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Validation of the 2015 diagnostic criteria for neuromyelitis optica spectrum disorders in a cohort of South Indian patients

Meena A Kanikannan*, Praveen Kumar Arepareddy, Neeharika L Mathukumalli, Sireesha Y, Rukmini Mridula Kandadai, Afshan S Jabeen, Suryaprabha T, Rupam Borgohain

Neurology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana 500082, India

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ABSTRACT

Background: Neuromyelitis Optica spectrum disorders (NMOSD) are one of the most common CNS demyelinating disorders as they will present with disabling recurrent demyelinating attacks. Hence, it is of paramount importance to diagnose early, and early diagnoses and intervention will prevent further relapses associated with NMOSD. New international consensus criteria have been proposed and studies validating its application towards diagnoses of NMOSD in south Asian population are meagre. Hence we validated the proposed International Panel for NMO Diagnosis (IPND), 2015 criteria to study the clinical, demographic profile and sero-status of patients who are presenting with core clinical symptoms of NMOSD in South India and compare it with 2006 criteria.

Methods: A retrospective study was conducted in a tertiary hospital for a period of one year. Patients who had at least one core clinical feature of NMOSD were included. Demographics and clinical data were recorded and analysed. Cases were evaluated using 2015 IPND and 2006 criteria for all patients, data was analysed using SPSS.

Results: A total of 110 patients were included and 91(82.72%) patients fulfilled IPND 2015 criteria. Out of 91 patients, 70 patients were AQP4 antibody positive and 21 were negative. Out of 110, only 30 (27.2%) satisfied 2006 criteria (24 or 80% were seropositive). 2015 criteria were more sensitive in identifying 61 new NMOSD cases juxtaposed to 2006 criteria, this difference was statistically significant ($P < 0.05$).

Conclusion: The 2015 IPND criteria were more sensitive and specific than previous 2006 criteria as it covered diverse clinical manifestations of NMOSD. Applying this criteria, NMOSD could be diagnosed among patients with monophasic illness, isolated recurrent optic neuritis, isolated recurrent myelitis, cerebral syndrome, diencephalic syndrome, brainstem syndrome and area postrema syndrome, thus improving the diagnostic yield.

1. Introduction

Neuromyelitis Optica (NMO), previously known as Devic disease is an autoimmune disorder, predominantly affecting the central nervous system (CNS). Preferentially affecting the optic nerve and spinal cord, it is characterized by chronic and recurrent inflammation, demyelination and axonal damage in the CNS. Historically, NMO was considered a variant of multiple sclerosis until the identification of a disease specific anti aquaporin-4 immunoglobulin G (anti AQP4-IgG) antibody, in patients suffering from it (Lennon et al., 2004). Discovery of this novel anti-aquaporin 4 antibody has helped in understanding the spectrum of disorders associated with the disease, and thus the disease is renamed as NMO spectrum disorder (NMOSD) (Wingerchuk et al., 2007). NMO and NMOSD were considered as two separate entities previously, but after the proposal of new criteria by the International Panel for NMO Diagnosis (IPND) in 2015, both are now called NMO spectrum disorders.

NMOSD are one of the most common CNS demyelinating disorders. Reports suggest that NMOSD might constitute 9 to 24% of all the demyelinating disorders in India and a survey among urban population in Mangalore reported a prevalence of 2.6/one lakh individuals (Pandit and Kundapur, 2014). The mean age of onset is between 32.6 to 44.7 years. The clinical presentation has been found to be universal with higher female predilection (Pandit et al., 2015). The onset of attacks in NMOSD has been associated with fever or vaccination in a third of cases (Wingerchuk et al., 1999), and the gene HLA -DRB1*03 has also been found to be associated with NMO in Indian population (Pandit et al., 2015).

Hallmark clinical features of NMOSD are bilateral optic neuritis causing severe vision impairment and LETM involving three or more

* Corresponding author.
E-mail address: meenaak@hotmail.com (M.A. Kanikannan).

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Table 1
The 2015 international panel for NMO diagnosis criteria for neuromyelitis optica spectrum disorder (NMOSD).

Diagnostic criteria for NMOSD with AQP4-IgG	At least 1 core clinical characteristic Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status	1.At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: 1a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome 1b. Dissemination in space (2 or more different core clinical characteristics) 1c. Fulfilment 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

vertebral segments. Spinal involvement in most cases cause total paraplegia or quadriplegia with a definite sensory and bladder involvement. The initial presentation of most NMOSD is monosymptomatic. Some cases might not present with the usual optic nerve and spinal involvement but present with intractable hiccups, vomiting and narcolepsy which might be the only symptoms of NMOSD (Wingerchuk et al., 2007; 1999).

The time of diagnosis is of paramount importance, as the disease is debilitating with relapsing demyelinating attacks. MRI at the earliest is warranted for early identification of NMOSD, preventing further relapses and morbidity associated with the disease. Several criteria have been proposed towards diagnosis of NMO/NMOSD. The most recent criteria, New International consensus criteria for NMOSD developed by Wingerchuk et al. (2015), (Table 1) is based upon core clinical criteria, anti AQP4 antibody status, and MRI imaging features. The new criteria were introduced to replace the previous 2006 NMO criteria as it had several limitations in diagnosing patients with monophasic illness, and symptomatology outside the spinal cord or optic nerve. However, there are no studies evaluating the application of the 2015 IPND criteria in south Asian population, especially those in Indian subcontinent. Hence we validated the proposed International Panel for NMO Diagnosis (IPND), 2015 criteria to study the clinical, demographic profile and sero-status of patients who are presenting with core clinical symptoms of NMOSD in South India and compare it with 2006 criteria.

2. Materials and methods

We conducted a single centre based retrospective study at the Department of Neurology, Nizam's Institute of Medical Sciences, Hyderabad, in the year 2018. The protocol for the study was approved by the Institute's ethical review board and consent from patients was obtained, whose medical records were to be used in this study. Medical records of patients, who had at least one core clinical characteristic of NMOSD, at the onset or during the course of the disease such as acute transverse myelitis (ATM), optic neuritis (ON), area postrema syndrome (APS), brainstem syndrome (BSS), narcolepsy or diencephalic syndrome (DS) and cerebral syndrome (CS); and who had attended the OPD/ were treated on inpatient basis at the institute were included. However, patients with other proven CNS inflammatory/demyelinating disorder, those with incomplete clinical or radiological data, and unknown antibody status were excluded.

Patient's demographic details such as gender, age, duration of disease, date and symptoms (type of core clinical feature) at the onset, serology status during first attack and during overall disease course, number of relapses, imaging characteristics, EDSS at the onset, second attack at the time of diagnosis of NMOSD and treatment details of each patient during the entire disease course were retrieved.

Serology test for Aquaporin IgG-4 (NMO) antibody testing was done using cell-based assay or ELISA method. Retesting was done when deemed necessary, as some typical NMOSD patients with classical MRI features lack seropositivity early and may later seroconvert.

Abnormalities on MRI brain i.e., NMOSD-typical lesions of optic nerve, brainstem, area postrema, spinal cord, diencephalon, peri-ependymal region surrounding lateral ventricles were noted down. Also, spinal cord MRI abnormalities were classified (Wingerchuk et al., 2015; Kim et al., 2010) as follows: longitudinally extensive transverse myelitis (LETM: lesions $\geq$ 3 spinal segments), short transverse myelitis (STM: only one lesion $\leq$ 2 spinal segments) and multi segmental (MSL: LETM/STM in two or more non-contiguous segments). In the first stage the 2015 IPND criteria was applied (Table 1), according to AQP4-IgG status, to determine NMOSD diagnoses in our cohort. We also applied the 2006 NMO diagnostic criteria to determine the diagnostic improvement of the 2015 IPND criteria. Second, we assumed an unknown AQP4-IgG status in patients of NMOSD with AQP4-IgG antibody and subsequently applied the 2015 IPND criteria to diagnose them based on the following: (1) at least one core clinical characteristic must be optic neuritis, LETM,or area postrema syndrome; (2) dissemination in space; and (3) fulfilment of additional MRI requirements, as applicable, to reflect real-world clinical practice in which theAQP4-IgG is not always available at presentation. We also applied the 2006 NMO diagnostic criteria to determine the diagnostic improvement of the 2015 IPND criteria within patients who were assumed to have an unknown AQP4-IgG status.

2.1. Statistical analysis

Data was analysed using SPSS, version 20.0, IL, CH. Categorical variables were compared using the chi-square test or Fisher exact test, and continuous variables using Student T test for independent samples. p value $\leq$ 0.05 was considered significant.

3. Results

A total of 110 patients who met the inclusion criteria i.e., presence of at least one core clinical feature of 2015 IPND diagnostic criteria were included in this study. The mean age of the participants was 31.3 years and the range was 7 to 66 years. Eighty five were female (77.3%) and 25 (23.7%) were male (Table 2). Ninety-one patients fulfilled 2015 IPND NMOSD criteria, whereas only 30 patients fulfilled 2006 NMO criteria

A total of 70 NMO sero-positive cases were found and of them, 59 were females and 11 were males ($P < 0.05$). Among anti AQP4-IgG seronegative patients, 21 patients fulfilled 2015 criteria, 19 patients failed to fulfil the criteria. None of the seropositive patients failed to fulfil 2015 criteria.

Comparison of 2006 criteria and the 2015 IPND criteria was done after assuming an unknown AQP4-IgG status (Fig. 1). Among 70 seropositive patients, 41 had at least two core clinical features with one or more attacks. Thirty-eight patients fulfilled first (1a) requirement of seronegative criteria i.e., presence of at least one major core clinical features; 41(58.5%) patients had dissemination in space (1b), and all 70 (100%) patients fulfilled the third criterion (1c) of MRI characteristics.

Table 2
Clinical and demographic profile of our cohort.

S.NO	IPND 2015	2006 Criteria	AQP4 +ve	AQP4-ve	TOTAL
Total	91	30	70	40	110
2015 IPND	91	30	70	21	91
FEMALE	68	21	59	26	85
MALE	23	9	11	14	25
F:M	2.9	2.3	5.36	1.85	3.4
AGE mean			30.31	32.9	31.25
Age <18	12	6	10	7	17
Age–18–30	32	18	35	15	50
Age >30	42	6	25	18	43
No OF ATTACKS	2.6	3.37	2.78	1.725	2.4
1	22	3	15	22	37
2	32	8	26	9	35
3	13	8	11	7	18
4	9	3	8	2	10
5	4	3	4	0	4
6	3	2	3	0	3
>6	3	3	3	0	3
ON	48	30	39	19	58
TM	65	30	53	23	76
APS	27	8	22	5	27
Diencephalic	9	0	6	5	11
BSS	18	3	11	9	20
cerebral	5	0	1	6	7
EDSS AT DIAGNOSIS	5.47	5.4	5.6	4.95	5.4
<4	33	9	24	19	43
≥4	58	21	42	19	67
EDSS AT 1st ATTACK	4.6	4.03	4.72	5.2	4.7
EDSS AT 2ndATTACK	4.56	5.2	5.72	5.37	4.6
TOTAL	91	30	70	40	110

With this overall 38 seropositive patients (54.3%) fulfilled sero-negative criteria (i.e. 2015 IPND criteria for unknown or negative AQP4-IgG4 antibody testing).

The average number of core clinical features using 2015 criteria was 1.95 compared to 2.33 in patients meeting 2006 criteria ($P<0.05$). Transverse myelitis was the most common symptom among patients meeting 2015 criteria ($n = 65$), followed by optic neuritis ($n = 48$), area postrema syndrome ($n = 27$), BSS ($n = 18$), diencephalic syndrome ($n = 9$) and cerebral syndrome ($n = 5$). In 2006 criteria, apart from mandatory optic neuritis and transverse myelitis, only eight had area postrema syndrome and three had BSS (Table 3). With regard to attacks, significantly greater number ($\mu=3.4$) was found in patients diagnosed using 2006 criteria compared to 2015 criteria ($\mu=2.6$) and there was a significant difference in mean number of attacks between seropositive (3.17) and seronegative (1.81) NMOSD (2015) patients (Fig. 2).

When the 2006 criteria were applied for diagnoses, only 30 fulfilled the criteria out of 110. Out of the thirty patients who fulfilled, 24(80%) were seropositive and 6 (20%) were sero-negative ($P<0.05$). Only six sero-negative patients met 2006 criteria compared to 34 who failed to fulfil it, indicating that 2006 criteria were fulfilled more in patients with NMO antibody positivity. 2015 IPND criteria was significantly sensitive in identifying 61 new NMOSD cases juxtaposed to the 2006 criteria and this difference was statistically significant ($P<0.05$, Fig. 3)

Further 2006 criteria failed to identify significant number of seropositive cases as effectively as 2015 criteria. Seropositive patients who failed to fulfil seronegative 2015 criteria (32 patients) after assuming unknown status had also failed to comply 2006 criteria ($P<0.05$). Thus, overall 2015 criteria was better in diagnosing NMO antibody positive patients in comparison to 2006 criteria.

4. Discussion

Neuromyelitis optica spectrum disorders are autoantibody mediated chronic inflammatory diseases of the CNS. Previous studies in India have reported that NMO may represent 9–24% or higher of all CNS demyelinating disorders (Jacob and Boggild, 2007). In another study by Pandit and Mustafa (2013), NMO prevalence of 15% was found among all demyelinating disorders reported. Hence, it is of paramount importance to diagnose NMOSD patients as early possible, since the disease cripples the individual with recurrent demyelinating attacks, and early identification will further enable the physician in preventing further relapses and morbidity associated with this disease. Wingerchuk et al. (2015) proposed New International consensus criteria for NMOSD, as the previous 2006 NMO criteria (Weinshenker et al., 2006) required an update to diagnose patients who had monophasic illness and symptoms localized outside the spinal cord or optic nerve. Since its introduction, the 2015 IPND criteria have led to increase in the rate of NMOSD diagnosis in European and Korean populations, thus proving the utility of the new proposed criteria (Hamid et al., 2016; Hyun et al., 2016). However, there are no studies evaluating the application of the 2015 IPND criteria in south Asian population, especially Indian population in comparison to the 2006 criteria.

Autoimmune disorders are more prevalent among women, and NMOSD are also more common in female (Borisow et al., 2017). Of 110 patients in our study, 85 were female (77.3%) and 25 were male (22.7%). Female to male ratio was 3.4 in our entire cohort, whereas more men were found in NMO negative group. In NMOSD (2015 IPND) group, 68 (74.72%) were female and the remaining were male (25.28%). Serology status was assessed using aquaporin antibody testing either by cell-based assays or ELISA. Seventy were found to be seropositive for anti AQP4-IgG Ab among the total 110 patients. Positive seroconversion was observed among four patients (5.7%) compared with 8% seroconversion in a study done by Hyun et al. (2016). Out of the 91 cases of NMOSD, 21 (23.1%) patients were seronegative and 70 (76.9%) were seropositive and none of seropositive patients failed to fulfil 2015 IPND criteria. 2015 IPND criteria was able to diagnose even seronegative patients well in our cohort. Most seropositive patients fulfilled the 2006 criteria (80%). In a study done by Hamid et al. (2016), 111 patients were diagnosed as NMOSD of which 81 (73%) were AQP4 IgG ab positive, and 226 out of 252 patients with NMOSD were seropositive in a study done by Hyun et al. (2016), and 65 out of 104 patients with NMOSD in another study in Latin American patients (Carnero et al., 2018). Twenty-nine patients (41.4%) of seropositive NMOSD had only one core clinical feature i.e. they had one or more clinical demyelination at one anatomical site only. Nine seropositive NMOSD patients had isolated optic neuritis. Nineteen seropositive NMOSD patients had isolated transverse myelitis, whereas none of the seropositive NMOSD patients had isolated diencephalic, brainstem or cerebral presentation. With all these findings, we validated that optic neuritis, transverse myelitis, and area postrema syndromes are major core clinical characteristics of NMOSD. Therefore, for the diagnosis of NMOSD in suspected patients who present with isolated CNS syndromes, rigorous repetition of the AQP4-IgG assays using validated methods is required (Wingerchuk et al., 2015; Waters et al., 2012; Jiao et al., 2013; Jarius and Wildemann, 2010).

2015 IPND criteria was able to identify 61 (67% of $n = 110$) new cases, a 203% increase in detection of NMOSD compared to the 2006 criteria, and 60% of them being seropositive. This finding suggests that 2015 IPND Criteria was significantly sensitive than the old 2006 criteria. Carnero et al. (2018) reported a 62.5% rise in new case detection, whereas Hyun et al. (2016) reports 46% rise in new cases. Significant rise in new cases diagnosed with NMOSD 2015 criteria in our study could be because of short duration of illness compared to other studies, as long follow-up will detect subsequent optic neuritis and transverse myelitis attacks, and thus fulfilling 2006 criteria. Of patients who did not fulfil 2015 criteria, none fulfilled the 2006 criteria indicating that 2015 IPND NMOSD criteria were specific in relation to 2006 criteria. Twenty-two patients who were AQP4-IgG negative status had single attack and only 3 of these patients fulfilled IPND criteria i.e.

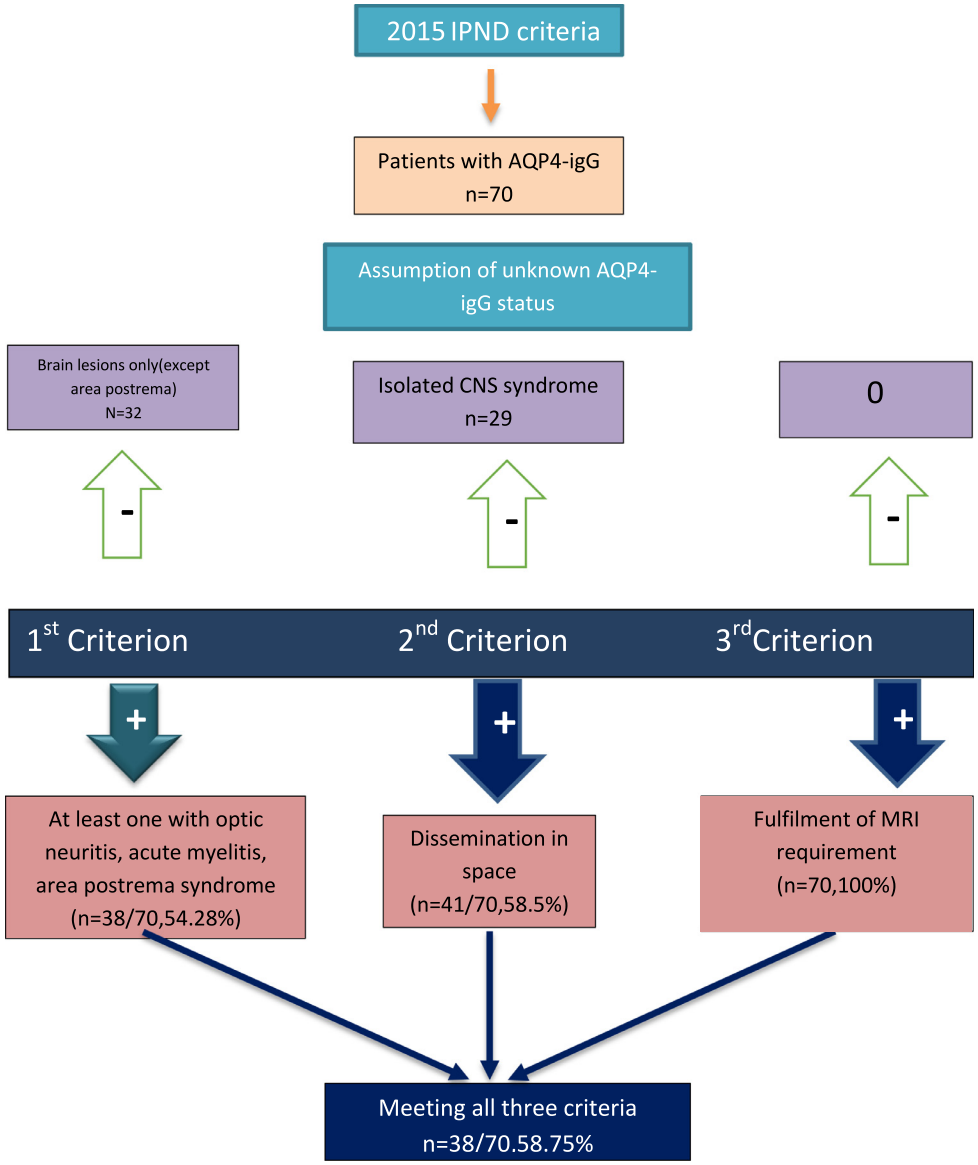

Fig. 1. Application of 2015 IPND Criteria under the assumption of unknown serostatus.

Table 3
Comparison of new cases vs 2006 in relation to core clinical symptoms.

Clinical Features	New Cases		2006 Criteria		p-value
	No.	%	No.	%	
ON	20	40	30	60	<0.001*
TM	37	55.2	30	44.8	<0.001*
APS	19	70.4	8	29.6	0.66
DIENCEPHALIC	10	100	0	0	0.019*
BSS	16	84.2	3	15.8	0.073
Cerebral	6	100	0	0	0.076

* $P < 0.05$ is considered significant.

dissemination in space. Rest of the others had only monophasic illness. 54.3% (38/70) of patients with AQP4-IgG Ab positive NMOSD were diagnosed by the 2015 IPND seronegative criteria. Under the assumption of an unknown or negative AQP4-IgG status, the difference in the diagnosis rate between the 2015 criteria and previous 2006 criteria was significant. In a south Asian setting, in which the AQP4-IgG assay is not always available, significant increase in diagnosis without AQP4-IgG Ab is of paramount importance. Till date only one study has reported data regarding fulfilment of individual seronegative criteria, in which, 162 out of 226 (72%)seropositive patients fulfilled the criteria under the assumption of unknown/seronegative criteria (97% had at least one major core clinical feature,74% had DIS, 99% had fulfilled MRI requirements) (Hyun et al., 2016). In comparison, our study had only 58.5% of patients fulfilling DIS because we had more patients with monophasic illness who didn't had dissemination in space or with recurrent disease at only one CNS site e.g. isolated recurrent optic neuritis (n = 14), and recurrent myelitis (n = 12). All patients with area postrema syndrome had dissemination in space. In previous study by Carnero et al. (2018), only 14% of total patients presented with monophasic illness. Seropositive patients without DIS should be followed up rigorously as most patients will experience relapses (73% had relapses in 5-year follow-up) (Hyun et al., 2016). Chances of seropositivity increases with the number of attacks. In study done by Mealy et al. (2012) mean number of attacks were 3.6 in a total cohort and 4.2 in patients who satisfied 2006 criteria which is similar to the results of our study.

We investigated the presence of the core clinical characteristics over the entire disease duration and at the disease onset. Transverse myelitis (n = 76, 69%) was the most common symptom in our study, followed by optic neuritis (n = 58, 52.7%) and area postrema (n = 27, 24.5%).

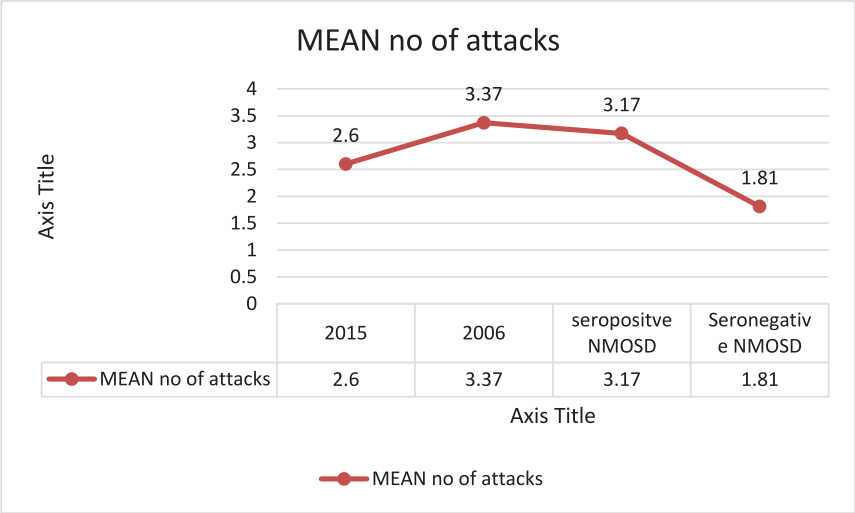

Fig. 2. Mean number of attacks among various groups.

Transverse myelitis was the most common symptom among patients meeting 2015 criteria ($n = 65$) as found in previous epidemiological studies (Hyun et al., 2016; Mealy et al., 2012; Nagaishi et al., 2011), followed by optic neuritis ($n = 48$), area postrema syndrome ($n = 27$), BSS (18), diencephalic syndrome ($n = 9$) and cerebral syndrome was the least common($n = 5$). Among those who fulfilled 2006 criteria, apart from mandatory optic neuritis and transverse myelitis only 8 patients had area postrema syndrome and 3 patients had BSS (Table 2). Mealy et al. (2012) in their study reported transverse myelitis 179 ($n = 95.7\%$) as the most common, followed by with optic neuritis 137 ($n = 73.3\%$) (Mealy et al., 2012). Optic neuritis was the most common presentation at first attack in seropositive patients as in other previous studies (Hyun et al., 2016). Presence of area postrema syndrome alone or with other core clinical feature, and a combination of optic neuritis with transverse myelitis correlated well with seropositivity for NMO antibody ($P < 0.05$), thus justifying inclusion of area postrema syndrome as a major core clinical feature in IPND 2015 Criteria. In our study there was a significant correlation for the presence of diencephalic syndrome, brainstem syndromes and cerebral syndromes between 2015 NMOSD cohort and 2006 cohort, thus justifying the inclusion of these as core clinical characteristic features of NMOSD.

We also noted that patients meeting 2006 criteria had more average number of core clinical features as compared to those meeting 2015 IPND criteria (2.33 vs 1.95, $P < 0.05$), implying that 2015 IPND criteria was able to diagnose patients early.

Further, there was no statistically significant difference observed in the mean EDSS at diagnosis, at first presentation, at second attack in relation to NMO status and mean EDSS at diagnosis in 2015 criteria was 5.47 ± 1.95 compared to 5.43 ± 1.63 in 2006 criteria.

All of our patients received either oral or IV steroids as rescue therapy on presentation with core clinical features. 45 patients received azathioprine as first long-term immunosuppressive therapy, 16 patients received mycophenolate as first long-term immunosuppressive therapy, 37 patients received rituximab as long-term suppression (either as first choice or after failure of other immunosuppression). Out of 37 who received rituximab, only one patient relapsed during our study period. The merits of the study are, we are the first to validate 2015 criteria among south Indian population compared to 2006 criteria in diagnosing NMOSD. However, we do have some limitations and they include the enrolment from a single-center, selection bias as most patients enrolled were of high disability and limited follow up.

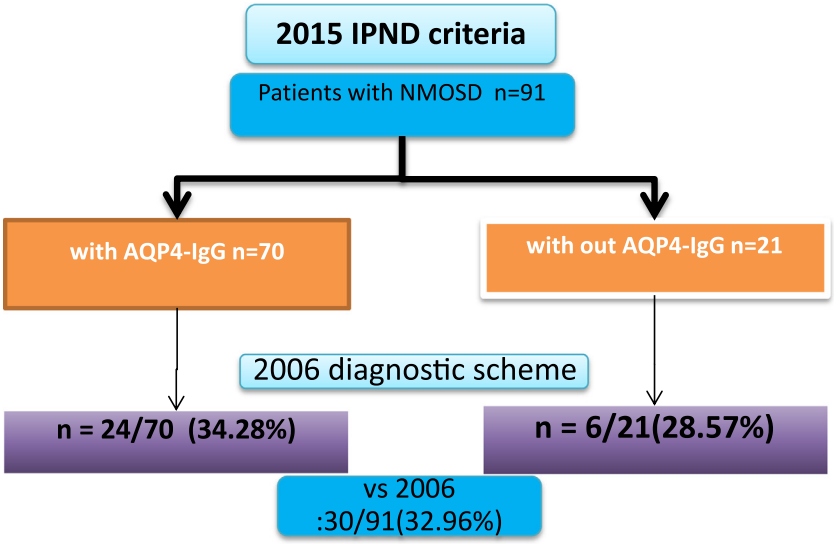

Fig. 3. Comparison of 2006 criteria and 2015 IPND criteria.

5. Conclusion

In conclusion, the 2015 international consensus criteria for NMOSD was more sensitive and specific than previous 2006 NMO criteria in diagnosing patients with features suggestive of NMOSD. Further, 2015 IPND criteria was more able to diagnose NMOSD among patients with monophasic illness, isolated recurrent optic neuritis, isolated recurrent myelitis and area postrema syndrome. Also, it could diagnose patients with diencephalic syndrome, brain stem syndromes and cerebral syndromes as NMOSD, thus improving the diagnostic yield. We suggest repeated testing for AQP4-IgG antibody in seronegative patients, especially during relapse and before starting immunosuppression and future prospective studies are warranted to validate 2015 IPND criteria.

Declaration of Competing Interest

None.

Role of funding

There was no funding for this study. None of Authors have any conflicts of interest.

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