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# MRI features and anti-AQP4 antibody status in Idiopathic inflammatory demyelinating CNS disease (IIDCD) in Thai patients

[1]Naraporn Prayoonwiwat *MD*, [2]Orasa Chawalparit *MD*, [2]Waraporn Pienpuck *MD*, [2]Chanon Ngamsombat *MD*, [2]Jitsupa Wongsripuemtet *MD*, [1]Sasitorn Siritho *MD*

*[1]Department of Medicine and [2] Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

### Abstract

***Objective***: To evaluate the MRI findings in different status of anti-aquaporin 4 (AQP4) antibody in Thai patients with idiopathic inflammatory demyelinating CNS diseases (IIDCDs). *Methods:* A retrospective study of 135 IIDCDs patients was performed. The available brain and spinal MRI were reviewed. All were tested for anti-AQP4 antibody. The MRI findings were analyzed for any difference between patients with seronegative and seropositive anti-AQP4 antibody. *Results:* Eighty cases included 47 seronegative and 33 seropositive anti-AQP4 antibody were reviewed. Forty seven brain and 20 spinal MRIs from the seronegative group and 32 brain MRIs and 27 spinal MRIs (one with only spinal MRI) from the seropositive group were analyzed. There was no significant difference between the two groups upon the number of patients who fulfilled Barkhof's MRI Criteria. When the patients were classified according to the location and pattern of abnormal MRI findings, more cases in the seropositive group had lesions at corticospinal tract or subependymal third/fourth ventricles *($p<0.05$).* Long-extensive spinal cord lesion and central gray matter location were found more in the seropositive group whereas the short segment, peripheral location were found more in the seronegative group *($p<0.05$).* Most of the seropositive cases had lesions at the cervicothoracic level in contrast to the seronegative cases which had more lesions at the thoracic cord level.
*Conclusion:* MRI features were different between IIDCDs patients with seronegative and seropositive anti-AQP4 antibody. The characteristics and locations of the MRI lesions were more appropriate in differentiating between the two conditions rather than the number of the lesions.

## INTRODUCTION

In the past, MRI findings in Asian multiple sclerosis (MS) were reported to be different from western MS.[1,2] Opticospinal MS (OSMS) has been proposed as a variant form of MS which has high incidence in Asian countries, especially in Japan.[3] After the discovery of anti-aquaporin4 (AQP4) antibody in serum of patients with neuromyelitis optica (NMO)[4], many previous information and studies in Asian MS were re-analyzed.[5-7] From previous studies, unexpectedly high incidence of NMO in Asian countries casted doubt to the appropriateness in using only clinical as well as MRI criteria to differentiate between MS and NMO.[3,8,9] Many reports from Asian countries showed different patterns of MRI findings between the two diseases.[5,6,10,11] Though anti-AQP4 antibody testing is currently accepted as a highly specific test in distinguishing NMO from MS, difference in sensitivity of each testing technique still remains. In the clinical context, MRI is usually more accessible than the anti-AQP4 antibody testing. Giving MS patients with the disease modifying therapy as early as possible even at their initial presentation has been proven to have great benefit.[12,13] On the contrary, misplacing an NMO patient in the MS category and treat them as such may lead to deleterious outcome.[14-16] Therefore, a prompt diagnosis is needed. MRI still has an important role especially to Radiologists as well as to Neurologists who are involved with the care of these patients. Our study was to evaluate the differences in MRI findings in patients presenting with idiopathic inflammatory demyelinating CNS diseases and the importance of anti-AQP4 antibody status in clinical practice.

*Address correspondence to:* Chawalparit O, MD, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkok, 10700, Thailand. Tel : 662-419-7086, Fax:662-412-7785, E-mail: oak_art@yahoo.com

## METHODS

Retrospective study of a total of 135 consecutive Thai patients with idiopathic inflammatory demyelinating CNS diseases (IIDCDs) visiting the MS clinic at our hospital during May 2009 to February 2010 were reviewed. Two neurologists (SS and NP) reviewed the medical records and made a clinical diagnosis without the results of AQP4-antibody status as described in our previous study.[7] In brief, diagnosis was made in the order as following. Firstly, we made diagnosis of NMO according to Wingerchuk 2006 Criteria[17] with the exception of anti-AQP4 antibody status. Secondly, other NMO spectrum disorders (NMOSDs) were assigned in patients who fulfilled either of the following criteria; (i) recurrent optic neuritis without brain lesions, (ii) acute myelitis with long spinal cord lesion extending more than 3 vertebral body segment (VBs) with or without brain lesions, or (iii) optic neuritis and/or myelitis without long spinal cord lesion but with brain MRI findings compatible with those seen in NMO.[18-22] Next, OSMS was applied if the patients had optic neuritis and acute myelitis with spinal cord MRI lesion not extending over 3 VBs and had normal brain MRI. Then classic MS (CMS) was classified if they fulfilled McDonald 2005 Criteria.[23] Clinical isolated syndrome (CIS) was next applied to the patients presented with first inflammatory demyelination.[24] Finally, patients who were "not CIS" were considered as not IIDCDs. Separately, all patients were tested for serum anti-AQP4 antibody (cell-based assay technique).[7,11,25] After disclosing anti-AQP4 antibody status, we re-evaluated the correlation between clinical diagnosis and anti-AQP4 status and then re-classified the patients. Patients who fulfilled Wingerchuk 2006 Criteria for NMO[17] with positive anti-AQP4 antibody were re-classified as definite NMO. Patients who had clinical diagnosis of CMS with negative anti-AQP4 antibody were re-classified as definite MS. In this study, only patients with MRI available in the hospital archive system were included. Three radiologists (OC, CN and JW) reviewed the MRI findings without acknowledge of the anti-AQP4 antibody status. The agreement was finalized by consensus. The study was approved by the Institutional Review Board.

### *MRI studies*

The MRI was performed on either a 1.5T or 3T machine. Abnormal lesions on MRI were recorded according to their location, configuration, relative size of involvement, number, and enhancement pattern.

Brain lesions (high signal T2 lesion) were classified as described by Kim *et al.*[26] into 6 groups as following: (1) involvement of corticospinal tract, (2) extensive hemispheric lesion, (3) subependymal third/fourth ventricles (SETFV), (4) subependymal lateral ventricles (SELV), (5) medulla oblongata extending to upper cervical cord, and (6) non-specific pattern (Figure 1). Barkhof MRI Criteria was also used in evaluating the abnormality of brain MRI.[27] Pattern of enhancement was classified as no enhancement, cloud-like enhancement and nodular enhancement. Evidence of vasogenic or cytotoxic edema was determined if any diffusion-weighted image was available.

For spinal MRI, extension of lesion, location on axial plane, and pattern of enhancement were recorded. The long-extensive spinal cord lesion was defined as a contiguous lesion extending equal to or more than 3 VBs. The axial location was classified into central gray matter, peripheral white matter and mixed patterns. Swelling of spinal cord at the location of visible lesion was justified by comparing with adjacent normal cord size. Cloud-like enhancement was defined as faint, patchy enhancement with no well-defined border of the enhancing lesion. If the lesion was homogeneously enhanced or had well-defined border, it was classified as nodular enhancement.

### *Statistical analysis*

Statistical analysis was performed by SPSS 18. Descriptive data were presented as frequency, mean and percentage where appropriate. MRI findings, clinical diagnosis and anti-AQP4 antibody status were analyzed for significant difference with predetermined p-value $<0.05$ by using Pearson's Chi square test or Fisher's Exact test.

## RESULTS

### *Demographic and clinical data*

Eighty cases with available MRI in the hospital system were included. Thirty-three patients (41.3%) had positive anti-AQP4 antibody. Demographic data and clinical diagnosis were shown in Table 1. There was no significant difference in sex and age of the patients between the two groups.

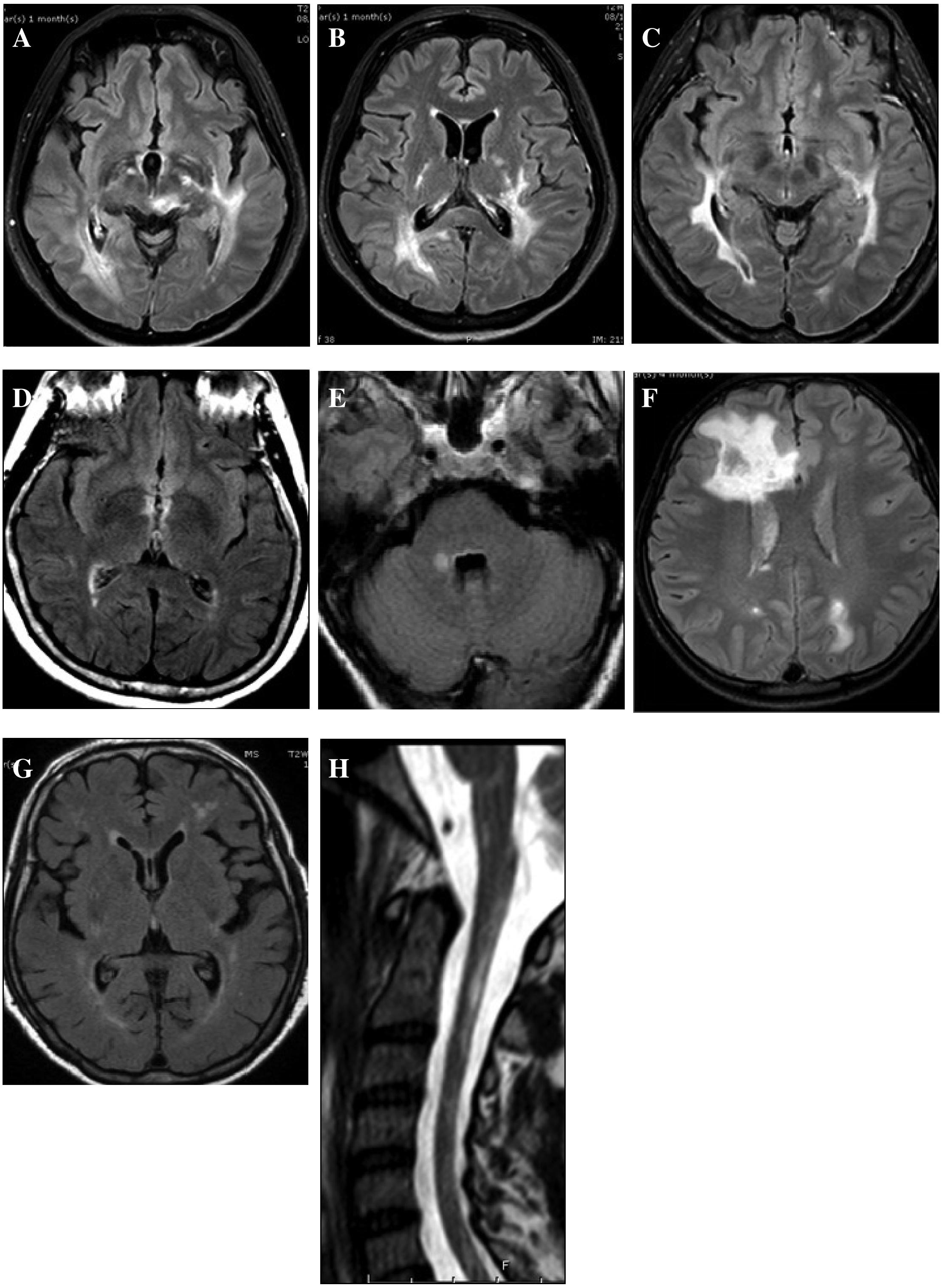


Figure 1. Brain MRI findings classified according to Kim *et al.*[26] (A, B): corticospinal tract, (C): subependymal lateral ventricle, (D, E): subependymal 3rd/4th ventricle, (F): extensive WM lesion, (G): nonspecific pattern, (H): medulla extending to cervical cord

**Table 1: Demographic findings and clinical diagnosis of patients with negative and positive anti-AQP4 antibody.**

| Variable | Anti-AQP4 antibody | |
|---|---|---|
| | Negative | Positive |
| Number of cases | 47 | 33 |
| Mean age; range (years) | 38.9; 8-67 | 42.7; 17-81 |
| Sex: F/M (%female) | 35/12 (74.5) | 31/2 (93.9) |
| Clinical diagnosis (without anti-AQP4 status): | | |
| -NMO | 3 (6.4%) | 9 (27.3%) |
| -NMOSDs | 11 (23.4%) | 8 (24.2%) |
| -OSMS | 1 (2.1%) | 1 (3%) |
| -CMS | 22 (46.8%) | 8 (24.2%) |
| -CIS | 10 (21.3%) | 0 |
| -Others: Sjogren disease | 0 | 2 (6.1%) |
| -Inconclusive | 0 | 5 (15.2%) |
| Available MRI: | | |
| -Brain MRI | 47 (100%) | 32 (97%) |
| -Spinal MRI | 20 (42.6%) | 27 (81.8%) |

NMO, neuromyelitis optica; NMOSDs, NMO spectrum disorders; OSMO, opticospinal multiple sclerosis; CMS, classic multiple sclerosis; CIS, clinical isolated syndrome

*MRI findings*

Interval from attack to imaging study varied from 1 day to 5 years. Interpretation was done in 47 brain MRIs and 20 spinal MRIs of the seronegative group, and from 32 brain MRIs and 27 spinal MRIs (one with only spinal MRI) from the seropositive group. When comparing brain MRI between the two groups, there was no significant difference in the number of patients who fulfilled Barkhof MRI Criteria. [27] According to Kim's classification[26], more cases in the seropositive group had lesions at corticospinal tract or SETFV with statistical significance. Nonspecific pattern was observed commonly in both seronegative and seropositive groups. The cloud-like enhancement was found more in the seropositive group whereas nodular enhancement was found more in the seronegative group (Table 2).

For spinal abnormalities, 66.7% of the seropositive patients had long extensive spinal cord lesion (LESCL) which was 4 times of those seen in the seronegative group (15%). Interestingly, there was a trend of having more cord swelling in the seronegative group (Table 3). Central gray matter location was demonstrated more in the seropositive group whereas peripheral location was found more in the seronegative group (Figure 2). Similar to those seen in brain MRI, cloud-like pattern was found more in the seropositive patients. Most of the seropositive group had lesions at the cervicothoracic level in contrast to the seronegative group which had more lesions at the thoracic cord level (Table 3).

*Subgroup analysis of the definite NMO and definite MS patients*

There were 22 definite MS and 8 definite NMO cases. Eight definite MS cases (36.4%) had extensive hemispheric hyper-intense lesion which was not found in definite NMO ($p<0.05$). No statistical significant difference was reached in other brain MRI findings, including Barkhof MRI criteria. The definite NMO group had a trend of having more SETFV lesion (50% VS 18.2%) and less SELV (12.5% VS 45.5%) compared to definite MS, however not significantly (Table 4).

Five definite MS and 7 definite NMO cases had available spinal MRI for comparison. Five of the seven definite NMO patients had LESCL which was not found among definite MS patients

**Table 2: Comparison brain MRI findings between negative and positive anti-AQP4 antibody.**

| Findings in brain MRI | Anti-AQP4 antibody (Number/number done, %) | | | | p-value |
|---|---|---|---|---|---|
| | Negative | | Positive | | |
| No lesion | 10/47 | (21.3%) | 5/32 | (15.2%) | 0.380 |
| Fulfilled Barkhof's criteria | 20/47 | (42.6%) | 16/32 | (50%) | 0.5 |
| Enhancement pattern | | | | | |
| -No | 24/46 | (52.2%) | 23/31 | (71.9%) | |
| -Cloud-like* | 5/46 | (10.9%) | 6/31 | (18.8%) | 0.013 |
| -Nodular* | 7/46 | (15.2%) | 2/31 | (6.3%) | 0.013 |
| Kim's classification[26] | | | | | |
| -Corticospinal tract* | 1/47 | (2.1%) | 5/32 | (15.6%) | 0.037 |
| -Extensive hemispheric lesion | 13/47 | (27.7%) | 4/32 | (12.5%) | 0.164 |
| -Subependymal 3rd/4th ventricle* | 6/47 | (12.8%) | 12/32 | (37.5%) | 0.014 |
| -Subependymal lateral ventricle | 14/47 | (29.8%) | 9/32 | (28.1%) | 1.0 |
| -Brain stem to cervical cord | 4/47 | (8.5%) | 6/32 | (18.8%) | 0.301 |
| -Nonspecific lesion | 30/47 | (63.8%) | 14/32 | (43.8%) | 0.107 |
| DWI: | | | | | |
| -Cytotoxic edema | 3/28 | (10.7%) | 1/15 | (6.7%) | 0.309 |
| -Vasogenic edema | 10/28 | (35.7%) | 10/15 | (66.7%) | |
| -Iso-signal intensity | 5/28 | (17.9%) | 1/15 | (6.7%) | |
| -No lesion | 10/28 | (35.7%) | 3/15 | (20.0%) | |

*statistical significance

**Table 3: Comparing spinal MRI findings between negative and positive anti-AQP4 antibody.**

| Findings in spinal MRI | Anti-AQP4 antibody (Number/number done, %) | | | | p-value |
|---|---|---|---|---|---|
| | Negative | | Positive | | |
| No lesion | 6/20 | (30%) | 4/27 | (14.8%) | - |
| LESCL* | 3/20 | (15%) | 18/27 | (66.7%) | 0.001 |
| Cord swelling | 9/20 | (45%) | 5/27 | (18.5%) | 0.051 |
| Axial location*: | | | | | 0.013 |
| -Central gray matter | 2/20 | (14.5%) | 13/27 | (48.1%) | |
| -Peripheral white matter | 10/20 | (50%) | 5/27 | (18.5%) | |
| -Mixed location | 2/20 | (14.5%) | 5/27 | (18.5%) | |
| Enhancement pattern*: | | | | | 0.011 |
| -No enhancement | 5/20 | (25%) | 11/26 | (42.3%) | |
| -Cloud-like | 9/20 | (45%) | 15/26 | (57.7%) | |
| -Nodular | 0 | | 0 | | |
| Level of the spinal cord*: | | | | | |
| -No lesion | 6/20 | (30%) | 4/26 | (15.4%) | 0.022 |
| -Cervical only | 2/20 | (10%) | 4/26 | (15.4%) | |
| -Thoracic only | 9/20 | (45%) | 5/26 | (19.2%) | |
| -Cervicothoracic | 2/20 | (10%) | 13/26 | (50%) | |
| -Cervicothoracolumbar | 1/20 | (5%) | 0 | | |

*statistical significance
LESCL, long extensive spinal cord lesion

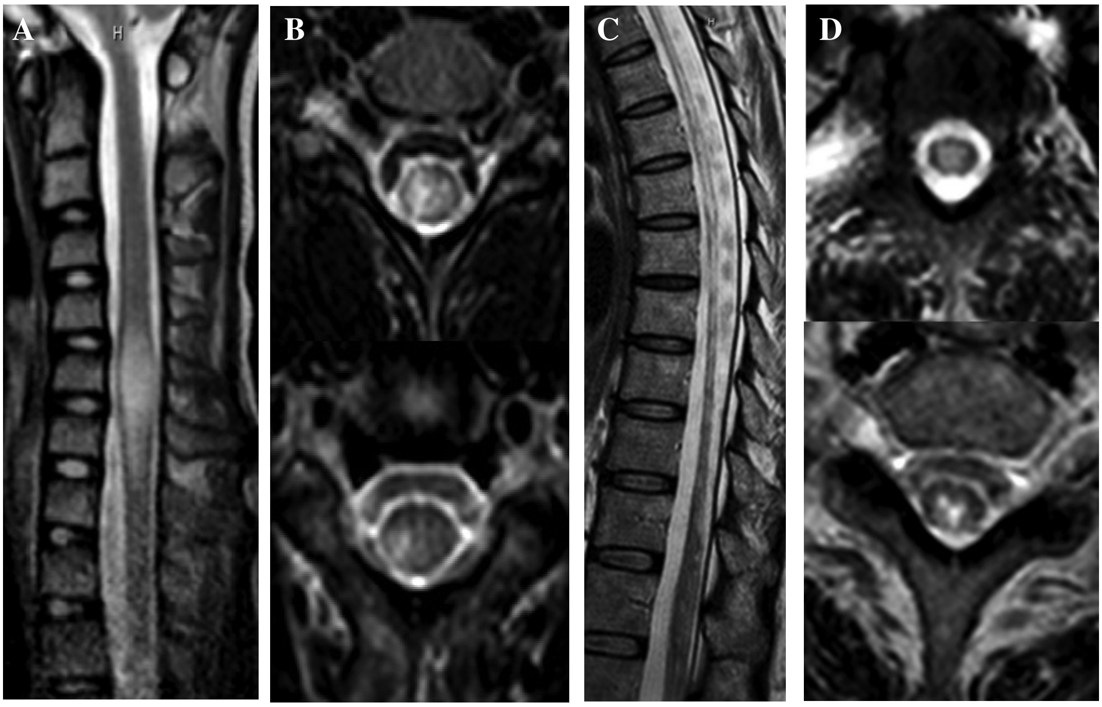


Figure 2. Typical spinal lesions on MRI in negative (A, B) and positive (C, D) anti-AQP4 antibody. Sagittal T2W (A) with short segment lesion at lower cervical level and axial T2W (B) the lesion locating at peripheral region are demonstrated in a seronegative patient. Another patient with long-extensive cord lesion (C) and locating at central cord (seen on D) has seropositive result.

($p<0.05$). On axial plane, there was a higher prevalence of central spinal cord involvement in definite NMO (100% VS 20%) in contrast to peripheral involvement in definite MS (80% VS 0%). There was a trend of more presence of the thoracic cord lesions in definite MS (80% VS 28.6%) and cervicothoracic cord lesion in definite NMO (42.9% VS 0%) (Table 5).

**Table 4: Comparison of brain MRI findings between definite multiple sclerosis (MS) and definite neuromyelitis optica (NMO)**

| Findings in brain MRI | Definite MS (22 cases) | Definite NMO (8 cases) | p-value |
|---|---|---|---|
| Corticospinal tract | 0 | 0 | |
| Extensive hemispheric lesion* | 8 (36.4%) | 0 | 0.046 |
| Subependymal 3rd/4th ventricle (SETFV) | 4 (18.2%) | 4 (50%) | 0.081 |
| Subependymal lateral ventricle (SLV) | 10 (45.5%) | 1 (12.5%) | 0.098 |
| Brain stem extending to spinal cord | 2 (9.1%) | 2 (25%) | 0.257 |
| Nonspecific white matter lesion | 15 (68.2%) | 3 (37.5%) | 0.129 |
| Fulfilled Barkhof MRI criteria | 12 (54.5%) | 2 (25%) | 0.151 |
| Enhancement (cloud like) | 8 (36.4%) | 0 | >0.05 |
| DWI (vasogenic edema) | 5 (55.6%) | 4 (100%) | >0.05 |

*statistical significance

**Table 5: Comparison of spinal MRI between definite MS and definite neuromyelitis optica (NMO) groups.**

| Findings in spinal MRI | Definite MS (5 cases) | Definite NMO (7 cases) | p-value |
|---|---|---|---|
| Cord swelling | 3/5 (60%) | 3/7 (42.9%) | >0.05 |
| LESCL* | 0 | 5/7 (71.4%) | 0.028 |
| Central gray matter* | 1/5 (20%) | 7/7 (100%) | 0.01 |
| Peripheral white matter* | 4/5 (80%) | 0 | 0.01 |
| Enhancement (cloud like) | 3/5 (60%) | 3/7 (42.9%) | >0.05 |
| Level of the spinal cord*: | | | >0.05 |
| - Cervical | 0 | 1/7 (14.3%) | |
| - Thoracic | 4/5 (80%) | 2/7 (28.6%) | |
| - Cervical to thoracic | 0 | 3/7 (42.9%) | |
| - Cervical+thoracic+conus | 1/5 (20%) | 0 | |

*statistical significance
LESCL, long extensive spinal cord lesion

## DISCUSSION

Multiple Sclerosis had been considered as a rare disease in Asia. In the past decade, many reports from the region[1,2,5,6] had shown differences from the western MS, especially abnormalities in MRI findings and presence of oligoclonal bands in the CSF.[28] Many studies in Asia, including Thailand, reported low sensitivity of McDonald Criteria 2001 and 2005 for diagnosis of MS.[1,2] Reports from Japan and Korea found high incidence of OSMS[9,29,30], which has some clinical findings similar to NMO. Many experts in the region used to consider that NMO and MS were the same disease with a spectrum of CMS and NMO at the opposite ends and OSMS stood in between[31] until a specific antibody for NMO was described and its relevant antigen (AQP4) was discovered.[4,32] It is more commonly accepted that NMO is distinct from MS upon a different pathogenesis, pathology and treatment. The accumulating information supports the concept that OSMS is a form of NMO, and should be classified as NMOSDs.[33] The evidence that not all OSMS had positive anti-AQP4 antibody and some patients had seroconversion to be positive later without an association with the severity of the symptoms, did not conform to this concept.[5] Due to its high specificity, anti-AQP4 antibody has widely been accepted as a marker for NMO. But whether anti-AQP4 is the cause of the disease or a modifying factor leading to frequent relapses and prolongation of vasogenic edema, remains to be elucidated. The International Panel on Diagnosis of MS in 2010 stated that the McDonald Criteria should be used with caution, especially in Asian and Latin American, the regions with high incidence of NMO.[34] Patients with clinical symptoms and MRI features compatible with NMOSD should undergo anti-AQP4 antibody testing to exclude NMO. The incidence of NMO in Asian countries is high and laboratory testing for the antibody is less readily accessible in many Southeast Asian countries when compared with MRI machine. Our data, hence, would be an additional information supporting radiologists when dealing with patients suspected of IIDCD. Different MRI abnormalities between patients with positive and negative anti-AQP4 antibody may help provide correct diagnosis and prompt treatment. The LESCL and central gray location in spinal MRI and subependymal 3rd /4th ventricle location in brain MRI were more common in the seropositive group, similar to previous studies.[6,10,26] These findings affirm the major immunologic role of anti-AQP4 antibody which selectively damaged to the water channel where high AQP-4 expression was found.[11,21] Due to small sample size and a retrospective study design, many typical locations of AQP4 were not found to be significantly different.

Our study implied that Thai patients presenting with spinal cord symptoms and lesions with LESCL and central gray location on spinal MRI, should undergo brain MRI to identify any asymptomatic typical NMO/NMOSD lesions.

On the other hand, patients with abnormal brain MRI typical for AQP4 locations should also undergo spinal MRI. Recently, in our institute, the brain MRI protocol for patients suspected of IIDCDs have been includes sagittal T2-weighted images for the whole spinal cord for screening, whilst the spinal MRI protocol for such patients have been also included an axial FLAIR of the whole brain for screening. Our study had some limitations. Firstly, there was small number of patients in each group. Secondly, its retrospective study design led to incomplete data collection, especially the number of patients who underwent brain and spinal MRI studies at the same time. In addition, our study did not correlate MRI lesions and timing at the onset, as well as the severity of the symptoms, therefore any predictive value of MRI findings for prognosis or clinical outcome were not demonstrated. Finally, and perhaps the most important one, among Asians where clinical features of MS and NMO are frequently overlapping and the sensitivity for anti-AQP4 antibody is not yet close to 100%. Then, a better diagnostic criteria or biomarker for each disease is still needed. Incorporated some characteristics finding in brain and spinal cord MRI in suggestive clinical presentation and anti-AQP4 antibody status will help in providing the more accurate diagnosis between NMO and MS.

In conclusion, MRI features were different between IIDCDs patients with seronegative and seropositive anti-AQP4 antibody. The characteristics and locations of the MRI lesions were more appropriate in differentiating between the two conditions rather than the number of the lesions.

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## DISCLOSURE

Conflict of interest: None

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