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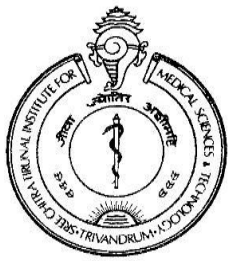

A COMPARATIVE STUDY ON CLINICAL AND RADIOLOGICAL PROFILE OF NMO SPECTRUM DISORDERS AND MOG ANTIBODY ASSOCIATED DEMYELINATION

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

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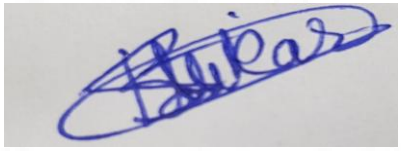
DECLARATION

I, **Dr. Radhika Sanjay Lotlikar**, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.



Thiruvananthapuram **Dr. Radhika Sanjay Lotlikar**

Date: 09-08-2021.

FORWARDED

The candidate, Dr Radhika Sanjay Lotlikar, has finished the project under my guidance.

Thiruvananthapuram,

Date: 09-08-2021.

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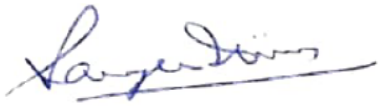
FORWARDED

The candidate, Dr Radhika Sanjay Lotlikar, has completed the minimum work required for the project.



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Dr . Radhika Sanjay Lotlikar

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SYNOPSIS

BACKGROUND AND PURPOSE: Recently described myelin oligodendrocyte glycoprotein antibody associated demyelination (MOGAD) has emerged as a distinct entity from neuromyelitis optica spectrum disorders (NMOSD). We aimed to compare the clinical, therapeutic and radiological profile among aquaporin—4 antibody (AQP4-Ab or NMO-IgG) positive NMOSD, AQP4—Ab negative NMOSD and MOGAD and assess the outcome predictors.

MATERIALS AND METHODS- Patients attending the inpatient/outpatient clinic at Department of Neurology, SCTIMST from January 2016 to March 2021 fulfilling the 2015 international consensus diagnostic criteria for NMOSD and cases with a diagnosis of MOGAD were included in the study. Cases were grouped into AQP4—Ab positive NMOSD, AQP4—Ab negative NMOSD and MOGAD according to serum antibody testing by fixed cell-based assays. These three groups were compared for demographic and disease characteristics including clinical phenotype, serology, radiological features, treatment related parameters and outcome. Outcomes assessed were total number of relapses, time to relapse and severity of disability at last follow-up.

RESULTS- 110 patients were included in the study of which 48 (43.6%) were AQP4—Ab positive NMOSD, 38 (34.6%) were diagnosed as MOGAD and AQP4—Ab negative NMOSD in 24 (21.8%) patients. The mean age of onset was 25.8 ±14.8 years and 30% had pediatric onset (<18 years). Significant female preponderance in AQP4—Ab group (M:F ratio of 1:5) with equalising effect on

other groups were noted (P-0.006). The initial phenotype of isolated optic neuritis (ON) was more common in AQP4—Ab and MOGAD while acute transverse myelitis (TM) was more frequent in AQP4—Ab negative NMOSD. AQP4—Ab negative NMOSD group had frequent isolated brainstem syndrome (P-0.007) and isolated cerebellar syndrome (p 0.001) with rarer ON (p 0.001) presentations. Area postrema syndrome (APS) was exclusively seen in NMOSD (p 0.005). Lhermitte sign (p 0.081) and painful tonic spasms (p 0.027) were exclusive in NMOSD groups predominantly in AQP4—Ab positive patients.

Optic nerve imaging showed predominant long segment involvement with rare chiasmal affliction in MOGAD (p 0.096). Brain imaging showed grey matter involvement in non AQP4—Ab positive groups (p 0.059) and subcortical involvement in MOGAD (p 0.008). Spinal cord imaging showed short segment lesions in 25.8% patients. Predominant location in all groups was cervicodorsal with predominant cervical (p 0.001) and cervico-medullary (CM) affliction(p 0.024) in non-MOGAD groups. Bright spotty lesions in spinal cord were specific for AQP4—Ab positive group (p <0.001). Coexistent serum autoantibodies were distinctly absent in AQP4—Ab negative NMOSD (p 0.024) and present in 20% among other groups. The mean disease duration was 78.8 months and mean follow-up period was 44 months. Among the 110 patients, 83% had relapse which was comparable within groups. Acute therapy was either intravenous or oral glucocorticoids and 95% received maintenance therapy with Azathioprine (53.6%), mycophenolate mofetil (38.2%) and rituximab(20%). Patients on Rituximab had significant lesser relapses in AQP4—Ab positive NMOSD group (p 0.04).

CONCLUSION

The three groups have distinct demographic, phenotypic presentations along with MR imaging features and treatment effects. AQP4—Ab positive NMOSD group had female preponderance and more frequent ON presentations and had shown significantly reduced relapse rate on rituximab. Whereas, AQP4—Ab negative NMOSD has more TM and brainstem presentations and ON presentation was rare. MOGAD has a unique spectrum with rarity of APS, tonic spasms, Lhermitte and chiasmal involvement which can be used for exclusion. The common thread remains the higher propensity for a relapsing course needing early immunomodulatory therapy.

INTRODUCTION

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) has now emerged as a distinct CNS inflammatory disorder with evolving spectrum in the last two decades and has characteristic clinical, pathological and radiological features, different from multiple sclerosis (MS)(1). The recent discovery of detectable highly specific serum antibody targeting the aquaporin 4 water channel protein (AQP4) immunoglobulin G (IgG) in NMOSD paved the way for further studies(2). Antibody detection has a pivotal role in the diagnosis of NMOSD and has led to constantly evolving diagnostic criteria in recent years.(3) This entity is accompanied by multiple unique presentations other than the myelitis and optic neuritis and varied radiological and immunopathological characteristics and temporal profile. The term, Neuromyelitis optica spectrum disorders encompassing the entire clinical spectrum was incorporated in International consensus diagnostic criteria 2015 and was further sub-classified into AQP4 antibody (AQP4—Ab) positive NMOSD (NMOSD AQP4+) and AQP4—Ab negative NMOSD (NMOSD AQP4-) based on the AQP4—Ab serostatus and clinical features. This has led to early diagnosis and formulating therapeutic strategies (4). Studies have revealed that early diagnosis and distinction from MS have significant therapeutic implications as some disease modifying drugs for MS are ineffective or can exacerbate the NMOSD.(5,6)

Initial studies showed a large percentage of patients who were AQP4—Ab negative were subsequently detected to have AQP4—Ab positive which was due to the introduction of cell-based assays. The cell based assays are highly specific and more sensitive than the conventional assays (ELISA or tissue-based

immunofluorescence)(7).However, a subset of persistently seronegative patients under NMOSD was revealed to have a different demographic profile (gender, ethnicity) and initial presentations (more of opticospinal and less severity)(8). Their relapse rate and disability outcomes have not shown significant differences but more in depth research is required for further differentiation for reliable diagnosis and for early management. The AQP4—Ab negative NMOSD has a stringent diagnostic criteria to exclude the mimics (4).

Detection of myelin oligodendrocyte glycoprotein (MOG IgG) by cell based assays in patients with AQP4—Ab negative NMOSD has led to further research and recognition of different entity termed MOG antibody associated disease (MOGAD)(9). They can have presentation similar to NMOSD as well as encephalitis like presentations. However, distinct differences exists between these two entities in the temporal profile with more of monophasic course in MOGAD and different demographic, pathological and radiological patterns(9,10).

The difference in immunopathological mechanisms with seropositive AQP4 NMOSD being an autoimmune astrocytopathy and MOGAD being an inflammatory demyelinating disease are bound to have a differential damaging effect and therapeutic implications(1,11).

The initial studies on NMOSD would have included MOG antibody positive cases diluting the significance of earlier studies. MOGAD has a unique spectrum going beyond the criteria for NMOSD and needs to be given special attention especially with regard to treatment strategies, prognosis and outcomes(12,13).

Hence this study is planned to to describe the clinical, laboratory and radiological features of AQP4—Ab positive NMOSD, AQP4—Ab negative NMOSD and MOGAD. We also aimed to study the treatment strategies both acute and maintenance therapy and outcome differences between these three groups.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Accounts of patients with bilateral visual loss and transverse myelitis has its roots dating back a century. John Abercrombie's edition on pathological and practical researches in Brain and spinal cord in 1829 has a mention of the term 'neuroencephalitis optica' for a case with intractable vomiting, relapsing loss of vision and spinal pain(14). Jacob Augustus Lockhart Clarke reported the case of a seventeen year-old-girl with bilateral optic neuritis and longitudinally extensive transverse myelitis in 1862(15). There were sporadic reports of such occurrences with no unifying syndrome or disease.

The term "Neuromyelitis optica" came into shape when Eugene Devic first used the term in French 'neuro-myélite optique aiguë' in his paper in 1894 to describe a clinical syndrome in a lady characterised by optic neuritis and acute myelitis(16). His student Fernard Gault in his doctoral thesis "De la neuro myélite optique aiguë" (November 1894) reviewed the previous 16 cases and clinicopathologically analysed Devic's cases which led to the Devic's NMO criteria.

EVOLUTION OF DIAGNOSTIC CRITERIA IN NMOSD

For decades, NMO was thought to be a variant of MS with a monophasic presentation restricted to bilateral optic neuritis (ON) and transverse myelitis (TM). Studies in Asian MS population revealed rapid progression and severe involvement of optic nerves and spinal cord along with relapsing patterns(17). This led to a concept of opticospinal MS with relapsing forms restricted to these sites and

included minor brainstem signs with classic Devic's NMO and classic MS being the two extreme spectrums of the continuum. However gradual studies on clinical, immunopathological and imaging findings have corroborated the distinct differences in both groups and has resulted in opticospinal MS and relapsing NMO to be considered not a separate entity(18). Many criterias since then have been put forth to define the clinical syndrome. Wingerchuk et al's diagnostic criteria for NMO was formulated in the year 1999 from a series of 71 patients in Mayo Clinic which included magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) features along with severity of the attack(19). Lennon et al reported an autoantibody unique to NMO in 2004 whose target was later identified as AQP4, a major water channel protein in central nervous system (CNS) predominantly on astrocytic foot processes(2). Before the advent of antibody detection, a distinct difference in behaviour of the syndrome led to typifying 2 groups as monophasic and relapsing NMO . Wingerchuk and Miyazawa et al highlighted the differences with relapsing NMO showing female preponderance, older age at onset, higher coexisting autoimmunity (30%) while monophasic subtype had concurrent opticomyelitis at onset and younger age (19,20).

The criteria was further revised in 2006 to include the AQP4 positive serostatus and nonspecific brain lesions found in MRI which were not typical for MS(3). The criteria was validated and became a standard for clinical and research. Around 19–31% of seropositive patients were found to have limited forms of NMO, and 20% patients did not fulfill the proposed criteria even after ten years follow up. In 2007, the term NMO spectrum disorder (NMOSD) was introduced to include the seropositive patients with these limited forms, other typical brain sites and other

autoimmune associations(21). In order to correctly delineate NMO from MS due to grave therapeutic implications, heterogeneity and widening of spectrum after detection of AQP4 antibody seropositive patients and early diagnosis of antibody negative patients with exclusion of other etiologies an International Panel for NMO Diagnosis (IPND) was convened to form an International consensus diagnostic criteria in 2015. Panel recommended an unifying term of NMOSD along with different criteria stratified according to serostatus with negative status having a stringent diagnostic criteria with additional neuroimaging findings along with red flags if there is diagnostic dilemma(4). The seropositive status was included irrespective of the phenotype which led to widening of spectrum further. Thus, NMOSD was subdivided into AQP4—Ab positive NMOSD and AQP4—Ab negative NMOSD.

Diagnostic assays in NMOSD

Detecting AQP4 antibodies is of prime importance in the accurate diagnosis of NMOSD and its management as the immunopathology and profile is unique for each subtype. The AQP4 antibody was first detected by indirect immunofluorescence with a mouse tissue composite substrate(2). A study on 181 suspected NMOSD cases from 23 centres in 2019 assessed for antibodies through the five different assays have found that the sensitivity of both fixed and live cell-based assays was greater (90–94%) than ELISA (60%) or tissue indirect immunofluorescence (78%)(22). All assays were highly specific (≥97%) with fixed cell-based AQP4 and live cell based assays being 100% specific. False positives were more common amongst cases with MS and other inflammatory diseases. The 2015 international consensus criteria

recommends testing with cell-based serum assays (microscopy or flow cytometry-based detection) to optimise detection with mean sensitivity of 76.7% in a pooled analysis(4).

Indirect immunofluorescence assays and ELISAs with lower sensitivity (mean sensitivity 63%–64% each) and occasional false-positive results (0.5%–1.3% for ELISA) at a low titre may miss out the outliers and could have lead to dilution of the results in the previous studies which used these assays predominantly.

Antibody negative NMOSD (NMOSD AQP4-)

Even though the NMOSD with AQP4—Ab positivity rate increased after the newer cell based assays, some cases showed persistent negativity on repeated antibody testing. This subtype has been not explored efficiently due to initial studies missing the seropositive patients and masquerading the actual comparison(22). A French study with cell based assays showed seronegative patients to have equal prevalence in males and females with more opticomyelitis as initial phenotype and reduced severity of visual impairment as against the seropositive patients(23). Other study by Mayo group corroborated these findings(24). The earlier monophasic NMO group by Wingerchuck et al reflects the now antibody negative NMOSD group predominantly. The stringent criteria to define seronegative NMOSD patients have led to lesser known clinical spectrum and possibility of another underlying immunopathogenic mechanism(4).

MOG antibody associated disease

After the introduction of cell-based assays (CBA) and role of conformational epitopes of myelin oligodendrocyte glycoprotein (MOG) in human demyelination, a new spectrum of inflammatory demyelinating disorder of CNS, MOG antibody associated diseases (MOGAD) has emerged in the last decade. Association of anti-MOG antibodies in pediatric population presenting as acute disseminated encephalomyelitis (ADEM) were first identified by O'Connor et al(25).

In AQP4—Ab negative NMOSD population, Mader et al identified presence of MOG antibodies by CBA which led to a unique phenotype amongst AQP4—Ab negative NMOSD. These patients had younger age at onset, less female preponderance, ADEM at presentation, recurrent ON, simultaneous bilateral ON or recurrent longitudinally extensive transverse myelitis (LETM)(26). Initial studies suggested monophasic course however relapsing cases are described in various studies(13). Further studies have expanded the spectrum of MOG beyond the NMOSD spectrum in the form of isolated ON, LETM, or ADEM, Brainstem and cerebral cortical encephalitis which led to its separate classification as "MOG antibody associated demyelination" (MOGAD)(10). The recent study on MOGAD population showed slight female preponderance, with major initial presentations as isolated optic neuritis (55% with almost half bilateral), transverse myelitis (18%) or ADEM (18%) with moderate relapse risk and residual disability predominantly in bladder function(12).

Comparison between the groups: NMOSD AQP4—Ab positive, MOGAD and NMOSD AQP4—Ab negative groups

Pathophysiological differences

Pathological studies indicate AQP4 seropositive NMOSD cases have astrocyte as the major substrate for immune attack with astrocytic destruction being more extensive than demyelination suggesting an autoimmune astrocytopathic disease(1). MOG-antibody-seropositive disease on the other hand has oligodendrocyte as the immune target suggesting an inflammatory demyelinating disease(11). The AQP4—Ab negative NMOSD (NMO—IgG and MOG—Ab negative) needs to be explored for its unique spectrum and its postulated that it acts through a different autoimmune mechanism other than AQP4 pathway and needs further exploration to detect unique biomarkers.

Acute exacerbations of AQP4—Ab positive NMOSD and MOGAD have significant upregulation of TH17 related inflammatory cells suggesting that disease modifying therapies for MS like interferons could not efficiently suppress the relapses due to their limited action on TH17 pathway(5).

Other autoimmune antibody associations

Occurrence of other antibody formation without a disease and coexistence of other autoimmune conditions in NMOSD is confirmed in several studies with theories for pathological mechanisms proposed as sharing of genetic and

environmental factors, AQP4—Ab production as an epiphenomenon, and vasculopathy and disruption of blood brain barrier with entry of AQP4—Ab to CNS (27). Among the systemic autoimmune diseases, SLE and Sjogren syndrome have the most common associations while myasthenia gravis and autoimmune thyroid disease are the most common organ specific autoimmune associations. Autoimmune tendency of NMOSD seropositive patients are more likely to have associated antibodies and has been reported in 38-75% patients in previous studies(28). Most commonly encountered being antinuclear antibody, antiphospholipid, anti SSA, anti TPO in different series. One study showed ANA-positive NMOSD to have a milder disease severity as against anticardiolipin positive NMOSD(29,30). The prognostic and therapeutic implications are yet to be explored in a larger series. In MOGAD cases, a multi-centre study showed concomitant autoimmune disorders in only 8.5%; however coexisting autoantibodies were present in 42% cases most commonly antinuclear antibodies (ANA) followed by cardiolipin antibodies(31).

Epidemiological differences

Literature review highlights higher NMOSD prevalence among East Asians (3.5/100,000) as compared to Caucasians and other Asian races with higher incidence among non-whites(32). The prevalence among South Indians was around 0.72 per 1,00,000(33). There are studies suggesting racial differences or ethnicity having effect on age at onset, the clinical phenotype and severity of NMOSD. Asian and African origin patients had a younger age of onset than the Caucasian cases amongst the NMOSD population.

Familial cases have been reported with HLA associations with NMOSD susceptibility which may account for the phenotypic variability among ethnic groups. MOGAD did not show any racial preponderance in hospital-based studies(32). Nationwide Dutch study reported the annual incidence of MOGAD as 1.6/million population

Demographic characteristics

AQP4—Ab positive NMOSD has a higher female preponderance while MOGAD and AQP4—Ab negative NMOSD seem to have an equalizing effect on gender(34,35). The age of onset for NMOSD is in the fourth decade (35-45 years) with elderly and children accounting for 18%. Females account for 70-90% cases however no gender predilection is seen in pediatric patients(36). Published series majorly suggest that MOGAD have an earlier age of onset with a wider spectrum ranging from 6 to 70 years(13).

Phenotypic characteristics

From the initial consideration of restricted involvement of optic nerve and spinal cord, the AQP4 antibody discovery led to a much more wider spectrum with involvement of AQP4 expression rich regions in CNS leading to inclusion of variety of syndromes according to location such as brainstem, area postrema, diencephalic and cerebral symptoms and signs. The subsequent addition of these syndromes as core clinical characteristics in the 2015 criteria led to early diagnosis of NMOSD despite AQP4—Ab negativity (4). The largest series of NMOSD seropositive cases

shows initial presentation of myelitis in 48% followed by ON (42%). Isolated area postrema was seen in10% and simultaneous occurrence of ON and myelitis in 4%. While myelitis and ON are predominant manifestations in NMOSD, brain/brainstem attacks occurred in 35% of patients throughout the disease course and area postrema syndrome (APS) occurred in 15%. Around 45% patients, the initial attack was severe (37). TM in seropositive cases were also severe causing sensorimotor signs symmetrically along with sphincter abnormalities(19). Extension of the cervical lesion rostrally involving medulla may lead to respiratory dysfunction and hiccups in these cases. Area postrema being the AQP4 rich area with no blood brain barrier and high vascularity frequently gets involved with isolated presentations of incoercible hiccups, nausea or vomiting as well as by cervical extension(38).

ON is distinguished by bilateral involvement with more severity at the onset, showing a relapsing course and poor recovery with residual deficit. Field and sectoral defects and bitemporal hemianopia is commoner due to long segment and chiasmal involvement in seropositive NMOSD as against other syndromes(39).

Brainstem involvement is commoner in NMO seropositive cases mostly among the non-Caucasians. Brainstem syndrome is seen in around one third cases with 50% as an initial presentation with symptoms of intractable vomiting (area postrema), hiccups (periaqueductal midbrain lesions), oculomotor abnormalities and also rare presentations of cranial nerve dysfunctions in the form of hearing loss, vertigo, facial paresis and trigeminal neuralgia(40). Diencephalic involvement in the form of narcolepsy, hypothermia and hypersomnolence has been noted in few cases.

In a recent study on initial non-optico-spinal manifestations in NMOSD which were found to be more in younger populations and with lower titre of AQP4—Ab, the areas involved in majority were the area postrema (44.83%), brainstem (20.69%) presenting as hiccups, vertigo, dysphagia or sensorimotor signs and facial palsy followed by parabrachialis involvement manifesting as diplopia, tinnitus, vertigo, facial palsy and facial numbness(41). The other presentations being of diencephalic (somnolence or psychiatric features) and cerebellar involvement with limb or gait ataxia and also cerebral (hemispheric) presentations.

Various case reports exploring the spectrum of NMOSD have been reported in recent years with cases having rare manifestations such as intractable pruritis, cervicogenic headache, hemi-aguesia, trigeminal cephalgia, hydrocephalus, wall eyed bilateral internuclear ophthalmoplegia , hearing loss and hyper CK emia(42). Other rare symptoms/syndromes that have been reported include hyposmia, posterior reversible encephalopathy syndrome (PRES), meningoencephalitis, behavioural disturbances and cognitive dysfunction.

MOGAD encompasses various presentations with clinically distinct phenotype in adults and pediatric population. In half of the episodes, the demyelinating attacks were found to be preceded by an infectious prodrome. In a study of 59 cases with relapsing MOGAD, the most common phenotype was found to be ON predominantly presenting initially as bilateral optic neuritis and majority being adults. ADEM like presentation was exclusively found in children while TM was commoner in adults(13). In another UK based cohort, a female predominance was seen with isolated ON being the most common phenotype with almost half

bilateral and others being isolated TM (18%) with majority LETM (14%) and 18% with ADEM like presentations and 9% with simultaneous ON and TM. ADEM like presentations were predominant in pediatric population whereas unilateral ON in younger adults and bilateral ON in older adults (43) There has been reports of focal and generalised seizures manifesting in MOGAD cases which can be in a background of a cortical encephalitis or ADEM like presentations or due to coexistent anti N-methyl-D-aspartate (NMDA) receptor encephalitis(44).

MOGAD cases with isolated ON were found to have recurrent ON in around 50% of patients. Two rare phenotypes have been associated with MOGAD, namely, chronic relapsing inflammatory optic neuropathy (CRION) which is steroid dependant and relapsing isolated optic neuritis (RION)(45). Very rare cases of MOGAD perineuritis have been reported without optic nerve involvement. Keratitis or uveitis simultaneously or after MOG-Ab positive ON has been noted.

TM commoner in adults with MOGAD and can affect any location. However, inflammation has a predilection for conus, explaining the higher incidence of neurogenic bowel and bladder involvement. Also rare reports of myelo-radiculitis has been noted involving the sacral nerve roots(46). Recurrent ADEM or ADEM like phenotype including multiphasic ADEM or associated with ON is characteristic of MOGAD especially in pediatric population. Cerebral symptoms are commoner in children and entities like FLAIR-hyperintense lesions in anti-MOG associated encephalitis with seizures (FLAMES) have been reported with presentations of encephalitis and steroid responsive focal onset tonic clonic seizures, headache and fever(47).

Brainstem involvement is found in 30% of the cases in association with other phenotypes and sometimes isolated. Any area can be involved but most common being medullary involvement. Disabling symptoms like motor weakness, cranial nerve dysfunction, ataxia, hypoventilation syndrome and impairment of consciousness have been reported. MOGAD can resemble infectious brainstem encephalitis presenting with fever and CSF leucocytosis with leptomeningeal enhancement or present as CLIPPERS (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids)(46).

Radiological spectrum

MRI is one of the essential tool for early diagnosing of NMOSD and to differentiate it from MS and other inflammatory disorders leading to appropriate management decisions. It is also vital for patients with seronegative NMOSD or whose AQP4 status is unknown to get an early diagnosis and treatment.

The initial diagnostic criteria of NMOSD in 2006 already had an inclusion of spinal cord imaging(3). Distinguishing it from MS by the length of the lesion. The criteria required lesion to be longitudinally extensive characterised by longitudinal involvement of three or more contiguous vertebral segments. NMOSD preferentially involve the grey matter along the central canal reflected in MRI involving more than fifty percent axial area involvement located centrally or both central and peripherally; predominant location being cervical and thoracic with extension to the brainstem region(48). Cord swelling and irregular non-homogenous enhancement can be seen in acute phases with severe or recurrent myelitis resulting in extensive

cord atrophy progressively. Yonezu et al highlighted the “bright spotty lesions” with strong T2 hyperintensity and dark T1 to be relatively specific for NMO suggesting the necrotic and microcystic changes from intrinsic cord demyelination(49). Short lesions with less than three vertebral segments are not uncommon and represent at initial presentation in around 14.5% cases; however these lesions are transversely extensive involving central region and are longer than MS lesions(50)

Optic neuritis in NMOSD typically had bilaterally longitudinally extensive optic nerve involvement affecting more than half of the length. It preferentially affects the posterior optic pathway, the intracranial segment with extension to chiasma and optic tract as well. Acute stages is identified by thickened nerve and neural enhancement with chronic stages showing atrophy and variable T2 hyperintensity(51).

Recent studies have shown prevalence of lesions in brain to be variable occurring in 24-89% of NMOSD(52,53). The 2015 NMOSD criteria thus incorporated brain MRI findings leading to defined lesions in NMOSD-typical sites(4). Subcortical or deep white matter lesions are possible with most being silent or nonspecific. The typical brain lesions are in the AQP4 expression sites including the circumventricular organs and peri-ependymal regions. Typical findings include confluent T2 hyperintensities asymmetrically distributed over ependymal lining of lateral ,third and fourth ventricles predominantly near the aqueduct(54). Corpus callosum, typically over the ependymal surface affecting most of the length is reported with acute phase showing oedema and typical arch bridge or marbled appearance(55). Diencephalic lesions include hypothalamus, thalamus or

periaqueductal grey matter (PAG) involvement. The most specific region involved in the brainstem is the peri-ependymal region of dorsal brainstem, area postrema (7-46%). Other distinctive features is the corticospinal tract involvement (23-44% cases) unilaterally or both sides with longitudinal and contiguous extension(54). Few seropositive cases may show tumefactive lesions. Although not frequent, cortical involvement – subpial layer with leptomeningeal enhancement have been reported. Enhancement has been seen variably (9-36%) with most common pattern being cloud like patchy enhancement with other patterns like pencil thin linear and nodular pattern in few cases(48).

In MOGAD, imaging helps distinguishing it from MS but has a significant overlap with features of NMOSD. However distinct differences for areas of predilection have been reported in studies. Spinal cord involvement in MOGAD is found more commonly in lower segments with conus and thoracolumbar spinal segment being preferentially involved(56).

In cases with ON, bilateral affliction with occurrence of optic nerve head swelling and anterior optic nerve involvement is described. Post—contrast imaging showing perineural gadolinium enhancement is characteristic(51). MRI abnormalities in supratentorial and infratentorial regions has been reported in 40-50%. Studies have revealed a distinct distribution of brain lesions in MOGAD patients involving predominantly deep grey matter and infratentorial regions especially the brainstem —often located in pons, adjacent to fourth ventricle and cerebellar peduncles and these lesions has a poorly demarcated pattern. In comparison with adults, pediatric population had numerous larger and fluffy lesions

which were frequently bilateral predominantly in deep grey matter and brainstem(57–59).

Therapeutic options

The need for early and correct differentiation from MS has been emphasized as studies have shown inefficacy of disease modifying therapies of MS like interferons, natalizumab, glatiramer, dimethyl fumarate in NMOSD and also disease exacerbation in few cases(5,6). The clinical relapses in NMOSD have more severe impact and aggressive management in the form of early acute therapies and long term immunosuppressive maintenance therapy for relapse prevention is the ideal approach(60).

Acute therapies

To curtail the ongoing inflammation and hasten recovery, the treatment should be started as early as possible. Parenteral (intravenous, IV) methylprednisolone high dose (1 gram) pulse therapy for 3-5 days is the mainstay treatment advocated(61). Limited data has suggested the use of consequent oral tapering of glucocorticoids to be useful in cases with higher severity(62). However, in refractory cases, plasmapheresis (PLEX) 5-7 cycles along with glucocorticoids that targets both cellular and humoral immune responses has shown to be beneficial. Early PLEX initiation following an attack predicts better remission rates(63).

MOGAD appears to be highly steroid responsive and cases of steroid dependence are higher(64). Typically acute cases are treated with high dose IV glucocorticoids

followed by an oral glucocorticoids which is tapered over few months to 1 year depending on the individualised response(65). PLEX has been tried in cases refractory to glucocorticoids(66).

Maintenance Therapies

Therapy for prevention of relapses in NMOSD and MOGAD is paramount and the treatment option have expanded recently with landmark clinical trials. Therapeutic agents most commonly used are Azathioprine, Mycophenolate mofetil and Rituximab(61). Other therapies like cyclophosphamide, methotrexate and mitoxantrone have shown benefit however their infrequent use and small population studies have precluded a wider efficacy trial(67–69). The choice of therapy is largely decided by the availability, cost, comorbidities, disease severity and side effect profile. Oral glucocorticoids are still being largely used as a long-term therapy or as a bridging therapy to other therapies to act in view of low cost and rapid onset of action. Adverse effects restrain their continuation for a very long time.

Azathioprine

Azathioprine therapy has been commonly used along with concomitant prednisolone to cover the initial period(70). Studies have indicated this concomitant therapy to reduce annualized relapse rate (ARR) by 76%. A greater reduction in ARR was observed with a higher dose of more than 2mg/kg/day. 37 % patients remained relapse free on a follow up of 24 months and 37% discontinued the medication in view of adverse effects(71).

Mycophenolate Mofetil (MMF)

MMF therapy has been beneficial along with initial concomitant prednisolone. Retrospective study in 24 cases showed significant reduction in mean ARR and improved Expanded Disability Status Scale (EDSS) in 91% cases at a median daily dose of 2 grams(72). In a study of 59 cases, ARR reduction of 88%, EDSS stabilisation in 91% and remission rate of 60% was noted. Discontinuation rates observed were 21-24%(73).

Rituximab

Multiple studies have demonstrated the efficacy and tolerability profile of rituximab in NMOSD(74,75). Meta-analysis of 25 studies on rituximab therapy demonstrated decreased ARR and EDSS(75). A prospective study with 7 years follow-up showed 94% cases experience significant ARR reduction and 70% were relapse free(76). A comparative study between the three therapies in 90 NMOSD cases showed superior efficacy of Rituximab and MMF in ARR reduction with lower failure rates when compared to Azathioprine(77).

Newer Therapies

In the recent years, landmark trials such as Prevent, N-Momentum, SAkuraSky have expanded a new option in the form of monoclonal antibodies with a better efficacy and outcome. Eculizumab can be used as an add on therapy in refractory cases on conventional therapies(78). The recent regulatory approval for

therapies in the form of Inebilizumab and Satralizumab have paved their future use as first line therapy in AQP4 positive cases(79,80).

The seronegative group has not been evaluated extensively for the efficacy of these medications. However, from the limited data which is available on the newer medications do not show similar therapeutic benefit in seronegative cases and need to be further studied.

The treatment of MOGAD is extrapolated from the management of NMOSD. Some evidence of relapse prediction by persistent MOG—Ab seropositivity has been reported and decision making regarding initiation of maintenance therapy can be helped by repeat MOG—Ab testing after 6-12 months. A retrospective study on 125 patients showed ARR reduction with Rituximab, MMF and azathioprine with overall EDSS stabilisation(81). A multicentre study showed less relapse with intravenous immunoglobulin (IVIG)(20%) as compared to MMF (74%), Azathioprine (59%) and Rituximab (61%) suggesting maintenance IVIG therapy to be efficacious(82).

Prognostication and outcome

20-30% cases were found to have residual motor and visual disability after the initial event; Early disability had an association with long-term disability outcomes(24). 11% -18% of individuals had vision of 20/200 or less in at least one eye, and 7%- 23% were wheelchair confined in a long term follow up of 5-6 years(83). A outcome study in NMOSD cases showed that the degree of recovery was higher in younger population despite slightly more severe attacks. 85 %

recovery seen at age 20 dropped to 60% at age of 60 suggesting increase in age leading to significant decline in the degree of recovery(84).(85)

In MOGAD studies, mean EDSS at initial presentation was higher in children than the adults. Median EDSS at recovery was higher for later attacks than for earlier episodes. Cumulative disability was noted with none coming to baseline after more than 7 episodes. Patients with ON were less likely to have a final EDSS of more than 2 while presentations with TM were more likely to have sustained residual deficits. Good outcome with no residual disability was noted in 42% of cases. Initial phenotype presenting as ADEM, Bilateral ON and unilateral ON had higher proportion of cases having complete recovery as compared to TM(31,43)

In a study comparing the 3 groups (NMOSD AQP4+, NMOSD AQP4- and MOGAD), patients with MOGAD had lower median EDSS score (1.0, range 0–3.0) than those with NMOSD AQP4+ (4.5, range 1.0–9.0) and NMOSD AQP4- (5.0, range 0–9.0). However, no differences were noted in disease severity at onset, time to first relapse (TTR), ARR and relapse frequency within first 1or 2 years(34).

OBJECTIVES OF THE STUDY

Objectives of the study

1. To compare the clinical and radiological profile of NMO spectrum disorders with AQP4—Ab positive, NMOSD with AQP4—Ab negative and MOGAD
2. To assess the therapeutic strategies and outcome analysis amongst these three groups and to assess the predictors of relapse and prognosticate the severity.

METHODOLOGY

Methodology

The study was a retrospective single centre study which included patients in the outpatient (general OPD and speciality Neuromuscular and MS clinic) and inpatient department of Neurology, Sree Chitra Tirunal Institute for Medical sciences and Technology, Trivandrum from January 2016 to March 2021 who were diagnosed with NMO spectrum disorders or MOGAD. All patients who visited the hospital as newly registered or in the form of follow up were included in the study.

Inclusion criteria:

1. All consecutive patients fulfilling the NMOSD diagnostic criteria(4) with availability of antibody status
2. All patients with primary demyelination and MOG antibody positivity(10)
3. Only the patients whose adequate information regarding clinical attacks , brain and spinal cord MRI are available
4. All age groups irrespective of gender.

Exclusion criteria:

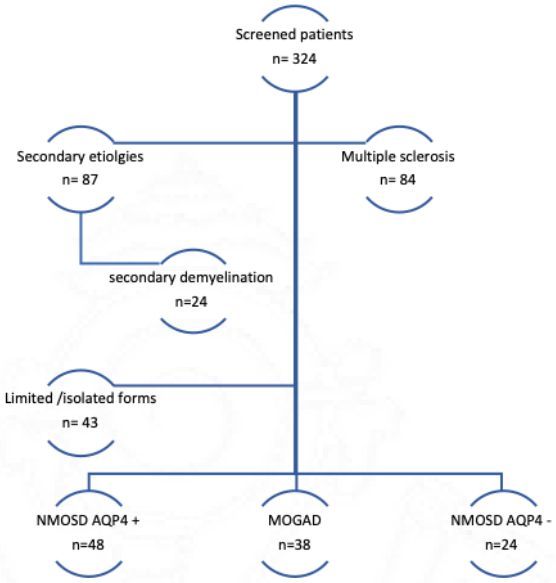
1. Diagnosed as Multiple sclerosis according to revised McDonald criteria 2017(86) and patients on disease modifying therapy for MS.
2. Clinical features indicating and confirmed alternative diagnosis such as sarcoidosis, neoplasms, infective, toxic or metabolic causes
3. Patients whose AQP4 and MOG antibody status is not available or unknown

Methods

Patients were screened retrospectively from the system database by putting the search words as “Neuromyelitis optica”, “NMO spectrum disorders”, “NMO”, “AQP4 positive”, “aquaporin”, “MOG”, “MOGAD”, “Optic neuritis”, “LETM”, “Transverse myelitis”, “Demyelination”. Patients were screened to look for secondary causes of demyelination and patients whose clinical features indicate and confirmed alternative diagnosis were excluded.

Patients were screened for antibody testing. Patients who were tested for AQP4—Ab and MOG-Ab in cases of seronegative AQP4 antibody were included in the study.

Study groups: Patients who fulfilled the International consensus criteria for NMOSD 2015(4) in both seropositive and seronegative cases were included and were sub-classfied as NMOSD with AQP4—Ab positive and NMOSD AQP4—Ab negative groups. In NMOSD AQP4—Ab negative group, MOG—Ab was also negative. All patients with clinical features indicating demyelination and MOG antibody positive were included under MOGAD group. Serum sample was tested for anti-MOG and aquaporin-4 antibodies using a commercially available fixed cell-based assay (Indirect Immuno-Fluoroscence Test – IIFT) (Euroimmun, Lübeck, Germany) at a dilution of 1:10.



Flow chart for screening of patients and selection of study group

Data collection: Evaluation of eligible patients during their visit or chart review was done with respect to demographic characteristics, age at disease onset, phenotypic presentations, MR based imaging characteristics, serology with CSF findings, therapeutic strategies and outcome. Detailed data was collected in a structured format by using the concerned proformas. Data regarding the disease onset, course of the disease and specific detailed information about each event with its phenotypic expression were noted. Association of other clinical findings such as Lhermitte sign and painful tonic spasms were also recorded.

Predominant clinical features at presentation were classified into following phenotypic groups

1.Isolated optic neuritis

2.Isolated transverse myelitis

3.Simultaneous optic neuritis and transverse myelitis

4.Brainstem syndrome

5.Isolated Area postrema syndrome

6.Diencephalic

7.Hemispheric/cerebral

8.ADEM

9.Isolated cerebellar

10.Mixed presentations

MR imaging characteristics: Event MRIs which were taken within the first six months of event onset in all the eligible patients were screened. Neuroradiologist and neurologist reviewed the MR images — optic nerves, brain and spinal cord with appropriate sequences.

Serological characteristics: CSF examination was assessed in available cases for cytology, protein and sugar along with oligoclonal band (OCB) and IgG index. Other coexistent serum autoimmune antibody positivity association was noted in available cases.

Therapeutic strategies: Details regarding the treatment given after each event were noted. Acute therapy was defined as treatment intended to be given for a period of less than or equal to three months. The initial therapy and multiple therapies used were recorded along with duration of therapy. In case of glucocorticoids, dose and total duration of treatment was noted. Side effects or adverse effects after each drug were noted. Data regarding maintenance therapy, the drug, its dose, duration of treatment and side effect side effect profile was also recorded.

Outcome variables: Variables predicting the prognosis, relapse rates, progression, long term treatment outcome and disability was assessed among these three study groups. Relapse was defined as recurrence of event or new onset symptoms after completion of one month after the previous event onset. Total number of relapses in each patient with or without therapy and on individual maintenance therapy (MT) were noted. Time to first relapse among the relapsing cases and time to relapse after initiating MT were noted for prognostication of groups.

Disability in all patients at last follow up were noted and was divided into 3 groups for prognostication of outcome.

1. Mild – Includes cases with very mild residual disability or near normal patients not affecting their daily routine activities; visual disability less than 6/18 in worse eye
2. Moderate—Needs minimal support for ambulation and partially dependant for daily activities; visual disability from 6/18 to 6/60 in worse eye.
3. Severe disability—patients who are bed bound or need two persons support to walk; completely dependant for activities of daily living; visual disability > 6/60 in either eye.

STATISTICAL ANALYSIS

Statistical analysis

The data was analysed using SPSS version 26 software (SPSS Inc, Illinois, Chicago). Categorical variables were analysed in proportions and compared using Chi square test of Fishers exact test. Numerical variables were analysed using mean and Standard Deviation and compared using ANOVA. Multinomial logistic regression was attempted; however no significant model was obtained. Binary logistic regression was attempted with only NMO and MOG with variables used as age of onset, disease duration, gender, follow-up duration, initial presentation, Lhermitte, painful tonic spasms and other serum autoantibodies. $P < 0.05$ was considered to be statistically significant.

RESULTS

Results

Total 110 patients fulfilled the inclusion criteria who comprised the study population. Among them, 48 patients (43.6%) were NMOSD AQP4—Ab positive, 38 (34.6%) were MOGAD and 24 (21.8%) were NMOSD AQP4—Ab negative.

1. Demographic profile

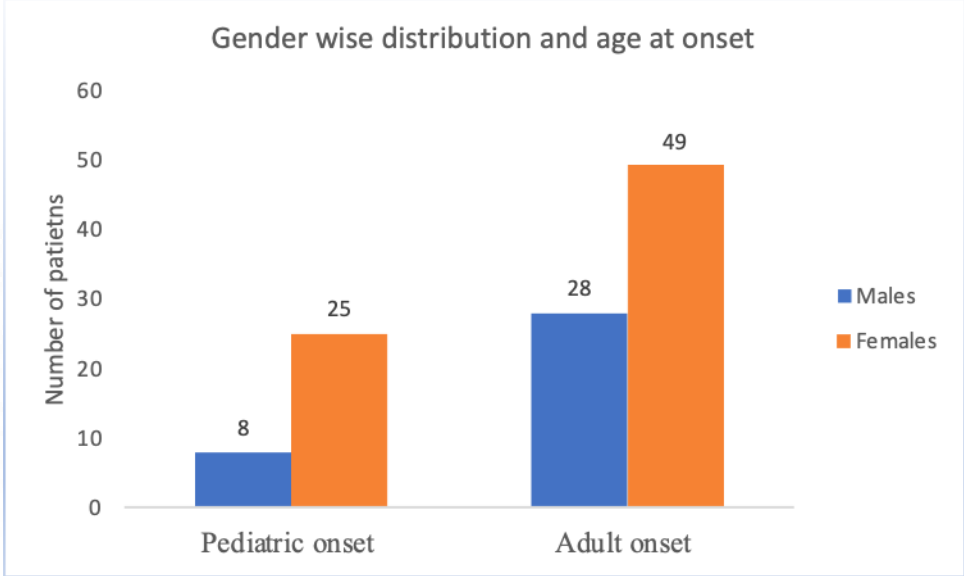
1.1 Age at onset

Mean age at onset was 25.8 ± 14.8 years. Mean age at last follow up was 32.2 years ± 14.8 years. 33 patients (30%) had onset of demyelinating events below 18 years of age and 77 (70%) had adult onset. Out of the adult population, 3 patients had older age of onset (more than 60 years of age) (Figure 1).

1.2 Gender

Among 110 patients, 74 (67.3%) were females and 36 (23.7%) were males(Figure 1).

Figure 1: Gender and age wise distribution of the study group

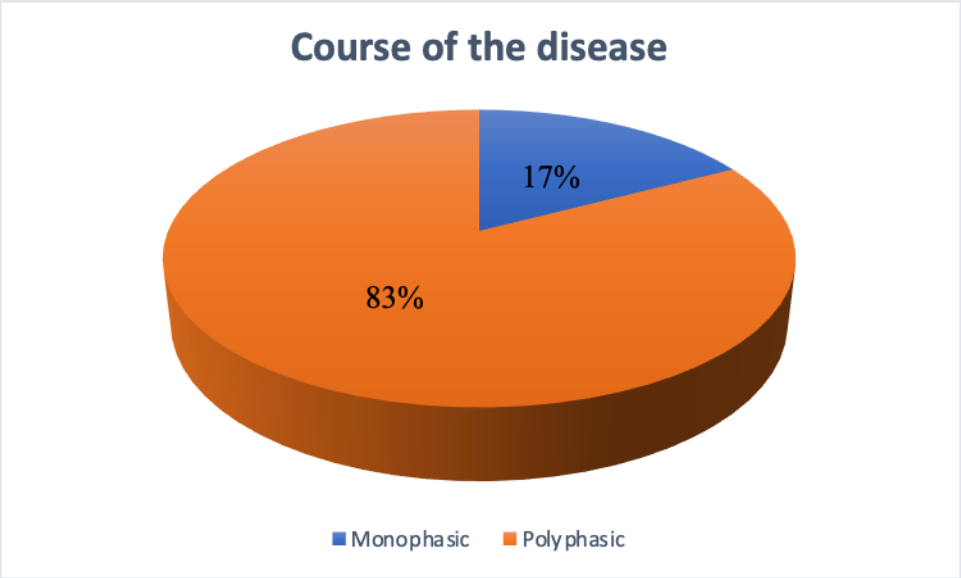


2. Disease Characteristics

2.1 Course of the disease

91 patients (82.7%) had a relapsing course while 19 (17.3%) had monophasic course. The mean disease duration from the first event till the last follow up was 78.8± months(Figure 2).

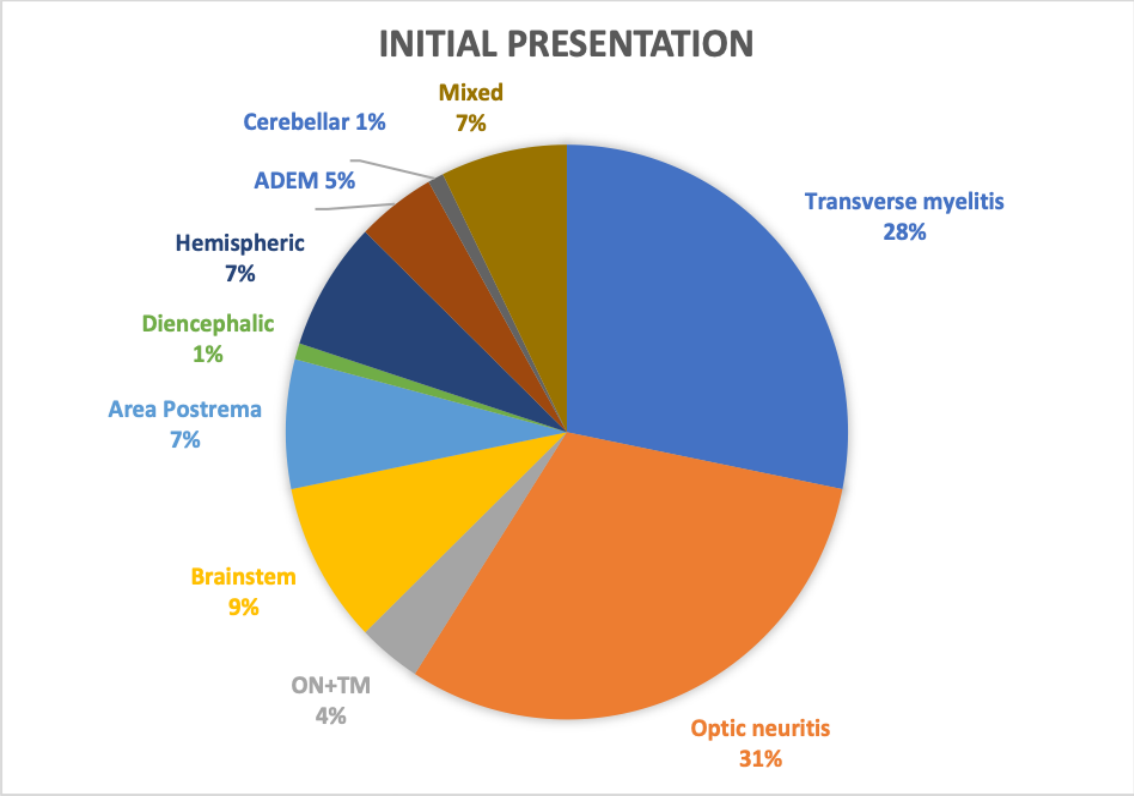
Figure 2- Course of the disease in the study group



2.2 Initial Presentation

Isolated optic neuritis (30.9%) was the most common initial presentation followed by isolated transverse myelitis (28.2%) and brainstem syndrome (9.1%). 4 patients had simultaneous ON and TM. 8 cases (7.3%) each had isolated area postrema syndrome and isolated hemispheric presentation. One patient each had isolated diencephalic and cerebellar presentation(Figure 3).

Figure 3: Phenotype at initial presentation in the study group



Among the patients with mixed presentations (8), three were MOGAD cases with one patient with cortical and subcortical involvement in the form of parkinsonism, frontoparietal dysfunction and myoclonus whereas another patient had

behavioural changes with episodic memory loss and limb ataxia. The third patient had focal seizures with diplopia and blurring of vision.

Among NMOSD AQP4 positive patients with mixed presentations (2), one patient had mixed brainstem and diencephalic presentation and the other had combined brainstem and TM presentation.

The three NMOSD AQP4 negative patients with mixed presentations, one had APS and ON, one with APS and cerebellar presentation and other patient had hemispheric and ON presentation.

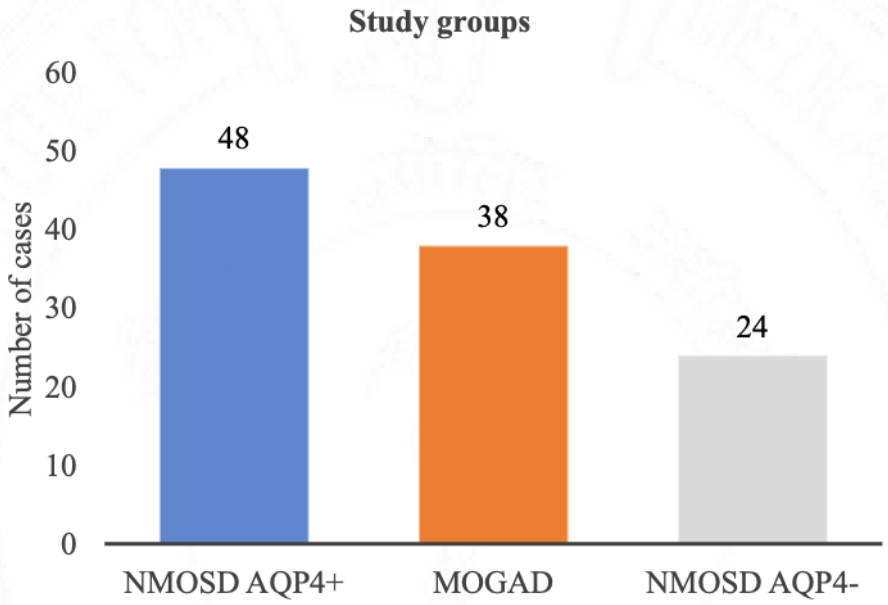
2.3. Number of events with maximum deficit event

The median number of total demyelinating events was 3 (range 1-16). Among the relapsing patients, maximum deficit occurred after the second event in 31 (34.1%) patients while 82 (90.1%) patients had experienced their maximum disability within the first four events.

3. Antibody positivity and grouping of the study population

The study population consisted of 48 (43.6%) patients with AQP4 antibody positive NMOSD and 38 (34.6%) patients with MOGAD based on cell-based assay; while 24 (21.8%) patients who were seronegative for both AQP4 and MOG antibodies were labelled as NMOSD with AQP4—Ab negative (Figure 4).

Figure 4: Antibody grouping within the study group



Comparison between the 3 distinct groups- NMOSD AQP4 positive, MOGAD and NMOSD AQP4 negative groups

4.Demographic characteristics

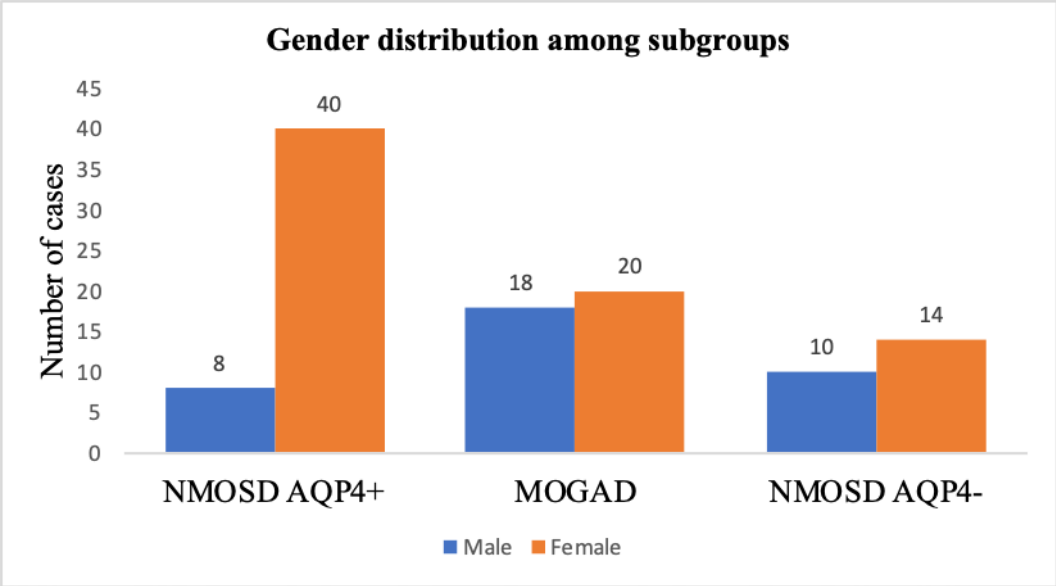
4.1 Age at onset

The mean age at onset was 24.9 ±15.7, 26.5±12.9 and 25.4 ±16.6 years in NMOSD AQP4 positive, MOGAD and NMOSD AQP4 negative groups respectively (p 0.895). Around two-third patients in each group had age of onset after 18 years of age while pediatric onset was seen in around one third. Age at onset >60 years was seen in only 3 cases (MOGAD—2 and NMOSD AQP4+ —1).

4.2 Gender Differences

There was significant female preponderance in NMOSD AQP4 positive group with a male to female ratio of 1:5 while MOGAD and NMOSD AQP4 negative groups had an equalizing effect on the gender (p 0.006) (Figure 5).

Figure 5: Gender distribution in the three groups



4.3 Course of the disease

Majority of the patients in all the three groups had a relapsing course. Relapsing course was found in 22/24 (91.7%) patients in NMOSD AQP negative group which was higher than in AQP4 positive (39/48, 81.3%) and MOGAD (30/38, 78.9%) but the difference was not statistically significant.

Table 1: Course of the disease in subgroups

Course	NMOSD AQP4+ (n-48)	MOGAD (n-38)	NMOSD AQP4- (n-24)	P Value
Monophasic	9 (18.8%)	8 (21.1%)	2 (8.3%)	0.470
Polyphasic	39 (81.3%)	30 (78.9%)	22 (91.7%)	
Mean number of events ± SD	3.8±3.1	3.3±2.2	3.3±1.4	0.542

A total of 384 events were reported in the study population of which 182 events were in NMOSD AQP4—Ab positive group while 124 were in MOGAD and remaining 78 were in NMOSD AQP4—Ab negative group.

The median number of demyelinating events per patient was three in all the groups. The maximum number of demyelinating events reported by patients was 16, 9 and 6 in NMOSD AQP4 positive, MOGAD and NMOSD AQP4 negative groups respectively. The second event was associated with maximum disability irrespective of the subgroup (p 0.310).

4.4 Disease duration and follow-up

The mean follow-up duration in MOGAD was 27.7 months which was less when compared to the other two groups (p 0.022). However, the disease duration from onset was not significantly different among the groups.

Table 2: Disease duration and follow-up in subgroups

Study groups	Mean duration from onset ± SD	Mean duration of follow-up ± SD
NMOSD AQP4 +	91± 75.6	53.9± 51.8
MOGAD	70.9± 80.1	27.7± 24.4
NMOSD AQP4-	67±52.8	49.5± 51.5
P value*	0.302	**0.022**

***ANOVA**

5. Clinical presentations

5.1 Initial clinical presentation—group differences

The most common initial clinical presentation in NMOSD AQP4—Ab positive and MOGAD was isolated ON followed by isolated TM. NMOSD AQP4—Ab negative patients presented most commonly as isolated TM followed by brainstem syndrome.

Isolated ON presentation was more common in MOGAD (42.1%) as compared to NMOSD AQP4—Ab positive (33.3%) and negative (8.3%) groups (p 0.018**)**. APS presentation was not reported in MOGAD. ADEM—like presentation was seen 5 patients of which 4 were MOGAD and 1 was NMOSD AQP4—Ab positive.

Table 3: Initial clinical presentation in the three study groups

Initial Presentation	NMOSD AQP4 +	MOGAD	NMOSD AQP4 -	P value
Transverse Myelitis	14 (29.2%)	10 (26.3%)	7 (29.2%)	
Optic Neuritis	16 (33.3%)	16 (42.1%)	2 (8.3%)	**0.018**
ON+TM	2 (4.2%)	0	2 (8.3%)	
Brainstem	4 (8.3%)	2 (5.3%)	4 (16.7%)	0.350
Area Postrema syndrome	6 (12.5%)	0	2 (8.3%)	**0.061**
Diencephalic	1 (2.1%)	0	0	
Hemispheric/cerebral	2 (4.2%)	3 (7.9%)	3 (12.5%)	
ADEM	1 (2.1%)	4 (10.5%)	0	0.119
Cerebellar	0	0	1 (4.2%)	
Mixed	2 (4.2%)	3 (7.9%)	3 (12.5%)	
Total	48	38	24	

*Fisher exact

5.2 Total clinical phenotypic presentations—group wise

When all demyelinating events were analysed, isolated optic neuritis (41.1%) was more frequent followed by isolated transverse myelitis (27.6%). Isolated ON was more common in MOGAD (50%) and NMOSD AQP4—Ab positive (42.3%) as compared to NMOSD AQP4—Ab negative group (24.4%) and the results were statistically significant. Brainstem syndrome was more common in NMOSD AQP4—Ab negative group (16.7%) as compared to other two groups (p 0.007). ADEM-like presentation was more frequent (p 0.018), whereas none had APS in MOGAD (p 0.005).

Table 4: Clinical presentations of total events in three groups

Clinical phenotype	NMOSD AQP4+ (n-182)	MOGAD (n-124)	NMOSD AQP4- (n-78)	Total (n-384)	P value
Transverse Myelitis	55 (30.2%)	27 (21.8%)	24 (30.8%)	106 (27.6%)	
Optic Neuritis	77 (42.3%)	62 (50%)	19 (24.4%)	158 (41.1%)	**0.001**
ON+TM	6 (3.3)	5 (4%)	5 (6.4%)	16 (4.2%)	
Brainstem	15 (8.2%)	5 (4%)	13 (16.7%)	33 (8.6%)	**0.007**
Area Postrema	12 (6.6%)	0	3 (3.8%)	15 (3.9%)	**0.005**
Diencephalic	1 (0.5%)	1 (0.8%)	0	2 (0.5%)	
Hemispheric	6 (3.3%)	10 (8.1%)	3 (3.8%)	19 (4.9%)	0.14
ADEM	1 (0.5%)	6 (4.8%)	0	7 (1.8%)	**0.018**
Cerebellar	0	2 (1.6)	5 (6.4%)	7 (1.8%)	**0.001**
Mixed	9 (4.9%)	6 (4.8%)	6 (7.7%)	21 (5.5%)	

5.3 Eye involvement

ON constituted 190 (49.5%) of the total events and 152 (80%) had unilateral clinical presentations (p 0.011). Unilateral ON was more common in NMOSD AQP4—Ab positive group whereas bilateral ON was more common in NMOSD AQP—Ab negative group.

Table 5: Pattern of optic neuritis in three groups

Optic neuritis	NMOSD AQP4+(n-94)	MOGAD (n-69)	NMOSD AQP4-(n-27)	Total (n-190)
Unilateral	80 (85.1%)	54 (78.3%)	18 (66.6%)	152 (80%)
Bilateral	14 (14.9%)	15 (21.7%)	9 (33.3%)	38 (20%)

p = 0.36

5.4 Other associated findings in study population

Lhermitte symptom and painful tonic spasms were not reported in MOGAD subgroup of patients and they were more common in NMOSD AQP4—Ab positive cases**.**

Table 6. Associated findings in the three study groups

Associated findings	NMOSD AQP4 +	MOGAD	NMOSD AQP4 -	Total	P value
Lhermitte symptom	6	0	3	9	0.081
Painful tonic spasms	8	0	4	12	**0.027**

6. Magnetic resonance imaging parameters

Event MRI was available for 177 events out of which 76 belonged to NMOSD AQP4—Ab positive patients, 54 of MOGAD patients and 47 of NMOSD AQP4—Ab negative patients.

6.1 Optic nerve involvement in MRI

88 MRI had optic nerve involvement of which 45 were NMOSD AQP4 Ab—positive, 25 were MOGAD and 18 were NMOSD AQP4—Ab negative group.

The laterality, segment involved, length of the involvement, presence of disc swelling, and presence of optic atrophy and enhancement are summarised in the table below.

Table 7: Optic nerve involvement pattern in three groups

Optic Nerve	NMOSD AQP4 (n-45)	MOGAD (n-25)	NMOSD AQP4- (n-18)	Total (n-88)	P value
ON Involvement	45	25	18	88	**0.052**
Laterality					0.308
Unilateral	16 (35.6%)	9 (36%)	10 (55.6%)	35 (39.8%)	
Bilateral	29 (64.4%)	16 (64%)	8 (44.4%)	53 ((60.2%)	
Segment involved					0.096
Isolated anterior (A)	6 (13.3%)	8 (32%)	4 (22.2%)	18 (20.5%)	
Isolated posterior (P)	3 (6.7%)	0	0	3 (3.4%)	
A+P	31 (68.9%)	15 (60%)	8 (44.4%)	54 (61.4%)	
A+P+ chiasma	5 (11.1%)	2 (8%)	5 (27.8%)	12 (13.6%)	
Length of segment					0.632
<50%	11(24.4%)	9 (36%)	6 (35.3%)	26 (29.5%)	
>50%	34 (75.6%)	17 (64%)	11 (64.7%)	62 (70.5%)	
Disc Swelling	30 (66.7%)	20 (80%)	15 (88.2%)	65 (73.9%)	0.243
Atrophy	21 (46.7%)	11 (44%)	6 (33.33%)	38 (43.2%)	0.488
Enhancement (n=contrast sequence available)	(n- 41)	(n-24)	(n-16)	(n-81)	
Neural	25 (61%)	12 (50%)	14 (87.5%)	51 (63%)	**0.052**
Perineural	3	3	1	7	0.371

Bilateral involvement was seen more commonly in NMOSD AQP4—Ab positive and MOGAD subgroups however the difference was not statistically significant. The segment location and the length of the involved segment could not differentiate between the three subgroups.

6.2 Brain involvement

176 MRI scans were analysed for periventricular, white matter, deep grey matter, cortical and infratentorial lesions. Subcortical white matter lesions were more commonly seen in MOGAD subgroup (p 0.008) whereas brainstem involvement was significantly associated with NMOSD AQP4—Ab negative subgroup (p 0.01)

Table 8: MRI brain imaging pattern

Brain lesions	NMOSD AQP4+ (n-75)	MOGAD (n-54)	NMOSD AQP4 - (n-47)	Total (n-176)	P value
Periventricular	25 (33.3%)	24 (44.4%)	13 (27.7%)	62 (35.2%)	0.191
Deep white matter	27 (36%)	24 (44.4%)	11 (23.4%)	62 (35.2%)	0.086
Grey matter	11 (14.7%)	17 (31.5%)	13 (27.7%)	41 (23.3%)	0.059
Corpus callosum	14 (18.7%)	9 (16.7%)	8 (17%)	31 (17.6%)	0.950
Hypothalamus	6 (8%)	10 (18.5%)	6 (12.8%)	22 (12.5%)	0.204
Area postrema	11 (14.7%)	9 (16.7%)	12 (25.5%)	32 (18.2%)	0.299
PAG	8 (10%)	7 (13%)	8 (17%)	23 (13.1%)	0.598
Cerebral peduncle	15 (20%)	12 (22.2%)	12 (25.5%)	39 (22.2%)	0.774
Brainstem	26 (34.7%)	16 (29.6%)	27 (57.4%)	69 (39.2%)	**0.01**
Cortical	7 (9.3%)	5 (9.3%)	9 (19.1%)	21 (11.9%)	0.204
CST	16 (21.3%)	12 (22.2%)	7 (14.9%)	35 (19.9%)	0.601
Juxtacortical	6 (8%)	11 (20.4%)	6 (12.8%)	23 (13.1%)	0.120
Subcortical white matter	17 (22.7%)	23 (42.6%)	8 (17%)	48 (27.3%)	**0.008**
TDL	8 (10.7%)	10 (18.5%)	12 (25.5%)	30 (17%)	**0.099**
Diffusion restriction	6 (8%)	0	3 (6.4%)	9 (5.1%)	**0.08**
Dawson's fingers	4 (5.3%)	1 (1.9%)	1 (2.1%)	6 (3.4%)	0.577

TDL= Tumefactive demyelinating like lesions

Corpus callosum involvement

31 MRIs showed corpus callosum involvement equally distributed in all 3 groups. The most common pattern seen was ependymal (15) followed by arch bridge pattern (12). Both patterns were common in NMOSD AQP4—Ab positive and MOGAD as against the NMOSD AQP4—Ab negative group. Marble pattern was seen in MOGAD (2) and 1 each in other groups. Sandwich pattern was seen in one NMOSD AQP4—Ab negative group. Among the 5 MRIs with cystic pattern, three were present in NMOSD AQP4—Ab positive and two in NMOSD AQP4—Ab negative group.

Brain enhancement patterns

Brain parenchymal or leptomeningeal enhancement was noted in 27 MRIs.

Table 9: Post Gadolinium enhancement pattern in three groups

Enhancement patterns	NMOSD AQP4 + (n-8)	MOGAD (n-10)	NMOSD AQP4 - (n-9)	Total (n-27)	p value
Cloudy/patchy	5 (62.5%)	6 (60%)	4 (44.4%)	12 (44.4%)	0.791
Nodular	4 (50%)	4 (40%)	2 (22.2%)	10 (37%)	0.541
Leptomeningeal	1 (12.5%)	2 (20%)	2 (22.2%)	5 (18.5%)	1

6.3 Spinal cord lesions

Spinal cord involvement was seen in 89 MRIs. Isolated cervical cord involvement was most commonly seen in NMOSD AQP4—Ab negative group as compared to MOGAD (p 0.001). Cervicomedullary (CM) involvement was most commonly associated with NMOSD AQP4—Ab positive subgroup (p-0.024). Involvement of all segments along with conus was significantly higher in MOGAD group (p 0.003). Dorsal cord and conus involvement were exclusively seen in MOGAD.

Table 10: Spinal cord involvement pattern in three groups

Spinal cord involvement	NMOSD AQP4 + (n-43)	MOGAD (n-22)	NMOSD AQP4 - (n-24)	Total (n-89)	p value
Location					
Isolated cervicomedullary	27 (62.8%)	6 (27.3%)	13 (54.2%)	46 (51.7%)	**0.024**
Cervical	18 (41.9%)	1 (4.5%)	14 (58.3%)	33 (37.1%)	**0.001**
Dorsal	2 (4.7%)	2 (9.1%)	0	4 (4.5%)	
Cervicodorsal	19 (44.2%)	6 (27.3%)	9 (37.5%)	34 (38.2%)	0.413
Isolated conus	1 (2.3%)	3 (13.6%)	0	4 (4.5%)	
Cervical+ conus	2 (4.7%)	6 (27.3%)	1 (4.2%)	9 (10.2%)	**0.012**
Dorsal+ conus	1 (2.3%)	0	0	1 (1.1%)	
All segments	0	4 (18.2%)	0	4 (4.5%)	**0.003**
Length of segment					0.580
Short segment	9 (20.9%)	7 (31.8%)	7 (29.2%)	23 (25.8%)	
Long segment	34 (79.1%)	15 (68.2%)	17 (70.8%)	66 (74.2%)	
Axial area					0.573
<50%	14 (32.6%)	6 (27.3%)	10 (41.7%)	30 (33.7%)	
>50%	29 (67.4%)	16 (72.7%)	14 (58.3%)	59 (66.3%)	
Axial Location					0.488
Central	10 (23.3%)	6 (27.3%)	8 (33.3%)	24 (27%)	
Peripheral	1 (2.3%)	0	2 (8.3%)	3 (3.4%)	
Central +peripheral	32 (74.4%)	16 (72.7%)	14 (58.3%)	62 (69.7%)	
Bright spotty	34 (79.1%)	5 (22.7%)	13 (54.2%)	52 (58.4%)	**<0.001**
Cord atrophy	8 (18.6%)	2 (9.1%)	1 (4.2%)	11 (12.1%)	0.194
Multiplicity*	17 (39.5%)	5 (22.7%)	4 (16.7%)	26 (29.2%)	0.106
Enhancement patterns					
Patchy/cloudy	21 (48.8%)	3 (13.6%)	11 (45.8%)	45 (50.6%)	**0.031**
Nodular	4 (9.3%)	2 (9.1%)	2 (8.3%)	8 (8.9%)	1

*= Two or more non-contiguous sites of spinal cord lesions

Figures depicting radiological characteristics in our cohort

Figure 6: Imaging patterns in NMOSD AQP4--Ab positive group

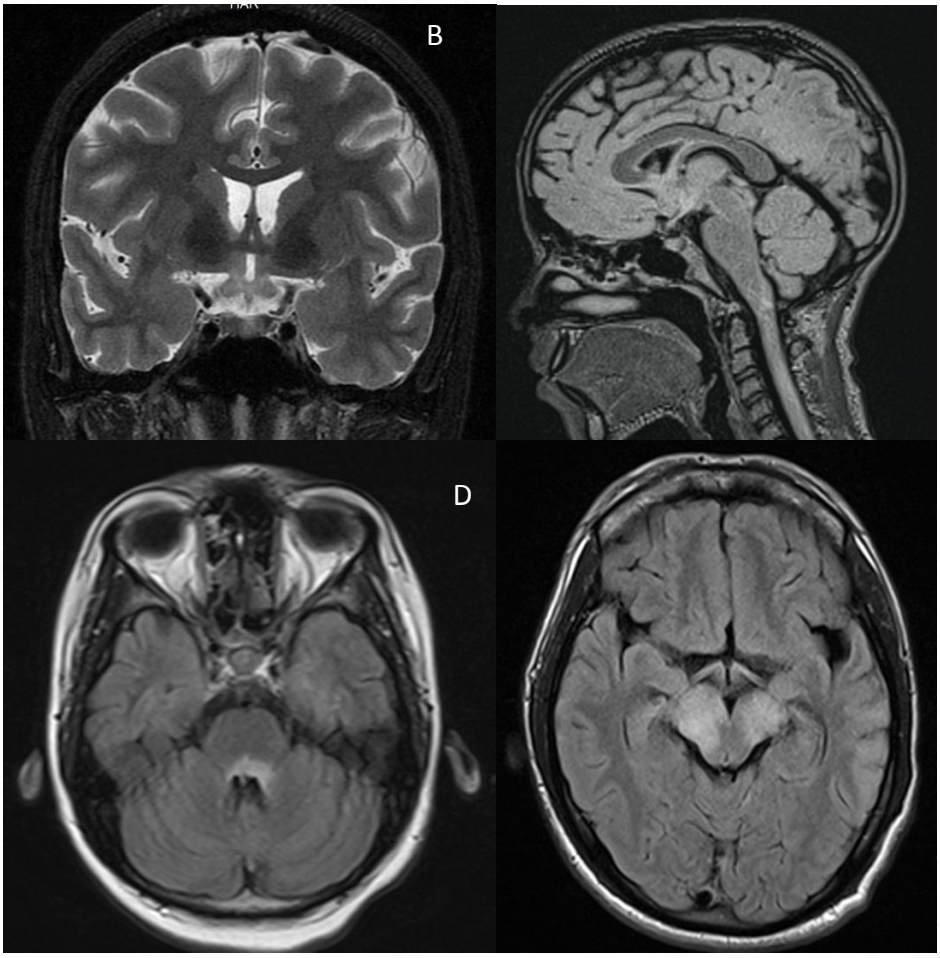


Figure 6- A. A case of bilateral ON with MRI Brain T2 coronal fat supressed image showing hyperintensities involving the optic chiasma and bilateral optic tract. **B.** A case of TM with MRI FLAIR sagittal 3D sequence showing hyperintensities involving cervicomedullary region **C.** Case of recurrent vomiting showing MRI FLAIR axial image with hyperintense area postrema region. **D.** Case of brainstem syndrome with MRI FLAIR axial suggestive of hyperintensity involving midbrain with bilateral cerebral peduncles.

Figure 7: Imaging patterns in MOGAD group

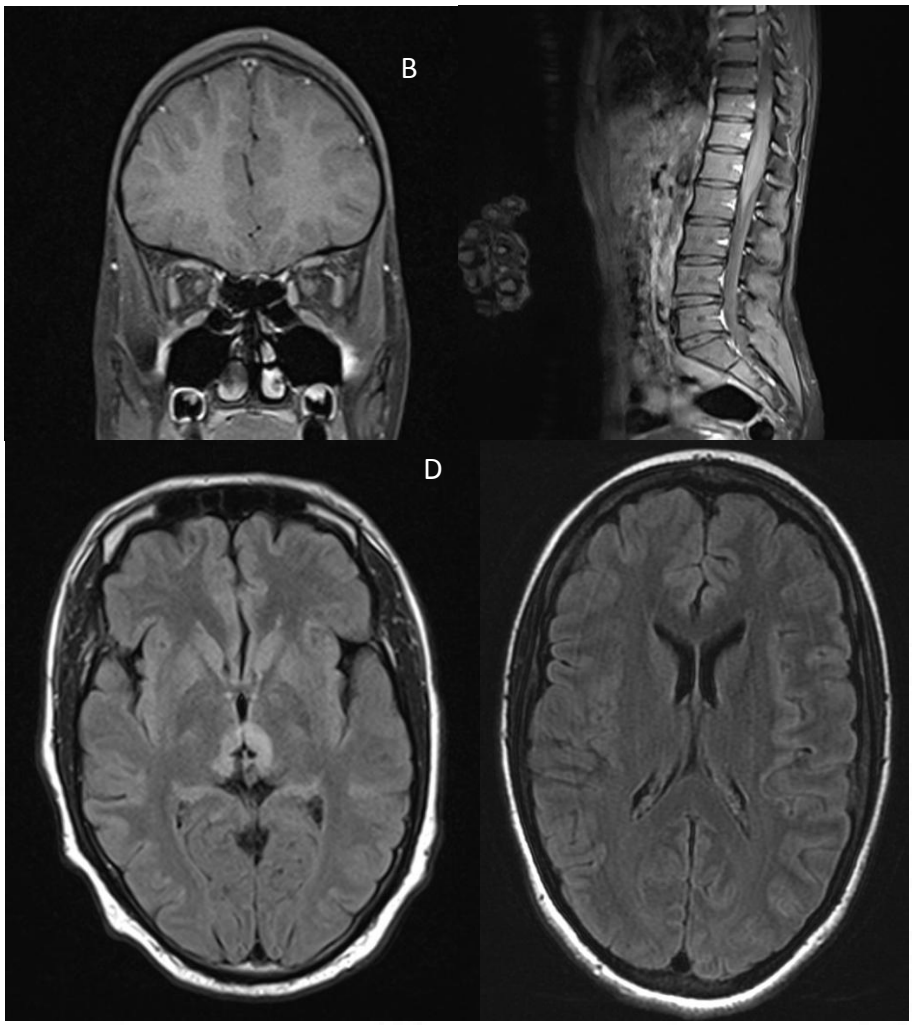


Figure 7- A. Case of ON with MRI T1 gadolinium contrast coronal sequence showing perineural enhancement in bilateral optic nerves. **B.** Case of TM with Post contrast T1 spine showing conus involvement. **C.** Diencephalic syndrome with FLAIR 3D axial sequence with hyperintensities in bilateral thalamus and PAG region. **D.** Case of focal seizures showing axial FLAIR 3D sequence showing sulcal hyperintensities in insular cortex.

Figure 8: Imaging patterns in NMOSD AQP4—Ab negative group

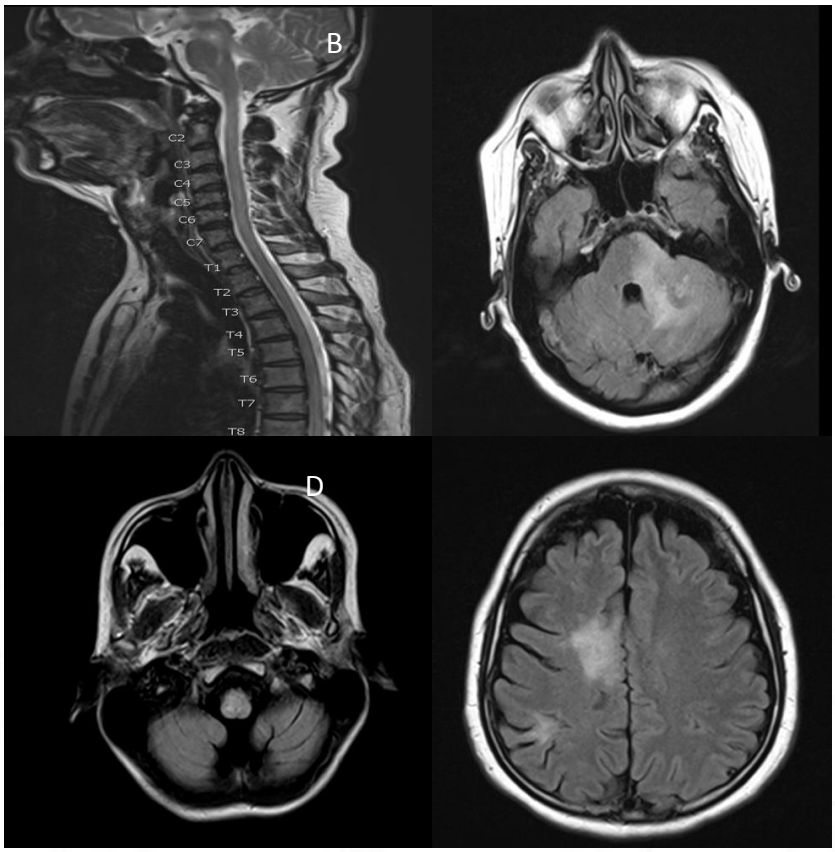


Figure 8- A. Case of TM with MRI T2 sagittal spinal cord showing long segment hyperintensities involving the cervical cord from C2 to C6. **B.** Case of ataxic presentation with MRI Brain FLAIR axial sequence showing hyperintensities in left cerebellar hemisphere and left MCP. **C.** Case of vomiting with hypoglossal palsy with MRI FLAIR axial sequence showing hyperintensities in medulla involving right hypoglossal nuclei. **D.** Case of focal seizures with MREI Brain FLAIR 3D sequence showing cortical hyperintensities involving the mesial frontal-cingulate region and parietal- postcentral region

7. Serological characteristics

7.1 Cerebrospinal fluid characteristics

CSF was done in 95 patients. CSF pleocytosis, elevated proteins, IgG index was analysed between three groups and there was no statistical difference.

Table 11: CSF parameters in three groups

CSF characteristics	Total (n-95)	NMOSD AQP4+ (n-44)	MOGAD (n-30)	NMOSD AQP4- (n-21)	p value
Cells					
Mean cubic mm± SD	15.16±48.34	5.52±7.28	15.43±40.6	21.53±64.75	0.391
≦5	71 (74.7%)	34 (77.3%)	23 (75.9%)	14 (66.7%)	0.643
>5	24 (25.3%)	10 (22.7%)	7 (24.1%)	7 (33.3%)	
Protein level					
Mean in mg/dl ±SD	43.81±29.12	42.4±30.12	42.7±28.25	48.3±29.18	0.726
≦45	63 (66.3%)	30 (68.2%)	20 (66.7%)	13 (61.9%)	0.881
>45	32 (33.7%)	14 (31.8%)	10 (33.3%)	8 (38.1%)	
IgG index	(n-46)				
≦0.7	31 (67.4%)	10 (66.7%)	11 (57.9%)	10 (83.3%)	0.356
>0.7	15 (32.6%)	5 (33.3%)	8 (42.1%)	2 (16.7%)	

7.2 Other serum antibodies

Other autoimmune antibodies were identified in 22 (20%) patients. 12 (25%) patients in NMOSD AQP4—Ab positive and 10 (26.3%) patients from MOGAD group were associated with coexistent antibodies. The most common antibodies detected were antinuclear antibody (ANA) followed by antibodies to mi-2 and SS-A. NMOSD AQP4 Ab—negative patients were found to be negative for other antibodies as well. (p-0.022)

8. Multi-variate analysis

Multinomial logistic regression was attempted among the three groups; however no significant model was obtained. Binary logistic regression was attempted with only NMOSD AQP4—Ab positive and MOGAD groups with variables as age of onset, disease duration, gender, follow-up duration, initial presentation, Lhermitte, painful tonic spasms and other serum autoantibodies. Only gender remained a significant predictor (p=0.026, Odds ratio = 0.317 ;95% CI 0.115-0.873) with female preponderance in NMOSD AQP4—Ab positive group.

Forcing a model with gender and painful tonic spasm, the significance of painful tonic spasm disappeared. Similar findings were observed when the model was forced with adding optic neuritis, Lhermitte symptom or other serum autoantibodies. These symptoms were common in female population and further exploration for gendering effect in NMOSD AQP4—Ab positive group needs to be explored.

9. Therapeutic strategies

9.1 Acute therapy (AT)

Among the 384 events, 350 (91.1%) received acute therapy. Pulse IV glucocorticoids, IVIG and PLEX was given for 330 (85.9%), 15 (4%) and 28 (7.4%) respectively and their distribution groupwise is given below.

Table 12: Acute therapy in the three groups

Acute therapy	NMOSD AQP4+ (n-182)	MOGAD (n-124)	NMOSD AQP4 – (n-78)	Total (n-384)	P Value
Acute therapy	165 (90.7%)	116 (93.5%)	69 (88.5%)	350 (91.1%)	**0.041**
IV pulse GC	159 (87.4%)	104 (83.9%)	67 (85.9%)	330 (85.9%)	0.83
Oral GC	52 (28.6%)	31 (25%)	22 (28.2%)	105 (27.3%)	0.217
IVIG	6 (3.4%)	3 (2.4%)	6 (7.7%)	15 (4%)	0.15
PLEX	16 (9.1%)	6 (4.8%)	6 (7.7%)	28 (7.4%)	0.381

* Oral steroids with increased dose for acute duration or started as acute and later continued as long term on a lower dose

9.2 Maintenance Treatment

Maintenance therapy (MT) was initiated in 105 (95.5%) patients with no significant differences between three groups. After the first event, MT was started in 22 (20%) patients of whom 10 (20.8%), 9 (23.7%) and 3 (12.5%) were NMOSD AQP4—Ab positive, MOGAD and NMOSD AQP4—Ab negative respectively. In 37 (33.6%) patients, MT was started after the second event. Frequently used agents were Azathioprine (53.6%) followed by MMF (38.2%) and Rituximab (20%).

Table 13: Maintenance therapy in three groups

Maintenance Therapy (MT)	NMOSD AQP4+ (n-48)	MOGAD (n-38)	NMOSD AQP4 – (n-24)	Total patients (n-110)	P value
Patients on MT	46 (95.8%)	37 (97.4%)	22(91.7%)	105 (95.5%)	0.716
Weekly or monthly IVMP	5 (10.4%)	5 (13.2%)	3 (12.5%)	13 (11.8%)	0.931
Oral GCs	41 (85.4%)	26 (68.4%)	83 (75.5%)	16 (66.7%)	0.101
Mean duration of GCs in months ± SD	29.71±27.26	22.27±24.16	19.88±18.88	25.48±24.98	0.303
Azathioprine	31 (64.6%)	18 (47.4%)	10 (41.7%)	59 (53.6%)	0.117
Mycophenolate Mofetil	16 (33.3%)	18 (47.4%)	8 (33.3%)	42 (38.2%)	0.354
Rituximab	13 (27.1%)	3 (7.9%)	6 (25%)	22 (20%)	0.068
Cyclophosphamide	3 (6.5%)	3 (8.1%)	0	6 (5.7%)	1
Methotrexate	1 (2.2%)	1 (2.7%)	0	2 (1.9%)	1

10. Outcome measures

The mean follow-up duration in our hospital from the initial visit was 43.9±45.4 months.

10.1 Relapse

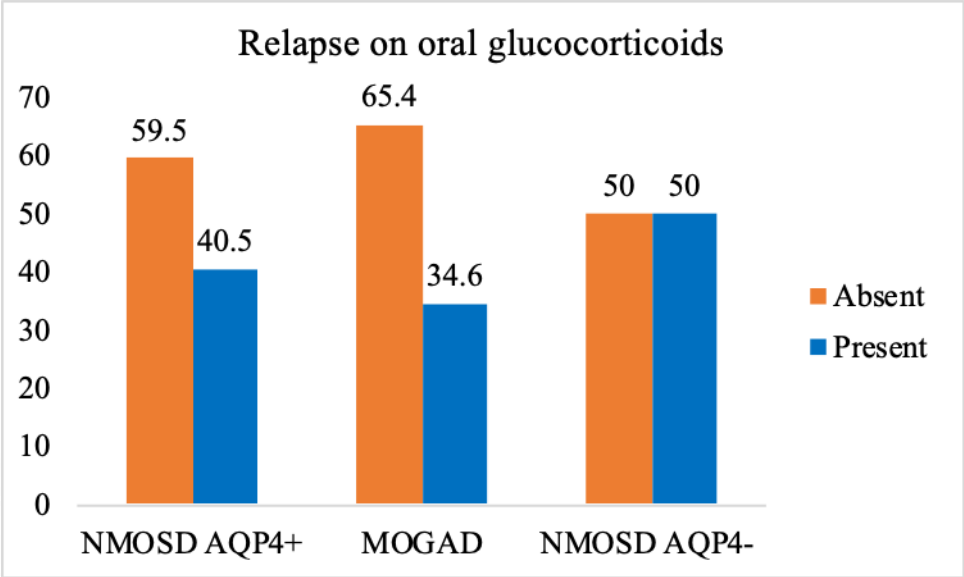
The mean number of relapses is 2.49 ±2.493 for all groups and was similar for three groups. Out of the 105 cases who were initiated on maintenance therapy, 61 (58.1%) patients never had a relapse.

Table 14: Relapse parameters in study groups

Relapse parameters	NMOSD AQP4+ (n-46)	MOGAD (n-37)	NMOSD AQP4 – (n-22)	Total (n-105)	P value
Mean number of relapses ±SD	2.79±3.094	2.26±2.165	2.25±1.422	2.49±2.493	0.542
Relapse					0.915
Present	19 (41.3%)	15 (40.5%)	10 (45.5%)	44 (41.9%)	
Absent	27 (58.7%)	22 (59.5%)	12 (54.5%)	61(58.1%)	

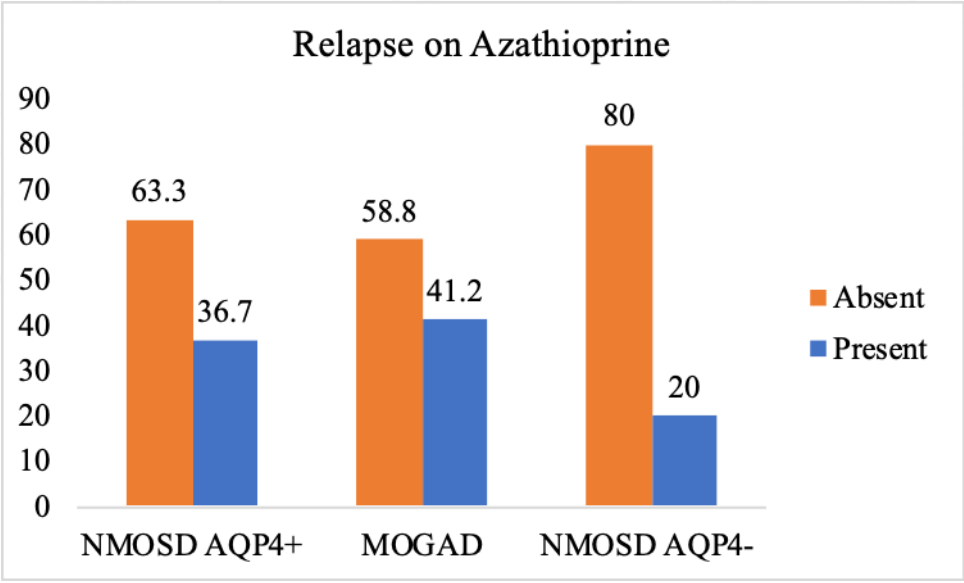
50 (59.5%) patients on oral glucocorticoid therapy did not have relapse as compared to 37 (64.9%) on azathioprine, 29 (69%) patients on Mycophenolate mofetil and 17 (77.3%) on rituximab.

Figure 9: Bar chart depicting oral glucocorticoids as MT and relapse rates in the three groups



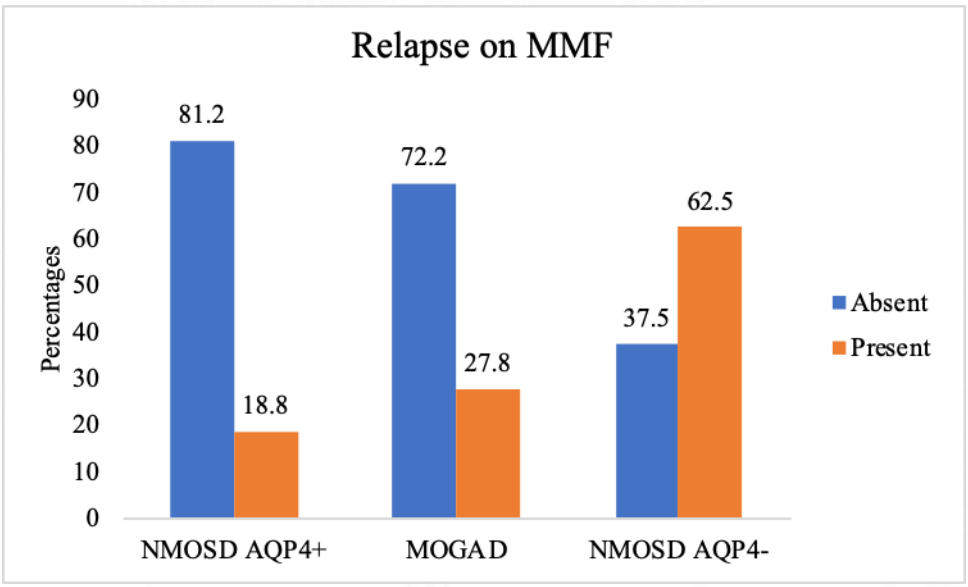
84 cases received oral steroid therapy out of which 50 (59.5%) maintained remission.34 (40.5%) cases relapsed, majority had a single relapse and commonly in NMOSD AQP4—Ab negative group(Figure 9).

Figure 10: Bar chart depicting azathioprine as MT and relapse rates in the three groups



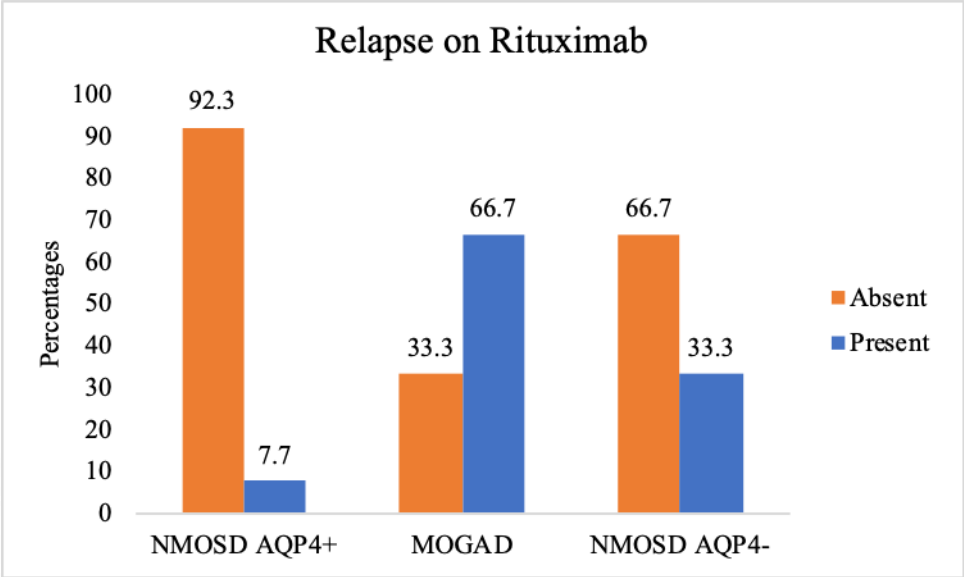
57 patients received azathioprine therapy with 37(64.9%) having relapse free period. Less relapses were reported in NMOSD AQP4—Ab negative group with maximum proportion in MOGAD group(Figure 10).

Figure 11: Bar chart depicting mycophenolate mofetil as MT and relapse rates in the three groups



Out of the 42 cases who received MMF, 69% did not have relapses while on therapy. Out of the 13 cases that relapsed, 12 cases had one relapse and one case had 2 relapses and these relapses were commoner in NMOSD AQP4 negative group as compared to others(Figure 11).

Figure 12: Bar chart depicting rituximab as MT and relapse rates in the three groups



Out of the 22 cases who received rituximab therapy, 17 did not have any relapses. NMOSD AQP4—Ab positive group had less relapse on rituximab therapy. Among 13 patients of AQP4+ NMOSD patients on Rituximab,12 maintained remission (p 0.04) (Figure 12)

10.2 Time to Relapse (TTR)

A. Time to first relapse (TTR) irrespective of therapy

Mean Time to first relapse was compared between the three subgroups and NMOSD AQP4—Ab negative subgroup had a lower mean time to relapse as compared to the other groups, however, the difference was not statistically significant.

Table 15: Time to first relapse in the three groups

Time to 1st relapse	Number	Mean	Std. Deviation	ANOVA p
NMOSD AQP4+	39	29.7	46.9	0.627
MOGAD	30	25.3	34.8	
NMOSD AQP4 -	22	19.3	34.9	
Total	91	25.7	40.2	

B. Time to first relapse after maintenance therapy

The NMOSD AQP4—Ab negative subgroup had a lower mean time to relapse despite being on immunotherapy. However, the difference between the groups was not statistically significant.

Table 16: Time to relapse after MT in the three groups

Time to first relapse after MT	N	Mean	Std. Deviation	p value
NMOSD AQP4+	19	26.37	24.779	0.2
MOGAD	15	19.6	18.73	
NMOSD AQP4 -	10	11.8	12.691	
Total	44	20.75	20.929	

10.3 Disability at last follow-up

62.7% of the study population had near normal to mild residual disability and were independent for activity of daily living. 16.4% had moderate disability and severe disability was noted in 20.9% cases.

Near normal recovery was more common in MOGAD patients.

Table 17: Disability outcome within the three groups

Disability	NMOSD AQP4+ (n-48)	MOGAD (n-38)	NMOSD AQP4 – (n-24)	Total (n-110)
Mild	26(54.2%)	27(71.1%)	16(66.7%)	69(62.7%)
Moderate	8(16.7%)	6(15.8%)	4(16.7%)	18(16.4%)
Severe	14(29.2%)	5(13.2%)	4(16.7%)	23(20.9%)

p=0.435

DISCUSSION

Discussion

The expanding spectrum of NMOSD with evolving diagnostic criterias along with overlapping though distinct MOGAD course and exploration of the NMOSD AQP4—Ab negative group has led to a renewed interest in comparison and typifying of these separate entities(4,10,23).

Our study is a single centre retrospective study comparing between these distinct groups and their phenotypic expression and disease course.

Our cohort of 110 cases showed a predominance of NMOSD AQP4—Ab positive cases(n-48) followed by the MOGAD cases(n-38) and 24 cases alone of the NMOSD AQP4 negative group in view of fulfilling the stringent criteria. There is a predominance of adult age of onset with mean age of onset in third decade which is in lines with the younger age group in Asian population when compared to Caucasians(37). Pediatric cases are seen with a percentage of 29-31% in all the groups which is consistent with MOGAD and NMOSD AQP4 negative groups showing varying percentage; however is higher in the AQP4 positive group with 3-5% percentage seen in previous studies(8,36,56). Significant female preponderance with a ratio of 1:5 (male: female) in NMOSD AQP4—Ab positive group has been in concurrence with previous studies who have shown female dominance with variable M:F ratios(34,37). Our study had equalising effect on gender in MOGAD and NMOSD AQP4 negative group which is consistent with few recent studies(31,32,34). With the mean disease duration of 78.8 months and mean follow-up of 44 months, nearly 83% cases relapsed. Among the NMOSD AQP4—Ab

negative group, 22 out of 24 cases relapsed; while NMOSD AQP4—Ab positive group had 81.3% relapses. MOGAD group even though having a significant lower follow-up duration(27.7months) due to recent discovery had relapse rate of 78.9% suggesting that all the 3 groups had a higher propensity to eventually relapse highlighting the need for early maintenance therapy. MOGAD which was earlier though to be a monophasic disease has a relapsing course corroborated in recent studies(13,46).

The most common initial phenotypic presentation in NMOSD AQP4—Ab positive and MOGAD group was isolated ON which is suggested in previous studies(34,39,56). NMOSD AQP4—Ab negative group (8.3%) had significantly lesser isolated ON (P-0.018) which is lesser than the recent study with 32% ON presentations(34).

Isolated TM was seen in all 3 groups in around 26-29% cases and was the most common presentation in NMOSD AQP4—Ab negative group which is consistent with previous studies(23). APS was not found in MOGAD cases(P-0.061). One Korean study showed the rarity of APS as initial attack in MOGAD highlighting its specificity in diagnosing NMOSD over MOGAD(87). Out of the total 384 events, phenotypic presentations in each group showed significant differences. Not only initial attack, but isolated ON events were much lesser in NMOSD AQP4—Ab negative group (24.4%) than the other groups(P-0.001). Interestingly, brainstem presentations were commoner in the NMOSD AQP4—Ab negative group and much lesser in MOGAD group(P-0.007). APS was exclusively present in non-MOGAD groups with maximum in NMOSD AQP4—Ab positive. (P-0.005) signifying its

AQP4 rich region expression(38). ADEM consistent with studies was seen in MOGAD group(P-0.018)(46). Isolated cerebellar presentations were commoner in NMOSD AQP4—Ab negative group(P-0.001). Clinically unilateral presentations were common in all the 3 groups however radiologically bilateral presentations were found to be common suggesting more propensity for bilateral involvement with silent lesions.

In our cohort, Lhermitte symptom(P-0.081) and painful tonic spasms(P-0.027) were exclusively present in non- MOGAD groups with twice as common in AQP4—Ab than the AQP4—Ab negative group. On multivariate forced model with gender, the significance was diluted suggesting a gender impact on these conditions being found in female population predominantly. The course of NMOSD AQP4—Ab positive expressing differently in females need to be explored. Tonic spasms and Lhermitte reported in NMOSD can be a differentiating feature from MOGAD cases.

Dual screening and reviewing of events MRIs in our study highlighted distinct differences in the 3 groups. ON was involved much more commonly in NMOSD AQP4—Ab positive group(P-0.052). Bilateral involvement was commoner except in NMOSD AQP4—Ab negatives where unilateral involvement was seen. Isolated anterior segment as seen in previous studies(57,65) was common in MOGAD; however also seen in other groups reducing its differentiating effect. Majority had both segment involved with > 50% length; however chiasmal involvement was rare in MOGAD(P- 0.096). Previous studies have corroborated the chiasmal predilection in non-MOGAD cohort; however studies have shown shorter lesions to be present in MOGAD(51,54,58).

Grey matter lesions (P-0.059) were commoner in non- NMOSD AQP4—Ab positive groups; while subcortical involvement(P-0.008) was significantly associated with MOGAD. Brainstem involvement (P-0.01) were common in NMOSD AQP4—Ab negative group which might be due to more brainstem presentations in our cohort.

Leptomeningeal enhancement as seen commonly in MOGAD(58) was seen in all 3 groups in our cohort along with cloudy and nodular pattern suggesting overlap amongst the enhancement patterns in the groups(48).

Spinal cord imaging showed significant occurrence of isolated cervical cord(P-0.001) or CM involvement(P-0.024) in non-MOGAD cases which is the common location in these groups. MOGAD has a predilection to conus(58) which was seen in our MRIs; however cervicodorsal region remained a common location in all 3 groups.

Predominantly long segment lesions were noted; however 25.8% had short segment lesions suggesting not so rare occurrence of these lesions(50).

NMOSD AQP4—Ab positive group had significant specificity to bright spotty lesions (P-<0.001); being a rare occurrence in MOG which was consistent with the literature(49).

Cloudy enhancement patterns were common in non-MOGAD groups (P-0.031) suggesting less enhancement of MOGAD in acute relapses.

Serological studies had shown consistent results with CSF cytology and IgG index with no intergroup differences. Association of other serum antibodies was present in around 20% of cohort with a striking absence in NMOSD AQP4 negative group(88). This might suggest a different pathophysiology of the NMOSD AQP4 negative group which needs to be further researched.

Acute therapy was received in 91.1% of the events with predominantly IV pulse steroid therapy followed by oral steroids which is the mainstay of therapy since decades. Other therapies in the form of IVIG and PLEX were received however initial therapy predominantly was IV pulse steroid therapy in all the groups. A small percentage of MOGAD also received oral steroids as initial therapy.

95.5% of our cohort received maintenance therapy predominantly in the form of oral steroids and azathioprine followed by MMF and rituximab with few cases on cyclophosphamide and methotrexate. 23.2 % cases relapsed while on some type of MT. 58.1% of the cases on MT were completely relapse free and the remaining had one or two relapses predominantly. Individually, oral steroids, azathioprine and MMF caused relapse free periods in 59.5%, 64.9% and 69% cases with no intergroup differences. Rituximab had a significant reduction in relapses with remission in 77.3% cases with significant relapse free patients in NMOSD AQP4—Ab positive group(P-0.04) with only 1 relapse out of 13 suggesting an efficacious therapy. Superiority of rituximab has been reported in various studies with 70% relapse free on 7 years follow up in NMOSD. However, the comparison among the groups has not been studied(75,76).

Among the outcome variables, time to first relapse irrespective of therapy administered was earlier in NMOSD AQP4—Ab negative group as compared to NMOSD AQP4—Ab positive group(34). No significance was noted; however it highlights the early suspicion and diagnosis of this NMOSD AQP4—Ab negative entity as it has no biomarkers causing delay in treatment which could lead to earlier relapses. Majority of the patients in all the groups had a near normal recovery or mild disability. MOGAD had a trend towards milder disability while NMOSD AQP4—Ab positive group had more proportion of severe disability cases as compared to other groups. A larger multicentre study will be required to validate these results and to typify the predictors of disability outcome

Strengths of the study

This is a single centre study from the south India with a fair number of cases

Cells based assays have been used for inclusion and categorising of the groups

AQP4 and MOG testing was mandatory for the inclusion with defining the NMOSD AQP4 negative group which is yet to be explored in detail.

Follow-up duration was sufficient enough to report the outcome and disability parameters

Limitations

Larger cohorts are needed for prognostication and outcome predictors with a multicentre study

Retrospective nature of study – event related details were taken from chart records

MOG positivity being higher in acute cases, need for testing after an event or attack might increase the possibility of more cases which was not taken into consideration for inclusion criteria.

CONCLUSION

CONCLUSION

- All the three groups have a higher propensity for a relapsing course thus need for early immunomodulatory therapy initiation
- NMOSD AQP4—Ab negative group is a distinct phenotype with rare isolated ON presentations and common TM presentations. Also, isolated Brainstem syndromes and isolated cerebellar presentations have significant association as compared to other groups.
- Area postrema syndrome is a characteristic of NMOSD group and can be used as a differentiating feature to exclude MOGAD.
- Tonic spasms and Lhermitte symptom is a distinct feature in NMOSD AQP4—Ab positive cases predominantly in females.
- MRI findings showed predominant involvement of more than 50% of the segment (anterior+ posterior) in all the groups; however absence of chiasmal involvement can be used to differentiate MOGAD cases.
- Association of serum antibodies was distinctly absent in NMOSD AQP4—Ab negative group suggesting a search for distinct pathophysiology.
- Rituximab has significant reduction in relapse rates in NMOSD AQP4—Ab positive group as compared to other groups.
- NMOSD AQP4—Ab negative group had an earlier time to relapse irrespective of therapy and need for early suspicion and treatment.

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APPENDIX

LIST OF ABBREVIATIONS

ADEM	Acute Demyelinating Encephalomyelitis
APS	Area Postrema syndrome
AQP4	Aquaporin-4
ARR	Annual Relapse rate
AT	Acute Therapy
CM	Cervicomedullary
EDSS	Expanded Disability Status Scale
LETM	Longitudinally Extensive Transverse Myelitis
MCP	Middle cerebellar peduncle
MMF	Mycophenolate Mofetil
MOG	Myelin oligodendrocyte glycoprotein
MOGAD	Myelin oligodendrocyte glycoprotein antibody associated demyelination
MT	Maintenance Therapy
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorders
ON	Optic Neuritis
TDL	Tumefactive demyelinating like lesions
TM	Transverse Myelitis
TTR	Time to Relapse

INTERNATIONAL CONSENSUS DIAGNOSTIC CRITERIA FOR NMOSD

NMOSD with AQP4-—Ab positive

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

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
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

PROFORMA

1. Identification information

1.1 Serial number ----------

1.2 Hospital number ----------

1.3 Name ----------

1.4 Residential address ----------

1.5 Phone number ----------

2. Demographic data

2.1 Age at onset ----------Age at last follow up---------- years

2.2 Sex ---------- 1. Male 2. Female

2.3 Occupation ----------

2.4 Education status ----------

3. Comorbidities (1= Yes, 0 = No)

3.1 Collagen vascular disease ---------- If yes, details ----------

3.2 Malignancy ---------- If yes, details ----------

3.3 Comorbidities- Hypertension/Diabetes/CAD/Dyslipidemia/Hypothyroidism

3.4 Other comorbidities (describe) ----------

3.5 Family history of neurological illness ----------If yes, describe ----------

---

4. Clinical presentation of first event (1 = Yes, 0 = No)

4.1 Year and month of onset ----------

4.2 Time of initial presentation ----------

4.3 Duration between onset and presentation ----------

4.4 Phenotype ----------

(1. Transverse myelitis 2. Optic neuritis 3. ON+TM 4. Brainstem 5. APS

6. Diencephalic 7. Hemispheric, 8.ADEM, 9.Cereebllar, 10.Mixed)

4.5 Other associating symptoms ----------

(Lhermitte/painful tonic spasms)

4.6. Description of phenotype symptoms ----------

4.7 Phenotype presentation of each events in the patient----------

Description----------No of events----------

5. Investigations (1 = Yes, 0 = No)

5.1 CSF study ----------

5.2 CSF cells ----------

5.2.1 CSF differential count ----------

5.3 CSF sugar / RBS ----------

5.4 CSF protein ----------

5.5 CSF OCB ----------

5.6 CSF Ig G index ----------

5.7 Aquaporin 4 antibody(NMO) ----------

5.8 MOG antibody

5.9 Other autoimmune antibodies ----------

5.10 VEP ----------

5.11 BAEP ----------

5.12 SSEP ----------

6. MRI features (optic nerve/Brain/Spinal cord)

6.1 Number of lesions ----------

1.2 Site (s) of lesions ----------

1.Optic nerve 2.Spinal cord 3. Area postrema 4.brainstem

5.Diencephalic 6.Cortical

6.3 Number of lesions ----------

Optic nerve---length----segment involved----atrophy----tortuosity

Brain-----site----1. Periventricular 2. Juxtacortical 3. subcortical 4. Deep grey 5. Corpus callosum

Spinal cord----Segment involved----length of segment-----axial-central/peripheral----axial area-----atrophy

6.4 Contrast enhancing lesions (present/absent) ----------

6.5 Contrast Enhancing patterns. Patchy/nodular/leptomeningeal----------

7. Treatment and course (1= Yes, 0= No)

A.Acute therapy

7.1 IV MP ---------- Dose ---------- Duration

7.2 Oral steroid ---------- Maximum dose ----------

Duration ----------

7.3 IVIg---------dose

7.4 Plasmapheresis-------no of cycles

B.Immunomodulatory agents ----------

.1 If yes, which one

Azathioprine ---------- Dose ---------- Duration ----------

Mycophenolate mofetil ---------- Dose ---------- Duration ----------

Rituximab ----------Dose ---------- Duration ----------

Cyclophosphamide ----------Dose ---------- Duration ----------

Methotrexate ---------- Dose ---------- Duration ----------

8. Treatment response (1= Yes, 0= No)

8.1 Number of relapses ----------

8.2 Duration between relapses ----------

9.Details of relapse (separate sheet to be attached for each relapse)

9.1 Year and month of onset of symptoms ----------

9.2 Precipitating factors ----------

(1. None 2. Treatment default 3. Tapering of treatment 4. Other)

9.3 Time to first relapse in months

9.4 Time to first relapse after MT

9.5 Relapses (present /absent). (No of relapses) on MT

Oral steroids…Azathioprine…MMF…..

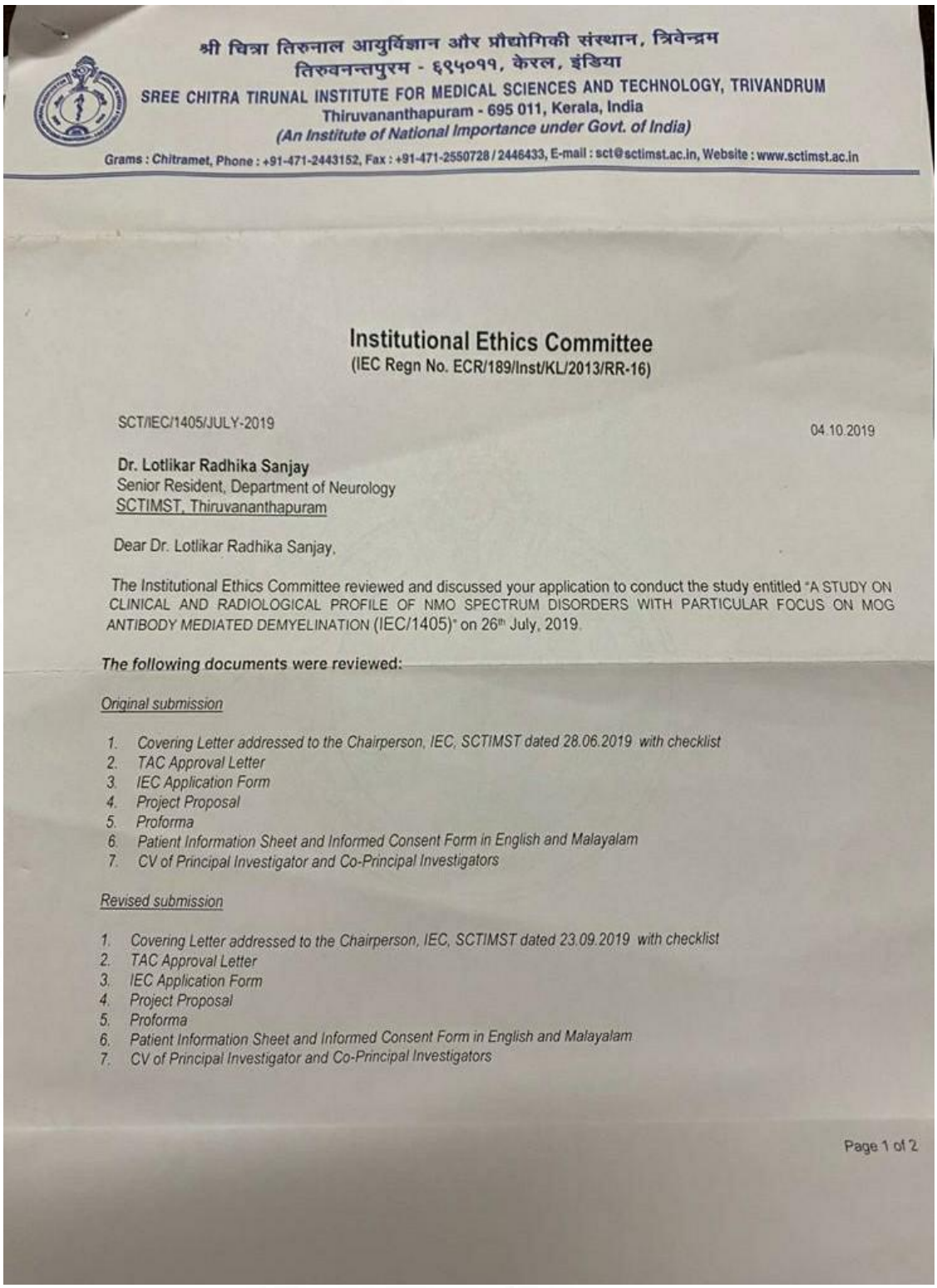
Rituximab…Cyclophosphamide…Methotrexate

10.Disability assessment:

Disability scores:

mRS rating:

IEC APPROVAL



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1405/JULY-2019 04.10.2019

Dr. Lotlikar Radhika Sanjay
Senior Resident, Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Lotlikar Radhika Sanjay,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "A STUDY ON CLINICAL AND RADIOLOGICAL PROFILE OF NMO SPECTRUM DISORDERS WITH PARTICULAR FOCUS ON MOG ANTIBODY MEDIATED DEMYELINATION (IEC/1405)" on 26th July, 2019.

The following documents were reviewed:

Original submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 28.06.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 23.09.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

Page 1 of 2

The following members of the Ethics Committee were present at the meeting held on 26th July, 2019 at Noshir H Wadia Conference Hall, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
2.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
5.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

PLAGIARISM CHECKER

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