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A characteristic analysis of longitudinally extensive transverse myelitis in South Indian population: A cohort study

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Abstract

This study described the clinical and paraclinical features of south Indian patients with longitudinally extensive transverse myelitis (LETM) and contrasted the findings betweenaquaporin-4 positive versus negative patients. The subjects were recruited between2010 and 2013.The distinctive features among71 LETM patients were compared and it was observed that 56% of the total subjects were found to be AQP4-Ab positive. The ratio of female tomale was found to be higher in the AQP4-Ab positive group. Magnetic resonance imaging showed holocord involvement more commonly in AQP4-Abnegative than positive group. The presence of hypointense lesions did not correlate with severity. The main distinctive features between AQP4-Abpositive and negative cases include older onset age, higher proportion of female, low frequency of conus involvement and higher prevalence of coexisting autoimmune disorders in AQP4-Ab positive cases. Therewas no difference in attack severity, onset of optic neuritis, and spasms between the two groups. Our results suggest that the clinical and spinal cord neuro-imaging information can aid in distinguishing between the positive and negative group of patients with LETM. The early detection of AQP4-Ab positive status predicts the recurrence of LETM or occurrence of optic neuritis duringthe study period.

Keywords: LETM, NMO, AQP4-Ab, MRI hypo-intense lesion

INTRODUCTION

Longitudinal extensive transverse myelitis (LETM) refers to spinal cord lesions extending at least three vertebral segments. LETM is observed in neuromyelitis optica (NMO)[1,2] and several other inflammatory disorders of the central nervous system (CNS) including paraneoplastic diseases.[3] NMO is an autoimmune disease that affects the optical nerve and spinal cord. Aquaporin4IgGautoantibody (AQP4-Ab) is a specific biomarker which helps to distinguish NMO from other causes of LETM.[4,5]

The presence of AQP4-Ab in patients with LETM predicts the recurrence of myelitis or optic neuritis in NMO.[6] Most of the patients whose serology is positive for AQP4-Ab have limited forms of disease such as monophasic or recurrent LETM or less commonly bilateral or recurrent optic neuritis or brain disease. These patterns can be found in various combination in the spectrum disorders of neuromyelitis optica.[7]

The present study aims to describe the clinical, radiological, immunological and genetic characteristics of patients with inflammatory LETM to improve the diagnosis and prognosis of the disease.

METHODS

We performed an observational retrospective analysis of our data base of patients with LETM who were admitted to the Neurology department of Nizam's Institute of Medical Sciences during 2011 to 2013. The clinical study was approved by the Human ethics committee. All the patients were provided with written informed consent prior to the study initiation. The patients who fulfilled the inclusion and exclusion criteria were recruited into the study. The inclusion criteria were: (1). Inflammatory transverse myelitis as defined by the Transverse Myelitis Working Group[8]; (2). Inflammatory lesion of the spinal cord extending over at least three contiguous

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vertebral segments; (3). Spinal cord MRI images performed within 1 week from LETM onset. The exclusion criteria were patients with vasculitis, infection and malignancies.

The patients recruited were subjected to neurological examination and imaging before starting immunosuppressive therapy. The functional scoring was performed using EDSS which had not been studied in the Indian population. NMO was diagnosed according to current diagnostic criteria.[9] Cerebrospinal fluid (CSF) analysis was done during the acute phase of myelitis in all patients. Serum and CSF was screened for viral infections which included varicella, herpes virus, rubella cytomegalo viruses and Epstein-Barr virus. Serum analysis for vasculitides (ANA, anti-dsDNA, anti RO, anti-LA antibody and RF antibody), B12 and copper levels were done. The patient's neurological disability at the nadir of the attack was evaluated by using the Expanded Disability Status Scale (EDSS) developed by Kurtzke.

The sera obtained from the patients were tested for AQP4-Ab by immunofluorescence assay. Visual evoked potentials(VEP)were measured and recorded using standard procedures. Relapse of LETM was defined as the occurrence, recurrence, or worsening of the symptoms of neurological dysfunction that lasted more than 24 hours with an intervalof one month or more. Fever related occurrence or worsening was not included as a relapse.

Brain and spinal cord MRI images were obtained using 1.5 Tesla scanner, including inversion recovery T2-weighted images and T1 weighted images before and after gadolinium administration. Fluid attenuated inverse recovery (FLAIR) sequences in axial and coronal planes for brain imaging, T1 and T2 sequences in axial and sagittal planes for spinal cord imaging were obtained.

Statistical analysis

Continuous variables were analysed using independent sample t test, categorical variables compared using chi square test, or Fisher exact test when the cell size is <5. Functional outcomes were evaluated using the initial event i.e., recovery after 3 months, and by the EDSS score during last follow-up. Statistical significance was set at P <0.05.

RESULTS

Demographic and clinical characteristics

There were a total of 105 cases of myelitis. Two patients had myelitis secondary to systemic lupus erythematosus, 3 due to multiple sclerosis, 6 had parainfectious myelitis, 4 due to tuberculosis, 2 sarcoidosis, 17 acute short segment transverse myelitis and 71 patients had LETM. Among the 71 patients recruited with LETM (Table 1), 40 (56.34%) patients were AQP4-Abpositive [AQP4(+)]. The mean age was 35.1 years for AQP4(+) patients and 30.7 years for AQP4-Ab negative[AQP4(-)] patients.

The median follow-up time was the same in both seropositive and seronegative groups. There was no difference in the proportions of patients with preceding infection or pain between the two groups. The first or the presenting neurological symptoms were similar in both the groups. There was no statistical difference in the prevalence of the optic neuritis or the initial presentation between the two groups. Bladder involvement was more common in the AQP4(-) patients though this was not statistically significant.

LETM was associated with severe disability in both groups. EDSS scores were similar in both groups at nadir and during the recovery phase (which included only patients with follow-up duration >6 months).

Treatment

Allthe patients received intravenous methylprednisolone 1gm daily for 5 days. Additional treatment with plasma exchange was used in steroid non-responders, which included 10/40(25%) of AQP4(+) and 4/31(12.9%) of AQP4(-) patients. Thirty-five(87.5%) AQP4(+) and 11(35.48%) AQP4(-) patients received long term immunosuppression.

Relapse

Most of the patients had relapses with LETM. Amongst them, 2 were AQP4(+) and 1 was AQP4(-) NMO patients.[9] None of the AQP4(+) patient died during the first LETM attack but 2 AQP4(+) patients subsequently died during relapses due to respiratory involvement.

Imaging

The MRI was done at a similar point in disease course in both AQP4(+) and AQP4(-) patients. The mean number of spinal segments in AQP4(+)

Table 1: Demographic, clinical, and paraclinicalfeatures of AQP4antibody positive [AQP4(+)] and negative [AQP4(-)]patients

Clinical/paraclinicalfeature	AQP4(+) (n=40)	AQP4(-) (n=31)	*P* Value
Female,%	34 (85%)	17 (54.8%)	**0.008**
Age at LETM in years, mean (SD)	35.10(13.43)	30.66(13.23)	NS
History of ON	15(37.5%)	10(32.2%)	NS
Devic phenotype at onset	7(17.5%)	8(25.8%)	NS
ANA positivity	14(35%)	2(6.4%)	**0.004**
First neurological symptom			
Weakness	14(35%)	12(38.7%)	NS
Paresthesias	14(35%)	9(29%)	NS
Backpain/neckpain	8(20%)	4(12.9%)	NS
Opticneuritis	4(10%)	3(9.6%)	NS
Urinary retention	0	3(9.6%)	NS
Abnormal VEP	18(45%)	10(32.2%)	NS
CSF	N=40	N=31	
Normal	24(60%)	24(77.4%)	NS
Pleocytosis	12(30%)	3(9.6%)	NS
Protein elevation	2(5%)	4(12.9%)	NS
Oligoclonal bands	2(5%)	0	
Nadir EDSS score, median (range)	8.5(4-9)	7.5(3-9)	
EDSS score at recovery, median (range)	3.5(1-6.5)	3.0(1-4.5)	NS
Relapse within 3 year of LETM, no. (%)	28	6	**<0.05**
FU since LETM in years	6 mon-4 years	6 mon-4 years	

NS-Non significant

patients was 7.7 when compared to that of 8.7 in seronegative group. Both groups demonstrated similar site of distribution i.e., cervicodorsal segments of the spinal cord. There was no correlation between lesion length and EDSS scores at nadir or during the recovery phase. Involvement of the conus was seen only in two AQP4(-) patients.

Brain MRI lesions not fulfilling the Barkhoff criteria were found in 21% of subjects with no statistical difference among the frequency of brain lesions between AQP4(+) and AQP4(-) patients (Table 2 and Figure 1).

Involvement of central grey matter was predominant in AQP4(+) patients (73.5%) compared to AQP4(-) patients (16.12%, $p = 0.004$).In contrast, AQP4(-) patients displayed a higher proportion of holocord involvement (19 or 61.29% vs. 8 or 20%, $p < 0.05$).

Similarly, the involvement of hypointense lesions of T1 images were more common in AQP4(+) (36; 90%) than AQP4(-) patients

Table 2: Autoantibodies presented in AQP4(+) and AQP4(-) patients with longitudinally extensive transverse myelitis patients (LETM)

Autoantibodies (number of positive tested/number tested)	AQP4(+) (*n*=40)	AQP4(-) (*n*=31)	Total (*n*=71)
ANA(%)	14/40(35%)	2/31(6.4%)	16/71
Anti-ds DNA(%)	5/40	0/31	5/71
Anti-SSA(%)	0/40	0/31	0/71
Anti-SSB(%)	0/25	0/18	0/43

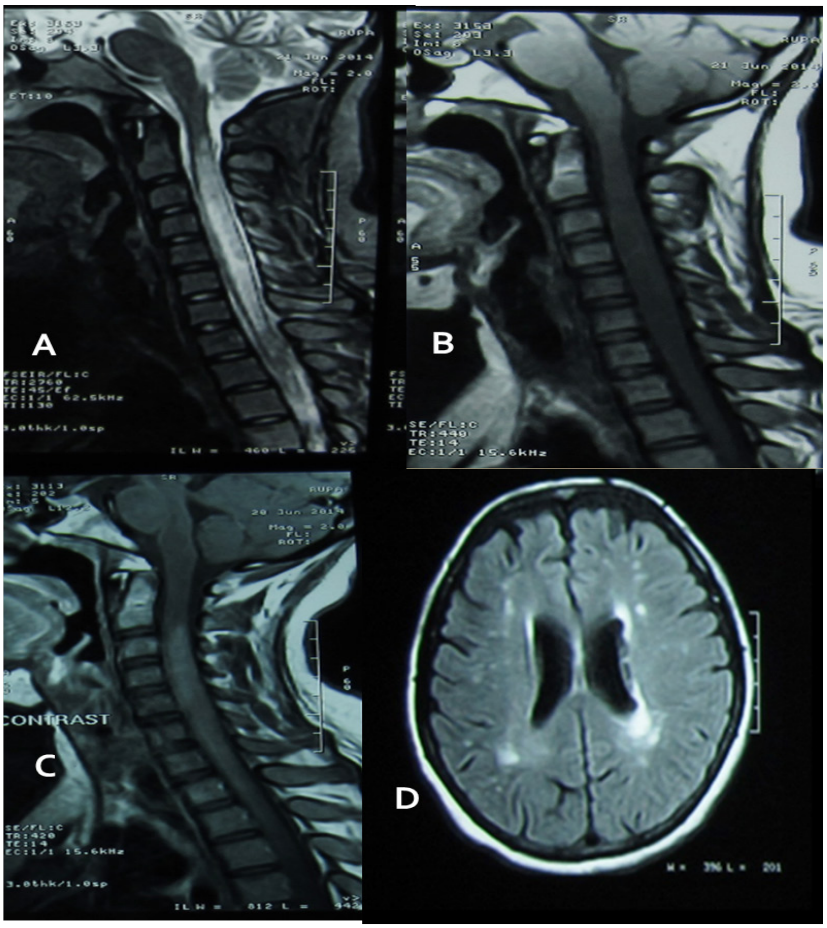

Figure 1. A. T2 sagittal image showing long segment hyperintense lesion; B. T1 image showing hypointense lesion with enlargement of the cord; C. Gd enhancement of the cord lesion; D. FLAIR axial section of MRI brain showing multiple white matter lesions.

(11;5.5%, p =<0.001), so was the involvements of peripheral white matter lesions, which was more common in AQP4(-) patients (23%, p =<0.09) .

Cerebrospinal fluid

Cerebrospinal fluid oligoclonal bands were positive in 2AQP4(+) patients and none of the AQP4(-) patients. There was a trend towards higher pleocytosis in AQP4(+) (30%) group than AQP4(-) (9.7%) patients (p=0.071).

Visual evoked potentials

Visual evoked potentials were done during the acute attack. Four of AQP4(+) patients and 3 AQP4(-) patients had delayed P100 latency period in the asymptomatic eyes, the difference was not statistically significant.

Autoantibodies

Autoantibodies were detected in 35% and 6.4% of AQP4(+) and AQP4(-) patients respectively. Antinuclear antibody was the commonest autoantibody detected though none had clinical features of other systemic disease. No patients were tested positive for anti-SSA or anti-SSB antibodies. (Table 3)

Follow up

The mean duration of the follow up period was 2.6+0.6 years. At the onset, 15 patients were presented with Devic's phenotype,7 AQP4(+) (17.5%) and 8 AQP4(-) (26%). By the end of follow up, 10 converted to Devic's phenotype, 8 in AQP4(+) (25%) and 2 in AQP4(-) group (6.5%); 25 satisfied the diagnosis of NMO, 10 were AQP4(-) and 15 AQP4(+). On the other hand, 25 were diagnosed with NMO Spectrum

Table 3: Distribution of spinal and brain lesions on AQP4(+) and AQP4(-) longitudinally extensive transverse myelitis (LETM) magnetic resonance images (MRI)

			AQP4 Antibody				p-value
			AQP4(-)		AQP4(+)		
			N	%	N	%	
Localization of lesion	Cervical		8	25.8	12	30.0	NS
	Cervicodorsal		16	51.6	18	45.0	
	Dorsal		5	16.1	10	25.0	
	Lumbosacral		2	6.5	0	0	
Character of lesion	Confluent		30	96.8	40	100.0	NS
	Patchy		1	3.2	0	0	
MRI axial cord	Central grey matter	Absent	26	83.9	11	27.5	<0.001
		Present	5	16.1	29	72.5	
	Holo cord	Absent	12	38.7	32	80.0	<0.001
		Present	19	61.3	8	20.0	
	Peripheral white matter	Absent	24	77.4	37	92.5	NS
		Present	7	22.6	3	7.5	
Contrast enhancement	Absent		8	25.8	4	10.0	NS
	Present		23	74.2	36	90.0	
Hypointense T1 lesions	Absent		20	64.5	4	10.0	<0.001
	Present		11	35.5	36	90.0	
MRI brain	Abnormal		4	12.9	7	17.5	NS
	Normal		22	71.0	29	72.5	

NS-Non significant

Disorder (NMOSD).[1] The remaining 21 patients who were AQP4(-) group were diagnosed with idiopathic LETM.

DISCUSSION

In this cohort study we reported the clinical and paraclinical features of 71 adult patients associated with LETM and contrasted the clinical features between AQP4(+) and AQP4(-) groups. In contrast to earlier studies our study patients did not show any difference in age of presentation.[10] More than half (56%) of the patients with LETM were found to have anti-AQP4 antibodies which is slightly lower compared to previous study.[11]

AQP4(+) patients had a higher relapse rate than AQP4(-) patients, as well as preponderance of female.[12] Over 70% of the AQP4(+) patients relapsed and were diagnosed with NMO or NMOSD compared to only 19% of AQP4(-) patients. At onset there were 15 patients with Devic's phenotype, 7 in AQP4(+) (18%) and 8 in AQP4(-) group (26%). During follow up 8 patients (25%) in AQP4(+) and 2(6.5%) in AQP4(-) group changed to Devic's phenotype. The present study revealed the high NMO conversion rate in seropositive LETM indicating that the presence of anti-AQP4 antibodies could be a critical factor in determining the treatment strategy of the disease. In the present study 2 AQP4(+) patients received interferon-β1a which could increase the relapserate[23-25], possibly due to a shift towards a type 2 T-helper cell dominated immunological reaction and potentiation of autoantibody production.[26] Immunosuppressants such as azathioprine and mycophenolate mofetil are reasonably effective in reducing the relapse rate.[28,31] The prior intervention with rituximab in AQP4(+) LETM could be helpful in improving the overall outcome of the patients. In comparison to the previous studies, the LETM attacks caused severe disability in both groups in our study.[13] The severity was similar at nadir and at the end of follow up period in both groups. The rate of simultaneous or rapidly sequential optic neuritis with LETM as a part of "classic" Devic syndrome was not significantly different between the two groups.

The presence of anti-AQP4 antibody is reported to be sensitive in the diagnosis of NMO; 90% of NMO patients in Japan and 83.3% in Korea were seropositive[15,16], though lower in Italian (47%)[17] and Caribbean patients (33.3%).[18]

Our study revealed that the sensitivity of anti-AQP4 is 64%.[10] Low sensitivity of anti-AQP4 in our patients with classic NMO phenotype can be explained by three reasons. We used indirect tissue immunofluorescence technique whose sensitivity is 75% compared to cell-based assays[19-21]; earlier treatment with intravenous methylprednisolone before the evaluation studies.[26] Some patients might have anti-MOG antibody, which was not tested.

The salient feature of NMO with AQP4-Ab seropositivity is the longitudinally extensive lesions of the spinal cord.[17,28] The length of cord lesions in both AQP4(+) and AQP4(-) patients was similar as noted previously.[30] Our study also revealed that the cervicodorsal segments were more commonly involved in both the groups which contrasted previous studies where the upper cervical segments was more frequently involved.[13,27] Involvement of conus was more common in AQP4(-) LETM.[29] Characteristic involvement of central gray matter in AQP4(+) LETM is in concordance with earlier reports.[10] T1 hypointense lesions were more frequently observed in AQP4(+) patients, consistent with previous studies.[26,30] Holocord involvement was more frequent in AQP4(-) LETM, which was similar to previous studies).[19,23] This finding could probably be explained by the intense inflammation seen in false negative NMOSD; causes other than NMOSD like anti-MOG or other inflammatory conditions. Similar to previous studies, we found that the percentage of the patients with abnormal brain MRIs were not significantly different among the two groups.[19,29] In AQP4(+) LETM patients, normal brain MRI is not essential to make a diagnosis of NMO. On the other hand, abnormal MRI may exclude AQP4(-) LETM patients from the diagnosis of NMO despite the presence of both LETM and optic neuritis. Location and morphology of brain MRI lesions are more important to differentiate NMOSD from multiple sclerosis.

The limitations of this study include its retrospective design, a small study population drawn from a single tertiary hospital and investigation methods.

In conclusion, the characteristic clinical and imaging features help in differentiating AQP4(+) fromAQP4(-) LETM patients. Early detection of AQP4 antibodies predicts the conversion of LETM into NMO. The involvement of central grey matter, T1 hypointense lesions, higher recurrence rate were more frequently observed in AQP4(+) patients. Whereas the involvement of holocord and conus occurred in AQP4(-)LETM patients. The early recognition of NMOSD aids in treatment strategy. Randomized control clinical trials are necessary to answer the role of immunotherapy in these patients.

DISCLOSURE

Conflicts of interest: None

REFERENCES

1. Wingerchuck DM, Lennon VA, Lucchinetti CF, Pittock SL, Weinshenker BG. The spectrum of Neuromyelitis Optica. *Lancet Neurol* 2007;6(9):805-15.
2. Iorio R, Lennon VA. Neural antigen-specific autoimmune disorders. *Immunol Rev* 2012;248(1): 104-21.
3. Kitley JL, Leite MI, George JS, Palace JA. The differential diagnosis of longitudinally extensive transverse myelitis. *MultScler* 2012;18(3):271-85.
4. Iorio R, Fryer JP, Hinson SR, *et al*. Astrocytic autoantibody of neuromyelitis optica (NMO-IgG) binds to aquaporin-4 extracellular loops, monomers, tetramers and high order arrays. *J Autoimmun* 2013;40:21-7.
5. Hinson SR, Pittock SJ, Lucchinetti CF, *et al*. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica. *Neurology* 2007;69(24):2221-31.
6. Weinshenker BG, Wingerchuk DM, Vukusic S, *et al*. Neuromyelitis opticaIgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol* 2006;59(3):566-9.
7. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*2007;6(9):805-15.
8. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology* 2002;59:499-505.
9. Wingerchuck DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66(10):1485-9.
10. Kitley J, Leite MI, Küker W, *et al*. Longitudinally extensive transverse myelitis with and without aquaporin 4 antibodies. *JAMA Neurol* 2013;70(11):1375-81.
11. JagtapSA, Mandliya A, Sarada C, Nair MD. Neuromyelitis optica and neuromyelitis optica spectrum disorder: Natural history and long-term outcome, an Indian experience. *J Neurosci Rural Pract* 2015; 6(3):331-5.
12. Pandit L, Asgari N, Apiwattanakul M, *et al*. Demographic and clinical features of neuromyelitis optica: A review. *Mult Scler* 2015; 21(7):845-53.
13. Matsuoka T, Matsushita T, Kawano Y, *et al*. Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. *Brain*2007;130:1206-23.
14. Palace J, Leite MI, Nairne A, *et al*. Interferon beta treatment in neuromyelitis optica: increase in relapses and aquaporin 4 antibody titres. *Arch Neurol* 2010;67:1016-7.

15. Warabi Y, Matsumoto Y and Hayashi H. Interferon beta-1b exacerbates multiple sclerosis with severe optic nerve and spinal cord demyelination. *J NeurolSci*2007;252:57-61.
16. Shimizu Y, Ota K, Kubo S, *et al*. Association of Th1/Th2-related chemokine receptors in peripheral T cells with disease activity in patients with multiple sclerosis and neuromyelitisoptica. *EurNeurol*2011;66: 91-7.
17. Jacob A, Matiello M, Weinshenker BG, *et al*. Treatment of neuromyelitisoptica with mycophenolatemofetil: retrospective analysis of 24 patients. *Arch Neurol*2014;66:1128-33.
18. Bichuetti DB, Lobato de Oliveira EM, Oliveira DM, *et al*. Neuromyelitis optica treatment: analysis of 36 patients. *Arch Neurol* 2010;67:1131-6.
19. Chang K, Lyu RK, Chen CM, *et al*. Distinct features between longitudinally extensive transverse myelitis presenting with and without anti-Aquaporin 4 antibodies. *Mult Scler* 2013;19(3):299-307.
20. Lim BC, Hwang H, Kim KJ, *et al*. Relapsing demyelinating CNS disease in a Korean pediatric population: multiple sclerosis versus neuromyelitis optica. *Mult Scler* 2011;17:67-73.
21. Takahashi T, Fujihara K, Nakashima I, *et al*. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain* 2007;130:1235-43.
22. Fazio R, Malosio ML, Lampasona V, *et al*. Antiacquaporin 4 antibodies detection by different techniques in neuromyelitis optica patients. *Mult Scler* 2009;15:1153-63.
23. Cabrera-Gomez JA, Bonnan M, Gonzalez-Quevedo A, *et al*. Neuromyelitis optica positive antibodies confer a worse course in relapsing-neuromyelitisoptica in Cuba and French West Indies. *MultScler*2009;15:828-33.
24. ZhongXN, Wang HH, Bao J, *et al*. Relationship between neuromyelitisoptica-IgG status and spinal cordmagnetic resonance imaging in patients with neuromyelitisoptica. *Chin Med J (Engl)* 2012;125(2):270-4.
25. Chan KH, Kwan JS, Ho PW, Ho JW, Chu AC, Ramsden DB. Aquaporin-4 autoantibodies in neuromyelitisoptica spectrum disorders: comparison between tissue-based and cell-based indirect immunofluorescence assays. *J Neuro Inflammation*2010;7:50.
26. Jarius S, Aboul-Enein F, Waters P, *et al*. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain*2008; 131:3072-80.
27. Barjate KS, Ganeshan M, Singhal BS. A clinical and radiological profile of neuromyelitis optica and spectrum disorders in an Indian cohort. *Ann Indian Acad Neurol* 2014; 17(1):77-81.
28. Takahashi T, Fujihara K, Nakashima I, *et al*. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain* 2007;130:1235-43.
29. Matsushita T, Isobe N, Piao H, *et al*. Reappraisal of Brain MRI features in patients with multiple sclerosis and neuromyelitis optica according to anti-aquaporin-4 antibody status. *J Neurol Sci* 2010;291(1-2):37-43.