Less common |
| Serum neuromyelitus optica antibody | Present | Absent |

Tab. 1:Differential diagnosis between NMO/NMOSD and MS

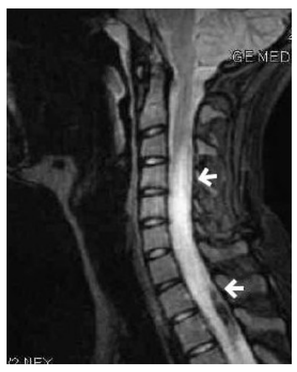

Fig. 1: Typical MRI spinal cord imaging showing longitudinally extensive lesions spanning three or more vertebral segments

**Diagnostic criteria for NMOSD with AQP4-IgG**
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses*

**Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status**
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses*

**Core clinical characteristics**
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

**Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status**
1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.

Tab. 2: NMOSD diagnostic criteria for adult patients

## Materials and Methods: (see also Tab. 3).

- We have analyzed clinical data of 6 pts, all females
- Aged between 46 and 73 years
- Mean disease duration between 3 and 7 years (mean 4.7 years)
- 2 pts met the 2015 criteria for NMO, 4 for NMOSD.
- 1 pts had a debut with complex partial seizures, followed by ON and 3 recurrent attacks of transverse myelitis; 1 patient had 4 ON.
- All pts were AQP4-IgG positive.
- 2 pts were naive to treatment (1 Rituximab and 1 Azathioprine).
- 4 pts, who have been already treated with first-line (IV Methylprednisolone, Plasma Exchange, IVIG, Azathioprine) and second-line (Cyclophosphamide) drugs with poor response, begun Rituximab (3 pts) and IVIG (1 pt. in whom the therapeutic choice was motivated by the simultaneous presence of a breast lump, a cystadenoma and a neuroendocrine tumor of the pancreas).

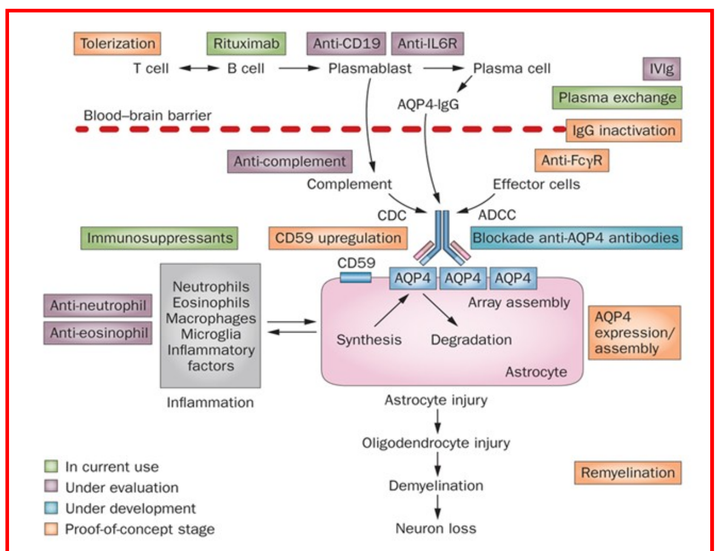


Fig. 2: Established and emerging long-term treatments for NMO/NMOSD according to the therapeutic target

## Results: (see also Tab. 3)

- During treatment with Rituximab (6, 5 and 9 cycles respectively) 3 patients were relapse-free, with improvement in EDSS from baseline for 2 of them (from 6.5 to 5.5 and from 6.5 to 3.5 respectively) and stabilization for 1 (EDSS = 7.5).
- None of them showed side effects.
- 1 patient (EDSS 8.0) had a relapse (at a repopulation of CD19) and sepsis, for which she interrupted the therapy.
- The patient treated with IVIG showed two additional spinal cord relapses, so she is waiting to start Rituximab.
- The patient treated with Azathioprine has started the treatment too recently in order to assess its effectiveness.

| | PM | SD | RM | SS | MZ | GD |
|---|---|---|---|---|---|---|
| Sex | F | F | F | F | F | F |
| Age | 55 | 50 | 53 | 73 | 57 | 42 |
| Disease duration | 6 | 3 | 5 | 3 | 5 | 7 |
| AQP4-IgG status | + | + | + | + | + | + |
| myelitis | + | +++ | ++ | ++ | +++ | - |
| cerebral syndrome | + | - | - | - | + | - |
| Optic Neuritis | ++++ | - | - | + | + | ++++ |
| Therapies pre-RTX | GA, MP, Cyc, PLEX | MP, Cyc | MP, IVIg, PLEX, Cyc | Naive | MP, AZA, IVIg | GA, Aza |
| N. RTX courses | 6 | 5 | 9 | 3 | - | - |
| Relapses before last therapy | 2 | 1 | 2 | 1 | 4 | 4 |
| Relapses during RTX | 0 | 0 | 0 | 1 (ON) | - | - |
| EDSS before last therapy | 6.5 | 6.0 | 7.5 | 8.0 | 2.0 | 3.0 |
| EDSS during RTX | 5.5 | 3.5 | 7.5 | 8.0 | - | - |
| CD19 during RTX | 0 | 0 | 0 | 1% | - | - |

**Tab 3:** demographics and disease charatcteristics pre- and post Rituximab (RTX) or others therapies. GA = Glatiramer Acetate; MP = Methylprednisolone; PLEX = plasma exchange; Cyc = Cyclophosphamide;Aza = Azathioprine

## Conclusions:

- In our experience Rituximab has proven to be a safe and effective drug in reducing relapses and improving or stabilizing disability.
- We stress the need to accuratey monitor B-cell repopulation.
- In selected cases, mainly in presence of comorbility, IVIG, which are relatively safe compared to other immunotherapies, my represent a treatment option to prevent relapses.

## References:

1.Trebst C et al. Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neuro*l. 2014; 261: 1-16
2. Wingerchuk D M et al. International consensus diagnostic criteria for neuromyelitisoptica spectrum disorders. *Neurology.* 2015; 85: 177-189
3. Sellner J et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *Eur J Neurol*. 2010;17: 1019-1031.
4. Collongues N et al. An update on the evidence for the efficacy and safety of rituximab in the management of neuromyelitis optica. Ther Adv Neurol Disord. 2016; 9:180-183
5. Viswanathan S et al. Intravenous immunoglobulin may reduce relapse frequency in neuromyelitisoptica. *Journal of Neuroimmunology* 2015; 282:92-96

Sin
XLVII CONGRESSO NAZIONALE
22-25 OTTOBRE 2016 – VENEZIA
WebPoster