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CLINICAL AND RADIOLOGICAL PROFILE OF AQUAPORIN-4(AQP-4) ANTIBODY POSITIVE NEUROMYELITIS OPTICA SPECTRUM DISORDERS (NMOSD) IN A LARGE TERTIARY CARE CENTRE OF NORTH WEST INDIA

Neurology

Dr. Deepak Jain	Associate Professor, Department of Neurology, SMS Medical College and Hospital, Jaipur, Rajasthan.
Dr.Rajendra Singh Jain	Senior Professor, Department of Neurology, SMS Medical College and Hospital, Jaipur, Rajasthan.
Dr. Sourabh Murarka*	Senior Resident, Department of Neurology, SMS Medical College and Hospital, Jaipur, Rajasthan. *Corresponding Author
Dr. Manu LS	Senior Resident, Department of Neurology, SMS Medical College and Hospital, Jaipur, Rajasthan.
Dr. Sripadma PV	Senior Resident, Department of Neurology, SMS Medical College and Hospital, Jaipur, Rajasthan.
Dr. Piyush Saavaliya	Senior Resident, Department of Neurology, SMS Medical College and Hospital, Jaipur, Rajasthan.

ABSTRACT

Background- NMOSD is an immune-mediated inflammatory demyelinating, necrotizing disease of the central nervous system (CNS) that mainly effects the optic nerves and the spinal cord. We performed this study to determine clinical and radiological features of AQP-4 antibody positive NMOSD patients in north west india.

Methods- We collected 25 patients who were AQP-4 IgG positive and fulfilled diagnostic criteria (IPND) for NMOSD. We screened all patients who presented with acute CNS demyelinating episodes and tested positive for AQP-4 antibody determined by cell-based assay (CBA). Data collected using a standardized form included epidemiologic data, clinical data, neuroimaging data and biological data.

Result - In our study of AQP-4 positive NMOSD patients , the female to male ratio was 4:1 and median age of onset was 29.5 years.Various presentations like Optic neuritis , myelitis , recurrent vomiting ,hemiparesis were noted. All 18 (72%) patients with myelitis had long extensive transverse myelitis (LETM) . Cervicomedullary involvement was seen in 16% (4/25) patients. Brain MRI imaging showed most common involvement of area postrema with involvement of other areas also like brainstem , thalamus ,hypothalamus ,subcortical periventricular and corpus callosum.

Conclusion- Our study highlights the important characteristics of patients with AQP-4 positive NMOSD. Varied presentations seen in NMOSD highlight the need for a high index of suspicion for NMOSD in demyelinating episodes not classical for MS.

KEYWORDS

NMOSD, AQP-4 IgG, myelitis ,optic neuritis

INTRODUCTION:

NMOSD is an immune-mediated inflammatory demyelinating, necrotizing disease of the central nervous system (CNS) that mainly involves the optic nerves and the spinal cord. The disease is prevalent worldwide and shows similarity in the age of onset of the illness and female preponderance[1].However, most of the NMOSD patients were AQP4-IgG positive, 10–40% of patients were seronegative[2].About one-third of AQP-4 IgG negative NMOSD patients are found positive for antibody against myelin oligodendrocyte glycoprotein (MOG).NMOSD is commonly associated with antibodies that target AQP-4, the most abundant water channel in the CNS, mainly present in the astrocytic processes at the blood-brain barrier (BBB)[3].

The International Panel for NMO Diagnosis (IPND) has eliminated the use of word NMO, and is now calling the disease as NMOSD. They given the diagnostic criteria for NMOSD in which they have included 6 core clinical characteristics 1.Optic neuritis 2.Acute myelitis 3.Area postrema syndrome 4.Acute brainstem syndrome 5.Symptomatic narcolepsy or acute diencephalic clinical syndrome 6.Symptomatic cerebral syndrome.

Diagnostic criteria for NMOSD with AQP4-IgG 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.

Diagnostic criteria for NMOSD without AQP4-IgG or unknown AQP4-IgG status-1.At least 2 core clinical characteristic 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 core clinical characteristics).c. Fulfilment of additional MRI requirements.2.Negative test for AQP4-IgG using best available detection method, or testing unavailable.3. Exclusion of alternative diagnoses[4].

The clinical-radiological analysis of AQP-4 IgG positive NMOSD patients in north west india had not been previously studied, therefore, we performed this study to determine clinical and radiological features of AQP-4 IgG positive NMOSD patients.

AIMS AND OBJECTIVES

1. To study clinical and radiological features of aquaporin-4(AQP-4) antibody positive NMOSD patients.

MATERIAL AND METHODS:

Study Design:

An observational study was carried out in the neurology department of a large tertiary care centre of north-west India from Jan 2019 to Jan 2021 and data was collected as per the proforma designed for the study. Institutional ethics committee approval was obtained prior to enrolment of patients.

Inclusion Criteria:

Patients admitted in our center who were AQP-4 IgG positive and fulfilled diagnostic criteria (IPND) for NMOSD.

Exclusion Criteria:

1. Other demyelinating disease like multiple sclerosis.
2. MOG antibody associated demyelination.
3.Other causes presenting as optic neuritis and myelitis like tuberculosis, autoimmune diseases and granulomatous lesion like sarcoidosis.

PROCEDURE:

We screened all patients who presented to us with acute CNS demyelinating episodes like optic neuritis (ON), transverse myelitis, acute disseminated encephalomyelitis (ADEM) and other focal or

polyfocal demyelination [5].We recruited total 25 patients that were tested positive for AQP-4 antibody and all of them provided consent for participation in the study.

Positivity for AQP-4 antibodies was determined by cell-based assay (CBA) with visualization of binding to human embryonic kidney cells. Data collected using a standardized performa included epidemiologic data (age at onset, gender), clinical data (phenotype at onset, associated symptoms), radiological data (3T MRI of the brain, optic nerve, and spinal cord with T1W, T2W, FLAIR, and gadolinium enhanced (GE) T1W axial, coronal, and sagittal sequences), biological data (serum MOG and AQP-4 antibody, antinuclear antibody [ANA], cerebrospinal fluid (CSF) protein, CSF cells , CSF oligoclonal bands)[6-7].

Statistical Analysis:
Descriptive statistics like frequencies and percentages were used to describe characteristics and profile of study population.

RESULTS:

EPIDEMIOLOGY AND CLINICAL PRESENTATION:

Total 25 patients who were AQP-4 IgG positive (AQP-4 IgG+) were included in the study. Out of 25 patients 20 (80%) were females and 5 (20%) were males. Mean age of presentation was 29.52 years. In 4 (16%) patients, we observed a preceding clinical event (fever - 3, upper respiratory tract infection-1) associated with clinical attacks.

The onset of disease was frequently with myelitis 18/25 (72%). Out of 16 (64%) patients of isolated myelitis, 9 (36%) patient presented with paraparesis with bladder involvement,6 (24%) patient presented with quadriparesis with bladder involvement and 1 (4%) patient presented with left hemiparesis and right hand grip weakness. 2 (8%) patients presented with myelitis in combination with other presentation, of which 1 patient presented with quadriparesis with bilateral optic neuritis with recurrent vomiting and 1 patient presented with quadriparesis with recurrent vomiting.

Optic neuritis was presenting feature in 5/25 (20%) AQP-4 IgG+ patients. Unilateral optic neuritis was present in 2 patient and bilateral optic neuritis was present in 2 patients.1 patient presented with bilateral optic neuritis with myelitis and recurrent vomiting.

2 (8%) patients presented with hemiparesis, of which 1 patient had isolated hemiparesis and other patient presented with hemiparesis with recurrent vomiting. One patient presented with recurrent vomiting , altered sensorium with respiratory distress. Recurrent vomiting was presenting features in 4 patients. 4 (16%) patient had a past history in form of optic neuritis in 2 patients, ADEM like episode in 1 patient and intractable vomiting in 1 patient.

Table 1: Epidemiologic And Clinical Features Of AQP-4 IgG+ Patients

	AQP-4 IgG+ Patients
DEMOGRAPHIC FEATURES	
Females	20(80%)
Average age at onset (years)	29.52
Onset in the first decade	1(4%)
Paediatric patients(<18 year)	4(16%)
Number of patients with relapses	4(16%)
CLINICAL PHENOTYPE AT ONSET	
Unilateral optic neuritis	2(8%)
Bilateral optic neuritis	3(12%)
Isolated transverse myelitis	16(64%)
Myelitis with Optic neuritis with interactable vomiting	1(4%)
myelitis with intractable vomiting	1(4%)
Isolated hemiparesis	1(4%)
Hemiparesis with intractable vomiting	1(4%)
Respiratory distress with altered sensorium	1(4%)
ASSOCIATED FEATURES	
Infectious prodrome	4(16%)

LABORATORY INVESTIGATIONS:

Table 2 - Serological And CSF Study Results Of The AQP-4 IgG+ Patients

	AQP-4 IgG+ PATIENTS
CSF pleocytosis (>5 WBCs/HPF)	7/25(28%)
Lymphocytic predominance	5/7(71.5%)
Neutrophilic predominance	2/7(28.5)
CSF proteins (>45 mg%)	7/25(28%)
CSF OCB	0/25(0%)
ANA positive	4/25(16%)
Prolonged VEP	20/25(80%)
Bilateral prolonged VEP	14/20(70%)
Unilateral prolonged VEP	6/20(30%)

NEUROIMAGING FEATURES:

MRI brain, spine and orbital cuts were done to study distribution and characteristics of lesions.

MRI of the spinal cord was abnormal in all AQ-4 IgG+ patients presented with myelitis. Spinal cord involvement in all patients were found to be LETM. Cervical and dorsal cord involvement was most common. Cervical cord was involved in 7 patients, dorsal cord was involved in 9 patients, 1 patient had cervicodorsal involvement and 1 patient had dorsal cord to conus involvement. Cervical cord lesions extending into the medulla were seen in 16% (4/25) patients.

Distribution of brain lesions in AQP-4 IgG+ patients involved subcortex, periventricular region, thalamus, hypothalamus, corpus callosum, brainstem, and cerebellum. Most common involved structure was brainstem. Brainstem lesion were found in 20% (5/25) patients of which area postrema was involved in all patients .Cerebellum and middle cerebellar peduncle was involved in 1(4%) patient. Subcortical periventricular and corpus callosal atypical white matter lesions seen in 1 (4%) patient. Bilateral thalamic involvement was seen in 1 (4%) patient.

Total 5 patients presented with optic neuritis, out of which 2 patients had bilateral optic neuritis , 2 patients had unilateral optic neuritis and in 1 patient MRI orbital cut was normal.

Table 3: Radiological Features Of AQP4 IgG+ Patients

STRUCTURE	PATTERN OF INVOLVEMENT	AQP-4 IgG+ PATIENTS
Optic nerve/chiasmal abnormalities	Total patients with ON	5(20%)
	Normal	1/5(20%)
	Bilateral	2/5(40%)
	Unilateral	2/5(40%)
Thalamus	Bilateral	1(4%)
Brainstem involvement	Midbrain	1(4%)
	Pons	2(8%)
	Medulla	5(20%)
	Cerebellum/peduncles	1(4%)
Hypothalamus	Bilateral	1(4%)
Periventricular/callosal WM		1(4%)
Cortex		0(0%)
Spinal cord	LETM	18(72%)
	Cervical Cord only	9/18(50%)
	Thoracic Cord only	7/18(39%)
	Cervicodorsal	1/18(5.5%)
	Dorsal to Conus	1/18(5.5%)

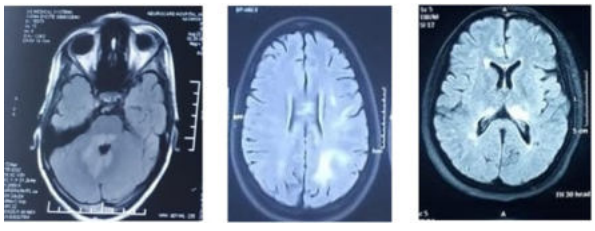

Fig.1: (a) (b) (c)

Figure 1: (a) FLAIR MRI sequence showing hyperintense signals in dorsal pons extending in right MCP and cerebellum. (b) FLAIR MRI sequence showing hyperintense signal in left subcortical periventricular area and corpus callosum. (c) FLAIR MRI sequence showing hyperintense signal in bilateral thalamus.

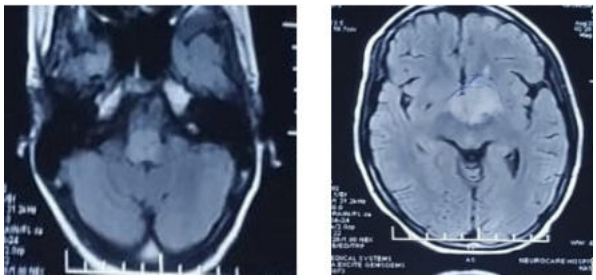

Fig.2:(a) (b)

Figure 2 (a) FLAIR MRI sequence showing hyperintense signals in area postrema. (b) FLAIR MRI sequence showing hyperintense signal in left hypothalamus.

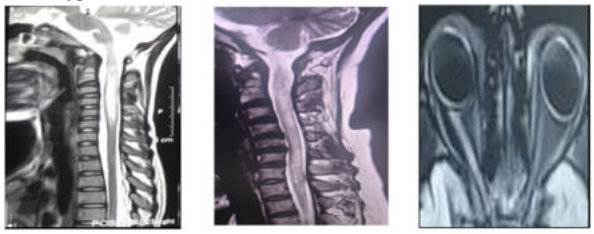

Fig. 3: (a) (b) (c)

Figure 3(a) MRI spine T2 weighted image showing lesion in cervical region extending up to medulla (b) MRI spine T2 weighted image showing lesion in cervico–dorsal region(C3 to D2 level) (c) MRI orbital cut showing long extensive involvement of right optic nerve.

DISCUSSION:

NMOSD is an inflammatory demyelinating disorder affecting typically optic nerves and spinal cord. Other commonly affected areas in NMOSD are area postrema, hypothalamus, brainstem and cerebral involvement.

A strong female preponderance has been reported for NMOSD in various studies in different patient populations[8-10]. The present study also found a high female:male ratio of 4:1.

Although the first episode of NMOSD may occur at any age, in most reported series the average age at onset was in the 4th decade[11-12]. In the present study, the median age at onset was 29.52 years, with a wide range of 10-52.

In our study we observed a preceding clinical events in 16%(4/25) (fever - 3, upper respiratory tract infection-1) patients associated with clinical attacks. In a study by Pandit et al., 2016, showed 28.9% (11/38) of the anti-AQP4+ patients had a preceding/ongoing clinical events (fever - 7, diarrhea - 1, postpartum - 1, pregnancy - 1, mumps - 1) associated with clinical attacks[13].

Classically, NMOSD patients present with isolated optic neuritis ,isolated myelitis or simultaneous ON and myelitis. In our study , myelitis was presenting feature in 64% patients, optic neuritis in 16% patients and simultaneous optic neuritis and myelitis in 4% patients. In a study by Barhate et al., 2014 , myelitis was the presenting feature in 59% patients, optic neuritis in 30% and simultaneous optic neuritis and myelitis in 7% of anti-AQP4+ patients [14].In a study by Pandit et al.,2016, myelitis was the initial attack in 63.1% (24/38) and optic neuritis was the initial event in 28.9% (10/38) patients[13].

In our study mri spine showed most frequent involvement of cervical and dorsal cord . Cervical cord was involved in 7 patients, dorsal cord was involved in 8 patients, 1 patient had cervico-dorsal involvement and 1 patient had dorsal cord to conus involvement.Cervical cord lesions extending into the medulla was seen in 16% (4/25) patients. In a study by Barhate et al., 2014, 77.5% (31/40) of the patients had cervicodorsal cord involvement .Cervicomedullary junction (CMJ) involvement was seen in 32.5% (13/40) of the patients [14]. In a study by Pandit et al., 2016 cervical and dorsal cord lesions were frequent in anti-AQP4+ patients.

Cervical cord lesions extending into the medulla was seen in 34.2% (13/38) of anti-AQP4+ patients[13].In our study cervicomedullary involvement was found to be less common as compared to other studies.

Total 5 patients presented with optic neuritis out of which 2 patients had bilateral optic neuritis , 2 patients had unilateral optic neuritis and in 1 patient MRI orbital cut was normal.

Apart from ON and myelitis, our study also noted other clinical presentations. Brainstem lesions presentations such as intractable hiccups, nausea and vomiting, ataxia ,vertigo, bulbar symptoms have been described in NMOSD[15]. Four patients in our study presented with intractable hiccups and vomiting and all four had area postrema involvement. In a study by Barhate et al., 2014, four patients presented with intractable hiccups and vomiting and all four had dorsal medulla involvement[14]. In a study by Pandit et al., 2016, brainstem attack as an initial event was seen in 7.9% (3/38) of anti-AQP4+ patients[13].

In NMOSD patients hypothalamic lesion presentations such as syndrome of inappropriate anti-diuretic hormone secretion (SIADH), narcolepsy as well as certain cerebral presentations such as impaired consciousness ,posterior reversible encephalopathy syndrome (PRES) and seizures have also been described[15]. Our study also noted thalamic ,hypothalamic and cerebral involvement.

Hemiparesis as a presentation of NMOSD has not been described in other studies. In our study two patients presented with hemiparesis, 1 patient had involvement of left subcortical white matter and periventricular and callosal involvement and other one had involvement of brainstem (midbrain to medulla).One patient presented with recurrent vomiting with respiratory involvement and altered sensorium who had involvement of b/l thalamus, hypothalamus, area postrema,right middle cerebellar peduncle ,cerebellar involvement and periventricular 3rd and 4th ventricle involvement.

CONCLUSION:

Our study highlights the important characteristics of patients with AQP-4 positive NMOSD. In our study AQP-4 positive patients most common presentation was myelitis (LETM) and optic neuritis . In brain, involvement of area postrema was most common but other regions like subcortex ,corpus callosum, thalamus , hypothalamus and brainstem were also involved.Varied presentations seen in NMOSD highlight the need for a high index of suspicion for NMOSD in demyelinating episodes not classical for MS.

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