International Journal of Advances in Medicine
Jagiasi KA et al. Int J Adv Med. 2019 Aug;6(4):1277-1280
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20193285

Original Research Article

Clinical and treatment patterns in neuromyelitis optica: a retrospective study from a single centre

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Received: 30 April 2019
Accepted: 30 May 2019

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ABSTRACT

Background: The aim of the study was to study the different presentations, treatment patterns and relapses on therapy in patients of neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD).
Methods: This is a retrospective, observational study in a tertiary hospital where Demographics, clinical manifestations at onset and at follow up and relapses, serum anti Aquaporin 4 antibody status, first line immunomodulatory therapy which was initiated and Relapses on first line therapy were noted.
Results: Demographics and clinical presentation was largely similar to published data. 80% patients presented with LETM/ON at onset. Ten patients relapsed on oral therapy and trend was to shift from oral therapy to RTX after relapse on oral agent. No relapses were noted on RTX.
Conclusions: Unaffordability and apprehension towards injections and cost were the factors affecting IMT decision, so majority received oral agents Aza/ MMF as first line therapy while remaining patients on oral therapy remained relapse free.

Keywords: Neuromyelitis optica, Optic neuritis, Rituximab, Transverse myelitis

INTRODUCTION

Neuromyelitis optica (NMO) is an autoimmune demyelinating condition of the central nervous system that is associated with aquaporin-4 (AQP4) autoantibodies manifesting as severe optic neuritis and long segment myelitis with tendency to relapse.[1,2] Seronegative patients and who do not meet the NMO criteria are classified as having NMO Spectrum Disorder (NMOSD), but are treated similarly to clinically definite NMO.

Clinically, it presents with optic neuritis (ON) and transverse myelitis, often characterized by poor or no recovery. MRI Imaging typically shows longitudinally extensive lesions spanning three or more vertebral segments. Histopathologically, it is characterized by astrocytic damage, demyelination, neuronal loss, and often pronounced necrosis.[3,4] The discovery of perivascular antibody and complement deposition within active lesions and the discovery of specific autoantibodies (aquaporin-4 antibodies, AQP4-Ab; also termed NMO-IgG) in the serum of NMO patients indicated that humoral immunity is involved in most of the cases. AQP4-Ab-positive NMO is now distinguished from MS as an independent disease entity.[5] Accordingly, serological identification of NMO-IgG has also been included as an additional criterion in the diagnostic criteria for NMO currently in use.[2]

The treatment of NMOSD is mainly immunosuppressive. In acute phase, high-dose methylprednisolone, plasma exchange, or intravenous immunoglobulin are used to control inflammation for rapid recovery.[6] However, the course is punctuated by severe clinical relapses with rapid and often permanent disability. Aggressive long-term treatment is essential. Immunosuppressive agents such as azathioprine (AZA) and mycophenolate mofetil (MYC) have been used to reduce relapse risk and preserve neurological function.

Recently, rituximab, a monoclonal antibody to CD20, has been found to be effective in several reports and some uncontrolled studies.[7] Rituximab is a mouse and human chimeric IgG1 monoclonal antibody that binds to CD20B-lymphocyte surface antigen, which is involved in B-cell activation, differentiation, and growth.[8,9] Rituximab depletes CD20+ B cells, which are precursors of short-lived antibody-producing plasma cells, thereby suppressing antibody-mediated immunity and reducing AQP4 antibody levels as well.

There are very few studies from India describing clinical manifestations and treatment patterns of Neuromyelitis Optica. Therefore our study observes these patterns from a single centre in Western India.

METHODS

Study population

This study was a retrospective, observational study in a tertiary hospital in urban India. Study population comprised of all patients admitted in a tertiary care hospital in Mumbai who had a diagnosis of NMO (Aquaporin 4 antibody positive) or NMOSD as per the 2015 international consensus on NMOSD.[1,2]

Study duration

This retrospective study included patients admitted with a diagnosis of NMO (Aquaporin 4 antibody positive) or NMOSD from Jan 2013 to October 2018.

Eligibility criteria

All patients satisfying all the inclusion criteria and none of the exclusion criteria were enrolled in this study.

Inclusion criteria

- Patients of either gender aged between 5 years and 85 years admitted irrespective of their present and past medical history.
- Patients admitted in a tertiary care hospital in Mumbai who had a diagnosis of NMO (Aquaporin 4 antibody positive) or NMOSD as per the 2015 international consensus on NMOSD.

Exclusion criteria

Patients who did not fulfil the criteria for NMO or NMOSD.

Study procedure

Retrospective data of diagnosed NMOSD patients was collected from single tertiary care Neurology center in Mumbai. Demographics, clinical manifestations at onset and at follow up and relapses, serum anti Aquaporin 4 antibody status were noted. First line immunomodulatory therapy which was initiated was noted. Relapses on first line therapy, and whether relapsed patient was shifted to another immunomodulatory therapy after he/she relapsed on first agent, was also recorded.

RESULTS

About 22 patients of NMO and NMO SD were included in this study from a period from January 2013 to October 2018. Age of the patients ranged from 10-57 years with an average and median age of 36 years. Out of 22 patients, 11 were male and 11 were female (Male: Female ratio-1:1). Commonest presentation in our study was longitudanally extensive Transverse Myelitis (15/22) patients (68%) of which two patients had longitudanally extensive lesion from brainstem to the spinal cord. One patient of these 15 had LETM as well as Optic Neuritis at presentation. Three patients had Optic Neuritis which was the second most common presentation. Two patients presented with Acute Brainstem Syndrome, while one patient each presented with Area Postrema syndrome and Symptomatic Cerebral Syndrome. In this study, 14 patients were positive for Aquaporin 4 antibody.

With regards to treatment, first line Immunomodulatory Therapy was Azathioprine (Aza) in 14 out of 22 patients. (Patients were started on dose of 50 mg twice a day), Mycophenolate (MMF) in 2/22 (Patients started on a dose of 500 mg thrice a day) and injection Rituximab (RTX) in 4/22 patients (Dose of 2 g given over 2 weeks). Two patient did not receive any Immunomodulatory Therapy. 8 out of 16 patients who received oral therapy as first line, relapsed. All 8 of them had received Azathioprine as the first line oral agent. 4 patients out of the 8 were able to receive Inj Rituximab as second line immunomodulatory therapy. Patients initiated on RTX, either as first- or second-line therapy, did not relapse. Rituximab was given as 2 g initial dose given as 1 g at interval of 15 days.

DISCUSSION

Neuromyelitis Optica is an immune-mediated chronic inflammatory disease of the central nervous system (CNS).[1] Clinically, it presents with optic neuritis (ON) and transverse myelitis, often characterized by poor or no recovery. MRI Imaging typically shows longitudinally extensive lesions spanning three or more vertebral

segments. Histopathologically, NMO is characterized by astrocytic damage, demyelination, neuronal loss, and often pronounced necrosis.[10]

The discovery of perivascular antibody and complement deposition within active lesions and discovery of specific autoantibodies (aquaporin-4 antibodies, AQP4-Ab; NMO-IgG) in the serum of NMO patients indicated that humoral immunity is involved in the majority of cases. Accordingly, serological identification of NMO-IgG has been included as an additional criterion in all diagnostic criteria for NMO currently in use.[1,2]

According to the criteria proposed by Wingerchuk et al, a diagnosis of NMO can be made with high specificity if, in addition to a history of at least one episode of ON and one episode of myelitis, two of the following three supporting criteria are met:[2]

- Contiguous spinal cord MRI lesion extending over three or more vertebral segments
- Brain MRI not meeting MAGNIMS' diagnostic criteria for MS at disease onset.[3] NMO-IgG seropositive status.

In the initial presentation or during exacerbation of NMO, the primary aim of treatment is to minimize the irreversible damage to the central nervous system and to restore neurologic function. The standard treatment for an acute attack of myelitis or optic neuritis is with high dose intravenous methylprednisolone at a daily dose of 1,000 mg for 3-5 days. This gives some amount of recovery to most of the patients. For those who show no response or poor and inadequate response after 7-10 days, therapy with IV methylprednisolone, plasma exchange (PE) (five cycles of PE, each removing a total of 1.0-1.5 volumes of circulating plasma).[11]

Patients who have the risk of relapse, AQP4-positive patients and those who fulfill the NMO criteria need long-term therapy. Immunomodulators that have been used as disease-modifying agent in MS have not been found to be effective in NMO. Several series have reported poor efficacy and even harmful effects of these agents, including beta-interferons, natalizumab, and fingolimod. Immunosuppressive agents have been found effective in studies in NMO are azathioprine, rituximab, mycophenolate mofetil, methotrexate, prednisone, and mitoxantrone.[12,13]

Rituximab is a monoclonal antibody to CD20 epitope present on all cells of the B cell lineage. Rituximab depletes CD20+ B cells, which are precursors of short-lived antibody-producing plasma cells, thereby suppressing antibody-mediated immunity and reducing AQP4 antibody levels.[14,15] The dosing of rituximab in the above studies was of two types: 375 mg/m^2/week for 4 weeks or two doses of 1 g each infused 2 weeks apart. Advantages such as reduced side effects and cost are obvious.

CONCLUSION

Author concluded from this study that, demographics and clinical presentation in our cohort was similar to published data. 80% patients presented with LETM/ON at onset. Unaffordability and apprehension towards injections and cost were the factors affecting IMT decision, so majority received oral agents Aza/ MMF as first line therapy while remaining patients on oral therapy remained relapse free. Ten patients relapsed on oral therapy and the trend was to shift from oral therapy to RTX after relapse on oral agent. No relapses were seen once the patient went on RTX.

This study, thus highlights different presentations of patients and also gives us an insight into the treatment patterns followed as well as the trend of relapses on therapy in patients of NMO and NMO SD. However larger studies are required to ascertain the best treatment to be followed so as to avoid relapses and prevent neurologic dysfunction.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jagiasi KA, Nagendra S, Ansari A, Barvalia P, Aglave V. Clinical and treatment patterns in Neuromyelitis Optica: a retrospective study from a single centre. Int J Adv Med 2019;6:1277-80.