



FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Eduardo Manuel Pinto Ferreira Silva Freitas
Neuromyelitis Optica Spectrum
Disorders associated with other
autoimmune diseases

março, 2014

FMUP



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Mestrado Integrado em Medicina

Área: Neurologia

**Trabalho efetuado sob a Orientação de:
Professora Doutora Joana da Cruz Guimarães Ferreira de Almeida**

**Trabalho organizado de acordo com as normas da revista:
Rheumatology International**

março, 2014

FMUP

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DATA DE CONCLUSÃO

20/03/2014

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurologia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Neuromyelitis Optic. Spectrum Disorders associated with other autoimmune diseases

ORIENTADOR

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Neuromyelitis Optica Spectrum Disorders associated with other autoimmune diseases

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Abstract

Neuromyelitis optica (NMO) is an inflammatory demyelinating autoimmune disease with severe, tremendously incapacitating, consequences in the patient's health and wellbeing. Until 2004, NMO was considered a restricted type of Multiple Sclerosis but in the same year an auto-antibody reacting against aquaporin-4 (NMO-IgG) was found to be related with NMO and it was considered the main etiologic agent of this disease. Its detection is very sensitive and specific allowing an early diagnosis and a better treatment and prognosis. With this tool, a spectrum of diseases including other autoimmune diseases was found to have NMO-IgG antibodies and a new classification named Neuromyelitis Optica Spectrum Disorders (NMOSD) was created. In this review, we sum up the developments in this field associated with other autoimmune diseases. We approach the latest discoveries in the diagnosis like the new biomarkers that will possibly be used in the close future or the developments in the neuroimaging techniques. We reviewed the literature and synthesized case reports of NMO patients with concurrent autoimmune diseases and the information from useful larger studies. Finally, we summarize the commonly used treatments in NMO and we try to specify the best treatment for NMO with simultaneous autoimmune disease. This review updates the information about this issue and raises the awareness of rheumatologists for these severe diseases.

Keywords: NMOSD; Autoimmune; NMO-IgG; Biomarkers; Treatment.

Introduction

Neuromyelitis Optica (NMO) is an inflammatory demyelinating disease of the central nervous system. NMO is a severe, idiopathic and immune-mediated disease that causes lesions predominantly in the optic nerves and spinal cord but usually spares the brain, unlike Multiple Sclerosis (MS) [1].

Until 2004, the diagnosis of NMO was made based on major and minor clinical and paraclinical criteria with special attention to the presence of pleocytosis (more than 50 leukocytes/mm³) on cerebrospinal fluid (CSF) and the lack of complete recovery after the attack. Because of the clinical similarity between MS and NMO patients were sometimes treated for MS for a long time until NMO diagnosis could be made [2].

In 2004, Lennon and colleagues identified for the first time in NMO or high-risk NMO patients the presence of serum IgG antibodies against glia limitans, brain vessel walls, Virchow-Robin spaces and ependyma, and named it NMO-IgG. This autoantibody showed high specificity (90.9%) for NMO and high-risk patients considered together and it was not detected in the group of patients with classical MS. It was also found in patients with “masked” NMO. The staining pattern distribution was compatible with the localization of the autoantigen in the blood brain barrier [3]. A year later the same group discovered that NMO-IgG reacts against the water channel aquaporin-4 (AQP4). The staining with NMO-IgG was intense in pial and microvascular elements in the brain and interestingly it was present in the distal urine-collecting tubules in the renal medulla and in gastric parietal cells. This staining distribution suggested that the AQP4 was a candidate antigen. This result was supported by the lack of staining of CNS tissue in AQP4-null mice and the selective staining of AQP4-transfected cells membranes. So, for the first time, an autoantibody associated with NMO was described and the responsible autoantigen was identified and implicated in the pathogenesis of this autoimmune disease [4].

With this discovery a new step was taken: the NMO diagnostic criteria were revised and NMO-IgG positive diseases broadened NMO to a spectrum of diseases [5,6].

Meanwhile some evidence demonstrated the close relationship between NMO and other autoimmune diseases and consequently a renewed interest in this area appeared [7].

There was an increase in the investigation in all these areas and our aim with this paper is to review the new data about this subject and approach the criteria used to diagnose the group of diseases that constitute the NMO spectrum diseases (NMOSD), the connections between NMO, NMOSD and autoimmune diseases and compile the information about the treatments available for this very incapacitating disease.

Pubmed was searched for articles in English from 01/01/2004 until 31/09/2013. Search terms included “Neuromyelitis optica spectrum diseases”, “Neuromyelitis optica AND autoimmune diseases”, “Neuromyelitis optica AND myasthenia gravis”, Neuromyelitis optica AND sjögren syndrome”, “Neuromyelitis optica AND systemic lupus erythematosus”, “Neuromyelitis optica AND treatment” and “Neuromyelitis optica AND sarcoidosis”. Titles and abstracts were reviewed and prioritized by relevance. Some articles were obtained through reference articles’ bibliography.

NMO and NMO spectrum disorders diagnosis

According to the latest guidelines (2010) from the European Federation of Neurological Societies (EFNS) the diagnostic criteria of NMO are:

Two absolute criteria:

- (i) Optic Neuritis (ON), and
- (ii) Myelitis.

At least two of three supportive criteria:

- (i) Presence of contiguous spinal cord magnetic resonance image (MRI) lesion extending over three or more vertebral segments,
- (ii) MRI not satisfying the revised (2010) McDonald diagnostic criteria for MS [8], and
- (iii) NMO-IgG in serum [1].

Since the demonstration of NMO-IgG, a spectrum of diseases with some similarities with NMO but not fulfilling the criteria for the diagnosis for this disease was created. The fact that the patients with NMO spectrum diseases were most of the time positive for NMO-IgG raised the need to find a new classification and the concept of NMOSD was created [9].

So the NMOSD comprises pathologies resembling NMO and/or frequently associated with NMO-IgG positivity:

1. Neuromyelitis optica;
2. Limited forms of neuromyelitis optica:
 - Idiopathic single or recurrent events of longitudinally extensive myelitis (LETM; ≥ 3 vertebral segment spinal cord lesion seen on MRI);
 - Optic neuritis : recurrent or simultaneous bilateral;
3. Asian optic-spinal multiple sclerosis;
4. Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease;
5. Optic neuritis or myelitis associated with brain lesions typical of Neuromyelitis Optica (hypothalamic, corpus callosal, periventricular or brainstem) [9,1,10,11].

Association with autoimmune diseases

There is some evidence that NMO-IgG seropositivity might be associated with organ-specific autoimmune diseases like myasthenia gravis (MG), hypothyroidism, pernicious anaemia, ulcerative colitis, primary sclerosing cholangitis, and idiopathic thrombocytopenic purpura. On the other hand Sjögren syndrome (SS), sarcoidosis, antiphospholipid syndrome (APLS) or systemic lupus erythematosus (SLE) are examples of non-organ-specific autoimmune diseases associated with NMO [12,13]. The mechanism by which this association exists is unknown and it is unknown if these diseases are the primary cause of NMOSD or a concomitant autoimmune disease [14].

One study evaluated the sera of 183 patients (153 from the USA and 30 from France) and suggested that NMOSD occurring with other autoimmune diseases is a concurrent pathology and not a vasculopathy or other complications of the connective tissue diseases (CTD) [7].

Smaller series and some case reports are present in the literature and we will try to review most of them.

Myasthenia gravis

One article from 2009 described a high frequency of MG (2%) and a higher presence of anti-acetylcholine receptors (anti-AchR) antibodies (11%) in NMO patients while in MS and healthy controls the antibody was not detected [15].

Another paper from 2009 analyzed 15 cases of MG and NMO and in all of them MG onset happened before NMO. 13 of the 15 cases had undergone thymectomy before NMOSD onset and this surgery has been associated with immune deregulation and triggering autoimmune diseases because of the inability to produce immunosuppressive T cells [16]. In 2011, a group of 26 patients with MG and NMOSD was described and the authors observed similar features [17]. In another multicenter study with 16 patients MG was developed before NMOSD in patients after thymectomy [18].

Usually NMOSD occurs after MG onset and after thymectomy. One case report, from 2008, was the first described case of a patient with NMOSD after MG onset without thymectomy performed at any stage of the follow-up. [19]

Another study, from 2010, analyzed 10 patients with thymoma (9 with MG) and demonstrated that these tumors (with or without MG) express AQP-4. The authors suggested that this can be a mechanism that predisposes to NMOSD if there is a predisposition for autoimmunity and the generated antibodies against AQP-4 from thymoma are available to cross the blood-brain barrier (causing a paraneoplastic NMOSD) [20].

One study from 2013 analyzed autoantibodies and autoimmune diseases associated with MG. 2 patients with NMOSD after the onset of MG in the group of early onset MG were described. This study concluded that the autoimmunity associated with MG is focused and not generalized or random deserving a more selective immunosuppression [21]. Another group studied antibodies detected by cell based assays in MG patients and calculated that anti-AchR antibodies and NMO-IgG occur together 70 times more frequently than would be expected by chance in the British population [22].

Sjögren syndrome

One study from 2008 described 25 patients with NMOSD and 13 in 24 patients had positive NMO-IgG and 4 patients of the 25 had criteria for the diagnosis of SS. Of 20 patients with labial salivary gland biopsy 16 were positive; however only 4 had elevated anti-SSA antibodies. The authors suggest a cross reaction with NMO-IgG and performing a labial salivary gland biopsy and anti-SSA measurement in patients with NMOSD and suspected SS [23].

In 2009 one group suggested that SS myelopathy can be a manifestation of NMO. The authors described 112 patients with SS and 8 of them had spinal cord lesions. In 5 patients NMO-IgG was measured: 4 were positive and the other had borderline levels of this auto-antibody. Three other patients had clinical and imagiological criteria for NMO diagnosis. The NMO-IgG was not detected in patients without CNS involvement [24].

Another group analyzed brain abnormalities in SS with recurrent CNS manifestations. 12 patients were evaluated and 10 had CNS manifestations demonstrated by CNS MRI before the onset of SS. NMO-IgG was positive in 6 of the 8 patients tested. After all the analyses 9 patients had NMOSD criteria. This study also showed a positive association between the NMO-IgG levels and the relapse frequency [25].

In another article 17 patients with acute myelitis were studied and followed up for 12 years. They were diagnosed with SS (6), SLE (5), SS/SLE overlap (2), MS/SS overlap (2) and NMO only (2). Amongst the patients with SS, 4 had positive NMO-IgG and no patient with SLE alone was positive for this antibody. Eight patients of the 15 diagnosed with CTD had criteria for NMOSD and of these 3 had a diagnosis of CTD before myelitis. The 6 patients with NMO-IgG positivity experienced disease relapses and of the NMO-IgG negative patients only 3 had disease relapse [13].

A case report from 2007 described a 10-year-old patient with NMO at presentation. NMO-IgG measurement was not available. He had anti-SSA and anti-SSB antibodies but SS was diagnosed with minor salivary gland biopsy because there were no other symptoms only 10 years later [26]. Another case report described a patient with myelitis, positive anti-SSA antibody and positive minor salivary gland biopsy without relevant brain MRI abnormalities at the onset of the disease. NMO-IgG was positive [27]. A recent case report described a patient with bilateral ON presentation with a history of sicca symptoms for 12 years without SS diagnosis at NMOSD onset. The authors suggest that with this case and the data available in the literature ON in patients with SS and NMO-IgG positivity are arguments to the coexistence of two concurrent autoimmune diseases instead of a consequence of vasculitic complications [28].

One case report described a patient presenting first with SS and brain lesions afterwards. One year later NMO-IgG was measured and it was positive. After this the patient had several relapses however without ON or LETM [29]. Another case report described a patient with anti-SSA antibodies but without sicca symptoms. She presented ON later and NMO-IgG was negative. However, with brain MRI and evidence of myelitis, NMOSD criteria were fulfilled [30].

Systemic Lupus Erythematosus

In 2012 one group evaluated 626 hospitalized patients with SLE or SS and measured NMO-IgG in 6 patients (3 with SLE and 3 with SS) with suspected NMOSD. One patient with SLE and one with SS were NMO-IgG positive while the other only had anti-SSA antibodies. As NMOSD doesn't develop in most patients with anti-SSA antibodies the authors conclude that it is unlikely that this antibody is responsible for NMOSD manifestations. The authors conclude that NMO-IgG is present in some patients with SLE and SS and it can have a reflection in the patient's outcome [31].

Two case reports of NMOSD presentation with previous history of SLE were available. One of those patients had several relapses after NMOSD onset [32]. The other also had APLS and a recent episode of cervical myelitis [33].

Another case report described a woman with sicca symptoms for 20 years presenting with myelitis and brain lesions with MRI confirmation. The serology verified the diagnosis of SLE/NMOSD. The patient had multiple relapses in the following years [34].

A recent case report described a 51-year-old female patient with type 2 diabetes mellitus, hypertension and peripheral arterial disease. She presented with NMOSD with MRI confirmation and NMO-IgG positivity. SLE features with positive antibodies were described in the following years [35].

Another paper reported the case of a 39-year-old woman without previous diseases. She presented with NMOSD with MRI findings suggestive of acute myelitis. The measured serological markers were positive for anti-nuclear antibodies (ANA), anti-double strand DNA antibodies (dsDNA) and anticardiolipin with low C3 and C4. NMO-IgG was not measured. During the follow-up she developed typical findings of SLE (malar rash and photosensitivity) [36].

Systemic sclerosis

A first case report describing NMOSD associated with Systemic Sclerosis (SSc) was available. A female patient presented with LETM (C6-T6) and brain lesions with MRI confirmation. CSF analysis and all the other tests were normal. She had a relapse with NMO-IgG positivity. Later the diagnosis of SSc was made [37].

Sarcoidosis

A single case from 2013 was available describing NMO with concomitant sarcoidosis. A 45-year-old patient presented with acute myelitis and 5 years later she had a relapse with positive NMO-IgG. Due to an abnormal thorax CT scan, a biopsy of the supraclavicular lymph node was performed which revealed noncaseating granulomatous lesions [38].

Because of all this evidence and clinical experience it is recommended that NMO-IgG should be measured in patients with CTD, atypical presentations of CTD neurological symptoms and signs or symptoms that are suggestive of NMOSD allowing a better diagnosis, treatment and prognosis [12].

The following table (table 1) summarizes the case reports referred in the text above.

Table 1 – NMOSD associated with other autoimmune diseases case reports

| Reference | Sex/Origin/age | Presentation/ age at onset | NMO-IgG | Brain-MRI | Spinal-MRI | CSF | Age at NMOSD diagnosis /Relapses | Other ABDs | Time until final diagnosis/Final treatment |
|----------------------------|----------------|-------------------------------|------------|-----------|------------|---------------------|-------------------------------------|---|--|
| MG | | | | | | | | | |
| Kay et al. 2008 | F/Jap/44 y.o. | MG/44 y.o. | + | + | + | N | 49 y.o./ 3 | - | 5 years/AZA |
| SS | | | | | | | | | |
| Gokcay et al. 2007 | F/-/20 y.o | NMO/ 10 y.o. | N.P. | N | + | N.P. | 10 y.o /7 | Anti-SSA and Anti-SSB + | 10 years/PRED +AZA + CYC |
| Min et al. 2010 | F/- /35 y.o. | SS/35 y.o. | + | + | N.P | N.P. | 38 y.o./3 | Anti-SSA and Anti-SSB + | 3 years/N.A. |
| Koga et al. 2011 | F/Jap/31 y.o. | SS?/25 y.o. | - | N | + | N | 31 y.o/1 | ANA and anti- SSA | 6 years/PP+ PRED |
| Kahlenberg et al. 2011 | F/AA/54 y.o | NMO/54 y.o. | + | N | + | N | 54 y.o. /0 | ANA and anti -SSA + | 0 years/PP+ PRED |
| Tan et al. 2012 | F/Chi/56 y.o. | NMO/56 y.o. | + | N | N.P. | N | 56 y.o./0 | ANA, RF, anti-SSA | 0 years/ MP+PP |
| SLE | | | | | | | | | |
| Birnbaum et al. 2008 | F/AA/38 y.o. | SLE/36 y.o. | + | + | + | N | 38 y.o./3 | ANA, anti- dsDNA + | 2 years/RTX |
| Mottaghi et al. 2009 | F/-/34 y.o. | NMO/34 y.o. | Not tested | - | + | N.P. | 34 y.o./ | ANA, anti- dsDNA, anti- cardiolipin + | 0 years/ PRED+CYC |
| Polgár et al. 2011 | F/ Cau/48 y.o. | NMO/48 y.o. | + | + | + | N.P. | 52 y.o./6 | ANA, anti- cardiolipin and anti SSA + | 4 years/ MPRED+CYC |
| Arul Selvan et al. 2013 | F/-/51 y.o. | NMO/51 y.o. | + | + | + | + (without OCBs) | 52 y.o./2 | Anti- dsDNA, ANA + | 1 year/AZA |

| | | | | | | | | | |
|------------------------|--------------|------------------------------|---|---|---|------------------|-----------|----------------------|---------------------|
| Mehta et al. 2008 | F/AA/47 y.o. | SLE/ "Long standing history" | + | - | + | N.P. | 47 y.o./2 | ANA, APLS antibody + | 0 years/ CST+PP+CYC |
| Sarcoidosis | | | | | | | | | |
| Sawaya e tal. 2013 | F/-/50 y.o | NMO/45 y.o. | + | + | + | + (without OCBs) | 50 y.o./1 | ANA, anti-dsDNA + | 5 years/ IVIG+RTX |
| SSc | | | | | | | | | |
| Franciotta et al. 2013 | F/-/62 y.o. | NMO/62 y.o. | + | + | + | + | 63 y.o./2 | ANA + | 1 year/ MPRED |

AA - Afroamerican. ABDs – antibodies. ANA- anti-nuclear antibody. APLS – antiphospholipid syndrome antibody. AZA – Azathioprine. Cau- Caucasian. Chi- Chinese. CSF – Cerebrospinal fluid. CST – corticosteroids. CYC – Cyclophosphamide. F – Female. IVIG – intravenous immunoglobulin. Jap- Japanese. MG- Myasthenia gravis. MP – Methylprednisolone. MRI - Magnetic resonance imaging. N.A. – not available. N.P – not performed. NMO – Neuromyelitis Optica. NMO-IgG – anti-aquaporin 4 autoantibody. NMOSD – Neuromyelitis Optica Spectrum Disorder. OCBs – oligoclonal bands. PP – Plasmapheresis. PRED - Prednisone. RF –Rheumatoid factor. RTX – Rituximab. SLE- Systemic lupus erythematosus. SS - Sjögren syndrome. SSc – Systemic Sclerosis. Y.o - years old. + (positive). - (negative).

Biomarkers

NMO-IgG is an autoantibody against aquaporin-4 (AQP4), the major water channel in the central nervous system. AQP4 is localized in the astrocytic foot processes and is the major agent responsible for the water balance in brain but also for glutamate and potassium regulation in the blood-brain-barrier, synapses and paranodes adjacent to the nodes of Ranvier [39,1,40]. The AQP4 is also expressed in the kidneys but renal function seems to be normal in NMOSD possibly because of its small role in water balance in the nephron [9].

Binding of NMO-IgG to AQP4 has several consequences, contributing to its downregulation which causes significant damage in the astrocytic foot processes and consequently in the affected neurons. It is accepted that this pathologic mechanism has inflammatory effects through different pathways including complement and cell-based damage which cause inflammation, demyelination and oedema of the CNS [40,41]. It is suggested that NMO-IgG increases the blood-brain barrier permeability leading to higher penetration of autoantibodies, complement-dependent granulocytes and antigen-specific T-cells [42].

The antibodies detection in the patients' serum can be achieved by indirect immunofluorescence or immunohistochemistry. The sensitivities and specificities are diverse but the used methods generally have an excellent specificity and a good sensitivity. Comparing the most commonly used assays (immunofluorescence, cell-based and fluorescence-based immunoprecipitation assays) it seems that the cell-based assay has the highest sensitivity (91%) and specificity (100%) comparable to the others [43,44]. Another study also demonstrated that the cell based assay is the most sensitive method and it is simple and easy to use in routine laboratories [45]. With this level of sensitivity is recommended that 2 different assays should be used and one of them should be indirect immunofluorescence [46].

In 2012 one group used 673 serum samples to study the specificity of the NMO-IgG in the context of autoimmune diseases and non-immune mediated diseases. This antibody was detected in none of the 585 samples without CNS manifestations. None of the SS or SLE patients had CNS involvement and NMO-IgG was negative. This study concluded that this test is very specific and if it is positive in other autoimmune diseases with CNS lesion, concurrent NMOSD is probable [47].

Routine CSF analysis can be useful in patients with NMOSD onset when clinical and imagiological distinction from Multiple Sclerosis is difficult. In contrast with MS, in NMO pleocytosis consisting of monocytes and lymphocytes is present in 14-79% of patients. The frequency of oligoclonal bands ranges from 0-37% in NMO unlike in MS where it is a common finding. Increased protein levels are present in 46-75% of the patients. Neurofilaments heavy chain levels are significantly higher than in patients with MS [48,13,1].

NMO-IgG detection in CSF didn't improve the sensitivity or specificity of the current diagnosis criteria [49]. In another study a Chinese group demonstrated increased sensitivity of NMO-IgG detection in CSF when compared with serum [50]. However, NMO-IgG analysis in CSF is recommended in cases where there are AQP4 seronegative NMO/ NMOSD with elevated clinical or image suspicion [1].

Other diagnostic exams are being tested. The complement activating antibodies against myelin oligodendrocyte glycoprotein (MOG), a biomarker associated with acute disseminated encephalomyelitis, and their detection in serum can be a useful tool in seronegative NMO-IgG patients that have criteria for NMO or NMOSD, suggesting an alternative lesion mechanism [51]. Another study demonstrated that during initial NMOSD attacks interleukin-6 (IL-6) and glial fibrillary acidic protein (GFAP) in CSF are elevated suggesting that their detection can also allow an early diagnosis [52]. Another study compared GFAP in patients with ON associated with MS and with NMO. The findings were statistically significant and demonstrated that GFAP levels in patients with ON related to NMO are higher than those in MS suggesting that it can be a good biomarker in atypical presentations [53]. One single study suggested that high-mobility group box 1 protein (HMGB1) in serum can be used as an early diagnostic tool in NMO, making its distinction from MS possible [54].

Recently, one group suggested that in NMOSD NMO-IgG seronegative patients anti-aquaporin1 antibody can be one alternative biomarker (another aquaporin present in the CNS) that was present in a subgroup of patient with demyelinating disease similar to NMOSD [55].

Brain MRI findings

After the discovery of NMO-IgG the brain lesions in NMOSD began being commonly described.

Characteristic abnormalities are:

-Transverse myelitis, clinically complete or incomplete, but associated with imagiological evidence of spinal cord lesion extending over three or more spinal segments on T2-weighted MRI and hypointensity on T1-weighted images when obtained during acute episode of myelitis.

-Non-specific brain T2 signal abnormalities not satisfying Macdonald criteria

-Lesions in the dorsal medulla, either in contiguity or not with a spinal cord lesion

-Hypothalamic and/or brainstem lesions

-“Linear” periventricular/ corpus callosum signal abnormalities, not ovoid, and not extending into the parenchyma of the cerebral hemispheres in Dawson finger configuration [56].

New MRI techniques are being used in NMOSD. Diffusion tensor image showed that multiple white matter tracts and other normal appearing white matter are involved. Magnetic resonance spectroscopy analysis was normal in normal appearing grey and white matter in NMO patients for the main metabolic parameters. Voxel based morphometry allows the study of structural changes of the brain and demonstrated that the decrease of global and focal white matter in NMO appears to be correlated with cognitive impairment [5].

In contrast with what was previously defended it was demonstrated that brain lesions can also be the first manifestation of NMOSD in two studies of 15 and 27 NMO-IgG seropositive patients [57,58].

In vasculitic diseases related with other autoimmune diseases the MRI abnormalities are diverse. One review of the imaging of cerebral vasculitis suggested a new organization of the signs of this type of brain disease in direct and indirect. The direct sign is applied mainly in large vessels and in this case a vessel wall thickening is detected with contrast enhancement. The indirect signs can be suggested by cerebral perfusion deficits, ischaemic brain lesions, cerebral haemorrhage and vascular stenosis unlikely to be atherosclerotic [59].

Another study analyzed, among other things, the differences in MRI imaging in the diagnosis of several autoimmune diseases. In SS myelopathy the MRI findings may be similar to those of NMO with LETM and gadolinium-enhancing. Concerning SLE, the MRI imaging pattern seems to be very similar to MS and acute SLE lesions often enhance with gadolinium. One common finding in these patients is cortical atrophy (which can be also found in MS and in other autoimmune diseases with SNC manifestations). The spinal cord imaging can show LETM (sometimes the entire length of spinal cord) differently from MS [60].

It is suggested that MRI evaluation in patients with autoimmune diseases, SNC lesions and positive NMO-IgG might be useful, allowing an early diagnosis and better prognosis, with a closer follow-up.

Treatment

There are no published randomized controlled trials for relapse prevention in NMOSD. However, there are recommended drugs based on small prospective or retrospective series of off-label use. For acute treatment methylprednisolone is the first line treatment [61]. When the patient doesn't improve, plasma

exchange can be a good alternative [62,63]. Cyclophosphamide also seems to be a good alternative in refractory cases [64].

For relapse prevention several drugs can be used. Azathioprine (first line drug), mycophenolate mofetil and methotrexate are immunosuppressant drugs that seem to be safe and significantly reduce annual relapses rate (ARR) and improve or stabilize Expanded Disability Status Scale (EDSS) [61,65,66]. Other alternatives are available: rituximab, for instance, is a promising drug in refractory cases reducing ARR and EDSS [67-69]. A new alternative is eculizumab (monoclonal IgG) that neutralizes complement protein C5 and seems to reduce ARR and stabilize or improve EDSS [70].

According with Wingerchuk and Weinshenker [14] the therapeutic regimen in NMO with concomitant rheumatologic diseases can be based in cyclophosphamide and methotrexate because these agents showed benefits in both conditions. However, azathioprine should be the drug of choice because of its safety profile and tolerance in long-term therapy. The authors recommend avoiding monoclonal antibodies or fusion protein therapies that can interfere with tumor necrosis factor-alpha function (infliximab, adalimumab, etanercept). These agents are commonly used in rheumatic disorders but are associated with demyelinating events and their effect in NMO is not known [14]. Another paper reporting 2 patients with NMO and SLE overlap described a good response to cyclophosphamide and azathioprine [34]. Another review described the efficacy of Rituximab in NMO, MG and SLE and in the latter it can be used alone or in combination with corticosteroids or cyclophosphamide [71]. Methylprednisone is also commonly used in autoimmune diseases and NMO mainly in acute manifestations [16,60]. Plasma exchange is also an alternative in these patients, as seems to be intravenous immunoglobulins [72,73].

Conclusions

NMOSD are very incapacitating diseases with serious consequences in the quality of life and causing serious loss of autonomy in these patients.

With the present review we tried to summarize the developments in diagnosis and treatment of NMOSD with special focus in the relationship with other autoimmune diseases and in the recent investigation made in this field.

There was an increase in the investigation in this area mostly motivated by the discovery of NMO-IgG antibody which allowed the identification of several diseases that previously were not considered as belonging to the field of NMO.

This antibody allowed an early recognition and diagnosis of NMOSD also allowing an accurate distinction between NMOSD, MS or other manifestations of autoimmune diseases (vasculitis e.g.) when the criteria previously mentioned are not clearly fulfilled.

There are some new biomarkers being discovered and associated with NMOSD and they can be useful for a more accurate diagnosis and early treatment in the future.

The neuroimaging is also in progress and new diagnostic tools are becoming available turning possible the identification of brain lesions where before it was not possible.

Further investigation is needed and new trials with recent drugs must be performed. The small number of patients with NMOSD restricts the possibility of large scale trials to demonstrate the efficacy of the old drugs and to show the advantage of new emerging drugs. We tried to summarize the most useful treatments that can be useful in both diseases NMO and other autoimmune diseases. The number of studies considering overlapping diseases is reduced and more investigation is needed to evaluate the efficacy and safety of different treatments.

The number of cases of NMOSD associated with other autoimmune diseases available in the literature is limited and further investigation is needed to increase the knowledge and the validity of the conclusions taken from the developed research.

Conflict of interest: The authors declare that they have no conflict of interest.

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doi:10.1177/1352458513495938

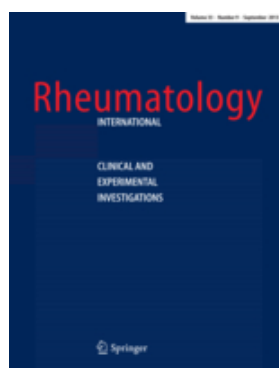
Agradecimentos

Gostaria de agradecer, em especial, à minha Orientadora do Projeto de Opção, a Professora Doutora Joana Guimarães, que foi inexcedível no acompanhamento do desenvolvimento deste trabalho, corrigindo aquilo que não estava bem conseguido e dando sugestões muito pertinentes para melhorar e enriquecer o trabalho, tornando-o mais consistente. As suas rápidas respostas às minhas dúvidas e as suas orientações foram essenciais para tornar esta monografia possível.

Agradeço também à D. Margarida, secretária da unidade de Neurologia e Neurocirurgia da FMUP, que foi extremamente eficaz nos seus esforços para obter aqueles artigos que não conseguia obter através dos processos habituais, possibilitando a realização de um trabalho mais completo.

Uma palavra de apreço para todos os meus amigos e colegas, os quais foram um enorme suporte nestes 6 anos, oferecendo conselhos, esclarecendo dúvidas, partilhando momentos felizes e sendo a melhor das ajudas quando os obstáculos, aparentemente intransponíveis, surgiam.

Por último, queria agradecer aos meus pais, ao meu irmão e à família mais próxima, por me terem acompanhado ao longo destes 6 anos, ajudando-me a enfrentar as adversidades e compartilhando comigo os vários momentos de alegria que foram surgindo durante esta caminhada que agora se aproxima do seu final.



Rheumatology International

Clinical and Experimental Investigations

Editor-in-Chief: Loreto **Carmona**

ISSN: 0172-8172 (print version)

ISSN: 1437-160X (electronic version)

Journal no. 296

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author lists will also be accepted:

Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. *N Engl J Med* 965:325–329

Article by DOI

Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. *J Mol Med.* doi:10.1007/s001090000086

Book

South J, Blass B (2001) *The future of modern genomics.* Blackwell, London

Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) *The rise of modern genomics*, 3rd edn. Wiley, New York, pp 230-257

Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. <http://physicsweb.org/articles/news/11/6/16/1>. Accessed 26 June 2007

Dissertation

Trent JW (1975) *Experimental acute renal failure.* Dissertation, University of California

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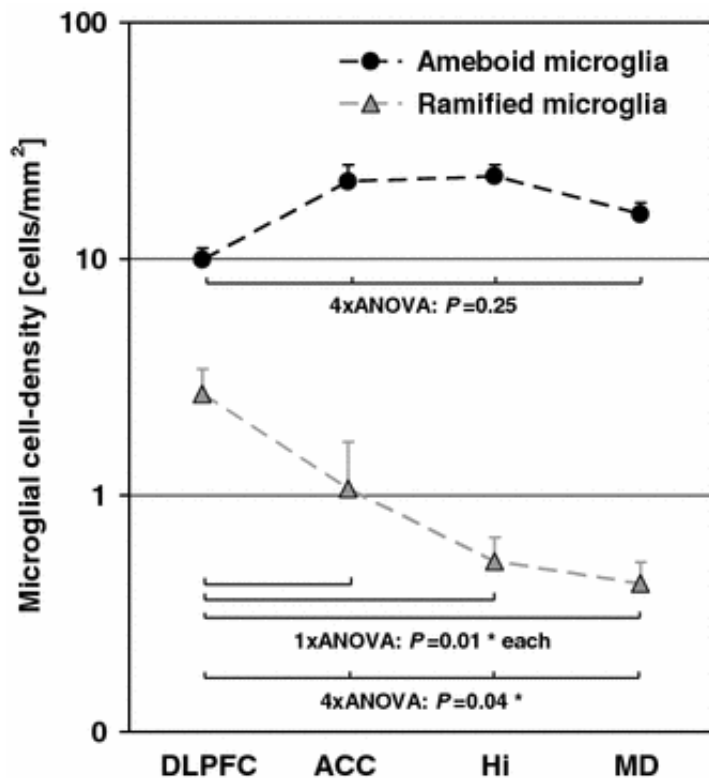
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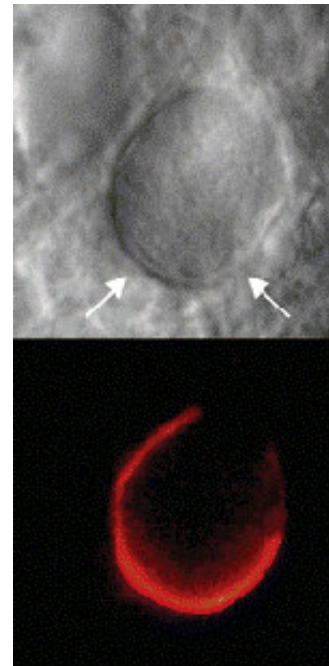
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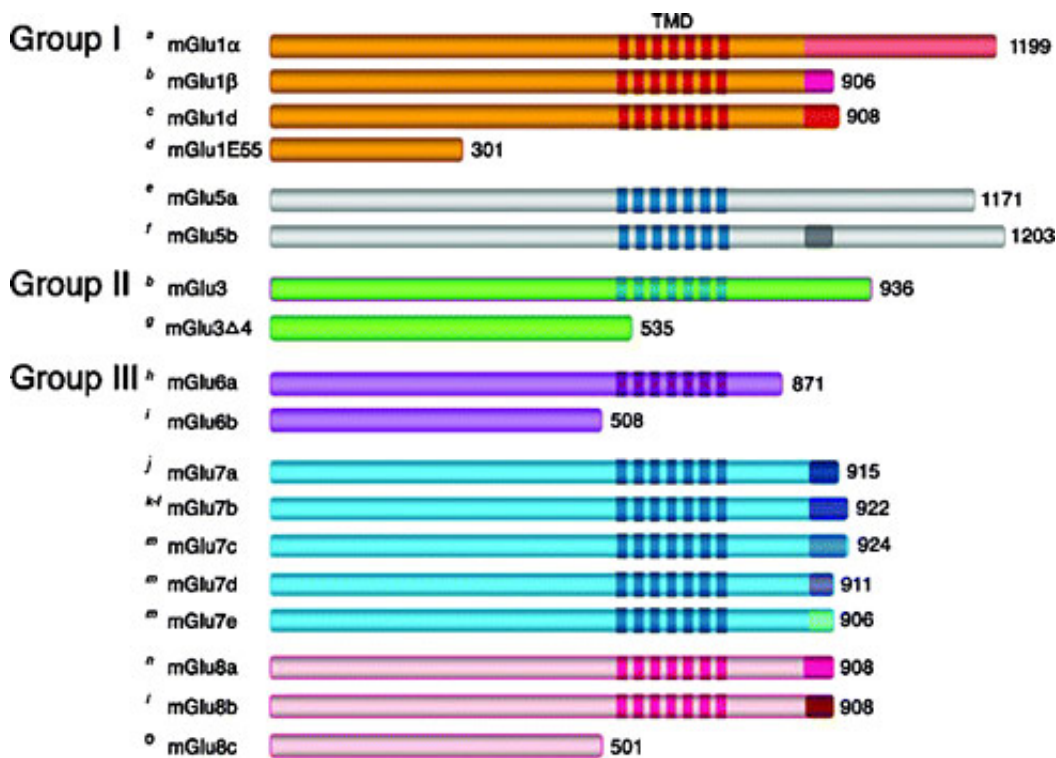
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