Medical Science, Vol. 20, No. 79, May 1, 2016

PERSPECTIVE

ISSN
2321–7359
EISSN
2321–7367

Medical Science

An International Journal

NMO-An Update

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Publication History
Received: 09 February 2016
Accepted: 05 March 2016
Published: 1 May 2016

Citation
Saumya H Mittal, Salony Mittal, Tuhina Govil. NMO-An Update. *Medical Science*, 2016, 20(79), 69-73

ABSTRACT

Neuromyelitis Optica is an autoimmune condition whose diagnostic criteria are expanding. The clinical features of the disease are different from multiple sclerosis, a disease that was considered a larger entity that included neuromyelitis optica until the last decade. The diagnostic markers are ever expanding and so are the treatment options, many of which are under trial.

Keywords: Neuromyelitis Optica, NMO, Anti Aquaporin 4 antibody, Neuromyelitis Optica Spectrum Disorders.

Abbreviations:
NMO- Neuromyelitis optica

MS- multiple sclerosis
Anti AQP4 IgG- Anti Aquaporin 4 antibody
NMOSD- Neuromyelitis Optica Spectrum Disorders
LETM- longitudinally extensive transverse myelitis
CSF- Cerebrospinal fluid
anti MOG- Anti myelin associated oligoglycoprotein

1. DISCUSSION

Neuromyelitis optica (NMO) is an autoimmune chronic inflammatory disorder that affects the central nervous system. It also affects many non neurological sites and leads to related manifestations. Till the last decade, the condition was considered a part of multiple sclerosis (MS). However, the discovery of Anti NMO antibodies (now renamed to Anti Aquaporin 4 antibody) in 2004 conclusively delineated the two conditions and proved to be a specific biomarker for NMO.[1]

NMO is likely to be present in one fifth of the patients who have a demyelinating condition in India. The prevalence of NMO in India may be as much as 0.7 per 100,000. The mean age of onset of the entity ranges from 32.6 to 45.7 years, and the time to relapse is 8 to 12 months. While a third of attacks are preceded by fever or immunization, no specific environmental agent has been implicated. While most of the cases are sporadic, familial forms are known giving rise to suspicion of genetic susceptibility. [1]

The aquaporin 4 antigen is a water transport protein which is expressed at the astrocyte feet at the blood brain barrier. It is present extensively in the neural tissue, but is seen in maximum concentration at the optic nerves and the spinal cord. Therefore, antigen antibody reaction affects the spinal cord and optic nerve predominantly. Anti Aquaporin 4 antibody (Anti AQP4 IgG) is largely produced by the plasma cells in the peripheral blood. The trigger to the production of antibodies is unknown. However, often the disease is preceded by fever or immunization. The antibodies gain access to the central nervous system via breach in the blood brain barrier. The antigen antibody interaction leads to activation of the complement system. Chemotaxis of neutrophils and eoinophils lead to cellular cytotoxicity which can lead to severe inflammation and necrosis if not treated. Of course other parts of nervous system are also involved. And as mentioned previously, non neurological manifestations are also known. [1,2]

Anti AQP4 IgG is present in as many as 70-80 percent of the cases of NMO. A variety of conditions are seen in patients with Anti AQP4 IgG positive patients. Limited forms of diseases exist e.g. isolated unilateral or bilateral recurrent optic neuritis, recurrent transverse myelitis etc. Therefore, the term Neuromyelitis Optica Spectrum Disorders (NMOSD) is now introduced. [1,2]

Table 1	
Absolute Criteria	
1	Optic Neuritis
2	Acute Myelitis
3	No evidence of clinical disease outside optic nerve and spina cord
Supportive Criteria	
Major	
1	Negative brain MRI at onset
2	Spinal cord MRI with signal abnormality extending over 3 or more vertebral segments
3	Csf pleocytosis of mre than 50 WBC/cmm or more han 5 neutrophils/cmm
Minor	
1	Bilateral optic neuritis
2	Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye
3	Severe fixed attack related weakness

The original diagnostic criteria for NMO was proposed in 1996 (Table 1) by Wingerchuk et al. This was modified in 2006 to include

a. 2 absolute criteria- optic neuritis and acute myelitis.
b. At least 2 of the 3 supportive criteria-
    I. A spread spinal cord lesion involving 3 or more vertebral segments
    II. Brain MRI that is not suggestive of MS
    III. Seropositivity for Anti AQP4 IgG.[1,3]

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This criterion has again been modified in 2015 (Table 2). Some salient features included are

a. Addition of area postrema syndrome – presents as nausea, vomiting and hiccups
b. Brain stem syndromes
c. Symptomatic narcolepsy
d. Symptomatic cerebral syndrome with MRI findings.[1,3]

Table 2	
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 diagnosesa
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
6	Symptomatic cerebral syndrome with NMOSD-typical brain lesions 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
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
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
3	Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4	Acute brainstem syndrome: requires associated periependymal brainstem lesions

Optic neuritis is one of the main features of NMO. They present with severe visual impairment. The optic neuritis in the two conditions, NMO and MS are difficult to differentiate. However, rapid succession of occurrence of bilateral simultaneous or sequential optic neuritis is more commonly seen in NMOSD. The other common feature is the involvement of spinal cord. The presentation may be in the pattern of complete transverse myelitis or involvement of 3 or more spinal segments, called as longitudinally extensive transverse myelitis (LETM). However, involvement of less than 3 segments may also be seen is seropositive patients. Besides, extension of the lesion into the brainstem may cause symptoms such as hiccups, vomiting and respiratory failure. The patients may also present with asymptomatic spinal lesions detected on evaluation of optic neuritis. Some patients also present with tonic spasms that are painful or Lhermitte's sign.[1, 3]

Monosymptomatic onset is known in NMO with presence of both optic neuritis and LETM seen together in 15-40% cases only.

Sites outside the spinal cord and optic nerve may also be involved in NMOSD, often in isolation. Brainstem manifestation may be seen in a third of the non Caucasian seropositive patients. The patients may present with intractable vomiting (area postrema syndrome) or hiccups (periaqueductal lesion in midbrain) or hypersomnolence (diencephalic involvement). Narcolepsy, hypothermia, deafness and vertigo are also frequent. Cranial nerve involvement like oculomotor dysfunction, trigeminal neuralgia, facial palsy may be seen. Other features include seizures, hyposmia, meningoencephalitis, myeloradiculopathy, cognitive dysfunction, posterior reversible encephalopathy syndrome, skeletal and smooth muscle involvement (oedema and myocarditis).[1, 3, 4]

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The patients may present with placentitis with risk of abortion, internal otitis, and gastritis. These features are present due to expression of aquporin in these extraneural tissues. NMOSD may also present with other coexisting autoimmune conditions such as Sjogren's syndrome, myasthenia gravis, systemic lupus erythematosis, autoimmune thyroiditis, autoimmune encephalitis and autoimmune mediated vitamin B12 deficiency.[1, 3]

MRI of the spine is crucial since the brain MRI may be indistinguishable from that of MS. The hallmark lesion is LETM which is a centrally placed oedematous lesion involving the cervical and thoracic cord commonly (in contrast to lesions in MS that are short posteriorly placed lesions most commonly affecting the cervical cord). MRI timing often affects the visualization of the lesion. Too early or post treatment MRIs may miss the classical tumefactive lesion or longitudinal lesions. In acute lesions, patchy enhancement may be seen in 35-70% patients. On therapy, the lesions ten to break up showing small segmental lesions associated with cavitations and cord atrophy. Brain MRI may be indistinguishable from that seen in MS. Absence of characteristic features of MS such as Dawson's finger, U fibre lesions, inferior temporal lobe lesions and paucity of lateral ventricles may also suggest NMOSD. There may be a variable enhancement in NMOSD lesions which are frequently seen at corpus callosum, pons, midbrain, medulla and cerebellar peduncles. Cervical cod lesions are often seen contiguous to the medulla lesions. Optic nerve should be examined in MRI to look for extensive bilateral lesions often involving the intracranial portions of nerve and the optic chiasma.[1, 3]

Optical coherence tomography, a non invasive method shows thinning of unmyelinated retinal axons otherwise called retinal nerve fibre layer and their neurons (retinal ganglion cells). It may help in differentiating NMOSD from MS and other inflammatory diseases. It may also help monitor disease progress and therapy. Visual evoked potentials may be altered in NMOSD showing prolonged P100 latencies and reduced amplitude or missing potentials.[1, 3]

Cerebrospinal fluid (CSF) shows a variable degree of pleocytosis, raised proteins and oligoclonal bands. Both eosinophilia and neutrophilia may be seen in the csf. Histopathological features are astrocytic damage, demyelination, neuronal loss and frequently pronounced necrosis is seen.[1, 2]

Aquaporin 4 antibodies were discovered in 2004 and have since been a crucial part of diagnosis of NMOSD. Aquaporin is expressed most in diencephalon, hypothalamus and aqueduct. Immunosuppresive therapy reduces the serum levels of the antibodies. Retesting may be necessary in cases of relapse. Almost 70% percent show these antibodies. However in the other seronegative patients, additional biomarkers may be discovered. Anti myelin associated oligoglycoprotein (anti MOG) is often seen in such seronegative patients. The antigen is present on the outer surface of myelin sheaths and oligodendrocytes. Patients with this antibody present with simultaneous and recurrent optic neuritis more commonly than NMOSD. The myelitis is also usually more caudal. Demographically, males and females have equal preponderance and the disease runs a monophasic course. Other antibodies such as Anti CV2 or CRMP% and NMDA receptor antibody may also mimic NMOSD in isolated cases.[1, 2, 5]

B cell dysregulation is a core of NMOSD pathogenesis. The B cells express anti AQP4 IgG. Plasmablasts are found in elevated levels amongst these patients. Focus on B cell subtype may help identify a prognostic or therapeutic B cell marker. Increased levels of inflammatory mediators are detected in the patients. This includes several interleukins e.g. IL1, 6, 8, 13, CXCL10, 13 etc. However they are expressed in other conditions as well. However, they may help differentiate NMOSD from MS on further evaluation. Breakdown of blood brain barrier gives access to anti AQP4 IgG. The markers that indicate blood brain barrier breakdown may serve to monitor disease activity e.g. matrix metalloproteinase 9, vascular endothelial growth factor A, intercellular adhesion molecule -1 and vascular cell adhesion molecule -1. Elevated levels of central nervous system proteins in serum and csf e.g. neurofilament heavy chai, GFAP, S100B, and csf haptoglobin levels may indicate blood brain barrier breakdown and tissue damage. While there has been no direct relationship between NMOSD and the individual gene or gene locus, HLA-DPB1,e52 HLADRB1* 03:01, PD-1.3A allele of PTPN22, and CD226 Gly307Ser are under evaluation and need larger cohorts to explore their role in the multifactorial etiology of NMOSD. There has been recent interest in T cell activation, expansion and the ratio of CD41:CD81cell ratios.[5]

In acute condition, steroids are prescribed despite the fact that there is no evidence based study. Use of intravenous methylprednisolone 1 gm per day for 3 to 5 days in combination with proton pump inhibitors and thrombosis prophylaxis is followed by most neurologists. This may be followed by oral steroidal therapy depending on the severity of the attack. A second course of steroids, two to five times the original dose may be considered if there is no improvement and alternative therapies like plasmapharesis and immunoglobulins are contraindicated. Therapeutic plasma exchange may be considered and is effective for both seropositive as well as seronegative patients. A patient may receive 5 to 7 cycles of plasma exchange. Intravenous immunoglobulins may also be administered in the dose of 0.4 mg/kg. However, their efficacy is not conclusively proven in patients with severe demyelinating condition such as severe visual impairment due to optic neuritis.[6]

Long term therapy has been attempted with multitude of drugs. Azathioprine, a prodrug of 6 mercaptpurine, is a purine antagonist that inhibits DNA and RNA synthesis. In reduces the elapse rate and ameliorates the neurological disability. Blood cell count and liver enzymes need to be monitored. Cyclophosphamide is another effective therapy and the dose needs to be adjusted as per the leucocyte count. Methotrexate is usually used a second line therapy which is usually well tolerated. Used as monotherapy or in combination with other medicines, it stabilizes or reduces the disability and the median relapse rates. Mycophenolate mofetil inhibits proliferation of B and T cells, dendritic cells, immunoglobulin production and T cell migration. Its response is quicker than azathioprine and it effectively reduces the disability and the relapse frequency. Rituximab depletes B cells in NMOSD. Used as treatment option in both treatment naive patients as well as second line therapy, the patients remain B cell deficient for 6 months and redosing every 6 months may be needed. Mitoxantrone causes 75-80% reduction in relapse rate. It interacts with topoisomerase

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2 thereby causing single as well as the double strands breaks. This delays cell cycles. Another mechanism is inhibition of B cell functions and antibody secretion. It's also known to abate teh activity of cytotoxic and helper T cells and the secretion of Th1 cytokines. However, there may be associated cardiotoxicity and there is a risk of developing leukemia limiting the use of the therapy. Clinical deterioration has been noted with interferon beta, natalizumab, and fingolimod.[6]

Interleukin 6 contributes in the persistence of plasmablasts that produce anti AQP4 IgG. Therefore interleukin 6 receptor blocking antibodies such as tocilizumab have been tried. Tocilizumab, licensed for use in rheumatoid arthritis may soon be used in conditions where other therapies have failed. Eculizumab, a monoclonal antibody against C5 has also been found effective in NMOSD. Eculizumab in a dose of 500 mg weekly every week for 4 weeks followed by 900 mg in the 5th week and 2 weekly subsequently for 48 weeks has to be verified. Serping 1, a serine protease inhibitor, controls bradykinin generation and prevents initiation of classical and lectine pathway activation. Its carbohydrate moiety shows interaction on with E and P selectin on leucocytes and endothelia. This may prove to be an effective therapy in future. Other possibly beneficial therapies include neutrophilesterase inhibitors, competitive non pathogenic AQP4 specific antibodies e.g. aquaporumab and enzymatic aquaporin 4 antibody deglycosylation or cleavage. Autologous hematopoietic stem cell transplant therapy may prove to be beneficial. Almemtuzumab has didnot show any benefit in NMOSD whereas this T and B cell depleting antibody was found to be effective in MS.[6]

2. CONCLUSION

The prognosis of the disease is improving. The mortality has improved. This may be due to a greater awareness of the disease, access to ever expanding testing options and use of increasing number of medicines that may be used for long term immunosuppresion.

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