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Clinical diagnosis rather than aquaporin-4 immunoglobulin status predicts the cognitive performance in central demyelinating disease

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Abstract

Background: Reports on the aquaporin-4 immunoglobulin G (AQP4-IgG) status for cognitive performance and neuroimaging correlations are limited in neuromyelitis optica (NMO) and multiple sclerosis (MS) literature. *Methods:* Cognitive results of 19 MS and 15 NMO patients were compared with 47 age-matched controls. Apparent diffusion coefficient (ADC) values were used to delineate gray matter and white matter damages and correlate with neuropsychological results. *Results:* Verbal memory test showed significant differences between MS and NMO in the late registration, early and delay recall ($p<0.05$), while their retention rates were even. In MS, ADC values were significantly elevated in the dorsolateral prefrontal and occipital gray matter which was in contrast with NMO group that showed elevation in the dorsolateral prefrontal gray matter and parieto-occcipital white matter. AQP4-IgG status exerted a limited effect on ADC values and neuropsychological results.
Conclusions: Verbal memory test might be helpful in differentiating NMO and MS. ADC values can be used as a surrogate marker for tissue injury in NMO and MS since they were in line with the cognition scores. Anatomical regions with elevated ADC values were different in NMO and MS.

INTRODUCTION

Neuromyelitis optica (NMO) and multiple sclerosis (MS) are both demyelinating diseases involving the central nervous system. MS affects the central nervous system more diffusely, whereas NMO affects the optic nerve and spinal cord more selectively, typically sparing the brain.[1] The geographic distributions of MS and NMO are uneven among different populations.[2] In Asia, NMO is more commonly diagnosed and represents 15-56% of previously-diagnosed MS patients in Japan and Taiwan.[3-5] The introduction of aquaporin-4 immunoglobulin G (AQP4-IgG) in revised NMO criteria has led to increased attention on its clinical impact.[6]

AQP4-IgG seropositivity in NMO and MS patients has been reported to be 73% and 9%, respectively.[7 8] Although AQP4-IgG status has not been fully established as pathognomic for NMO, it enables the differentiation between NMO and MS with a specificity of 91-100% across different races.[7 9-11] Identifying these two diseases is of clinical relevance based on the therapeutic perspective and pathogenesis.[12] Although the prevalence of NMO is higher in Asia, the link between AQP4-IgG status and cognitive performance has rarely been reviewed. That the presence of AQP4-IgG was added as an additional feature in the revised criteria[6] and the association with astrocyte membranes in the brain has raised research questions on whether the existence of AQP4-IgG poses any effects on the cognitive performance.[7]

Diffusion-weighted magnetic resonance imaging (MRI) has enabled the researchers to obtain a quantitative assessment of the diffusion changes in areas exhibiting signal abnormality in conventional MRI or in areas with normal appearance white matter (WM).[13] By measuring the apparent diffusion coefficient (ADC) value, pathological processes that modify tissue integrity could be quantified and analyzed[14] since increase of ADC had been repeatedly reported in disorders with gray matter (GM) pathology[13] and WM diseases.[15-18] Among demyelinating disorders[19-22],

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ADC value also possesses significance in outcome prediction and with pathology correlation.

The purpose of this study was to use ADC as a surrogate marker for tissue injury and to evaluate the regional distributions of injury in the GM and WM in patients with MS and NMO. The correlations between ADC values with cognitive performances were performed to ascertain whether changes in ADC reflected cognitive deficits in these two groups. NMO patients with positive AQP4-IgG status (AQP-IgG (+)) were further examined as compared with either MS or controls to understand the clinical significance of AQP4-IgG status on cognitive performance.

METHODS

The study subjects were patients who visited the Department of Neurology, Kaohsiung Chang Gung Memorial Hospital and registered as central demyelinating disease cohort. They were screened for eligibility while those who fulfilled the clinical diagnosis of MS or NMO criteria as well as the inclusion and exclusion criteria would be recruited for study. Nineteen MS patients and 15 NMO patients were recruited to participate in this study for clinical symptoms registration, blood sampling, and cognitive assessment. Antecubital venous blood was collected for serum AQP4-IgG testing [23] after an overnight fasting of eight hours. The study received approval from the human ethics committee of the Chang Gung Memorial Hospital.

Inclusion criteria for MS or NMO

MS patients were included in this study by using the McDonald's revised criteria[24] and the Barkhof criteria[25] as follows: (1) At least one gadolinium-enhancing lesion or at least nine T2 hyperintense lesions if there was no gadolinium-enhancing lesion; (2) At least one infratentorial lesion; (3) At least one juxtacortical lesion; (4) At least three periventricular lesions. Equivocal signals from the T2 sequences in the brain were rechecked by the fluid-attenuated inversion recovery sequences, particularly in regions surrounding the ventricles. Length of myelitis was assessed both by sagittal T2 sequences and axial T2 fat-suppression sequences.

NMO patients were diagnosed based on the presence of optic neuritis, myelitis, and at least two of the three supportive criteria: (1) MRI evidence of a contiguous spinal cord lesion $\geqslant$3 segments in length; (2) Onset brain MRI non-diagnostic for MS; and (3) AQP4-IgG seropositivity.[6]

Exclusion criteria

The exclusion criteria were: (1) Expanded Disability Status Scale (EDSS)[26] > 7.5 because of the difficulty of applying cognitive tests in patients with more severe disabilities; (2) Confirmed extraneural autoimmune disease as revealed by the serology results and clinical profiles; and (3) Psychological presentation that may interfere with the cognitive assessment; (4) < 20/100 visual acuity under correction.

Cognitive assessment

Cognitive assessment was done during the remission stage to avoid delirium or other physical illness that might confound the cognition performance. General cognitive function was assessed by using the MMSE.[27] Episodic verbal memory was assessed by the Chinese version verbal learning test (CVVLT)[28] consisting of 4 registration trials (T1 to T4), 30-second delay (CVVLT-30s) and 10-minute recall (CVVLT-10m). Total correct scores (CVVLT-total) from T1 to T4 were also calculated.

Visuospatial abilities were assessed by a modified Rey-Osterrieth Complex Figure[29], pentagons, a cube copying, and by the number location test from the Visual Object and Space Perception Battery.[30] The executive function was assessed by digit backward span, design fluency, Stroop Interference test[31], Modified Trails B test[32], and semantic fluency. Abstract thinking, problem solving, and Wisconsin Card Sorting test[33] results, in which the performance of perseveration response, perseveration error, conceptual level response, category achievement, and inability to remember the rule, were recorded as part of frontal lobe function assessment. Neuropsychiatric inventory (NPI)[34] was used to assess behavioral symptoms.

MRI rating and ADC of region of interest correlation

MR imaging was performed using the 3.0T scanner (Signa Excite HD, GE Medical System, Milwaukee, WI) equipped with echoplanar capability. We obtained diffusion weighted images using a single-shot echo-planar spin echo technique with the following parameters: FOV, 24 × 24 cm; matrix size, 128 × 128; section thickness, 5 mm; section gap, 1.5 mm, and NEX, 1. The TR and TE in diffusion weighted images at b=1000 s/mm2 were 7000/72 ms with the six combinations of diffusion gradient vectors as follows: 1, 0, 1;

–1, 0, 1; 0, 1, 1; 0, 1, –1; 1, 1, 0, and –1, 1, 0, where x, y, z directions correspond to read-out, phase, slice, respectively. All selected images were transferred to our offline workstation equipped with Functool DTI for ADC images (GE Medical System, Milwaukee, Wisc).

The ADC value was measured in the following anatomical ROI modified from Galloway *et al*[35] (Figure 1): included dorsolateral prefrontal area, cingulate gyrus/corpus callosum, temporal area, parietal area, occipital area, area abutting cerebral aqueduct, and anterior/posterior perventricular spaces. Orbitofrontal area was not assessed due to its vulnerability to noise.

Statistical analysis

All the cognitive tests were compared between the NMO and MS groups and age-matched controls

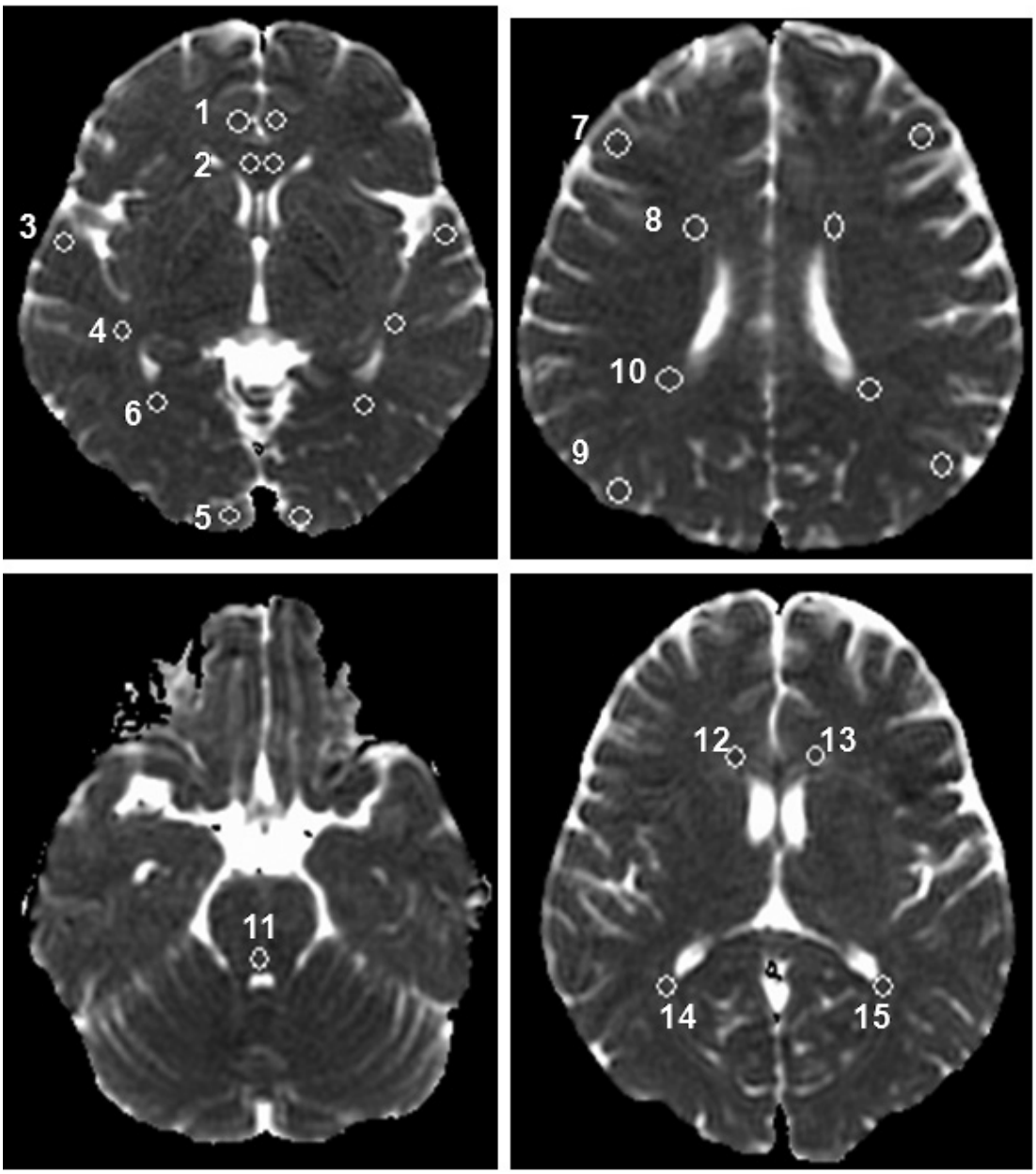

Figure 1. Template of regions of interests: 1: Anterior cingulate cortex, 2: Corpus callosum, 3: Temporal cortex, 4: Temporal white matter, 5: Occipital cortex, 6: Occipital white matter, 7: Dorsolateral prefrontal cortex, 8: Dorsolateral prefrontal white matter, 9: Parietal cortex, 10: Parietal white matter, 11: cerebral aqueduct, 12/13: anterior periventricular area, 14/15: posterior periventricular area.

selected from the normative database (n=47). The chi-square test was applied for categorical variable comparisons. The nonparametric Mann-Whitney U test was used to assess group differences in continuous variables since they were not normally distributed. Spearman correlation analysis was applied to check the correlation between continuous variables. All statistical analyses were conducted using the Statistical Package for Social Sciences software package (version 13 for Windows®, SPSS Inc, Chicago, IL). Statistic significance was defined as $p < 0.05$.

RESULTS

Demographic Data

Table 1 shows the clinical symptoms, demographic data and MRI characteristics of the MS and NMO patients. All NMO patients were female, which was significantly different from the MS group (p=0.02). The age, educational level, symptom duration and EDSS showed no significant differences between the NMO and MS patients.

With regards to clinical symptoms, NMO had trends for optic neuritis (p= 0.590) while other clinical symptoms were not different from the MS group. The AQP4-IgG positive rate was 66.7 % in the NMO group, which was significantly higher than that in the MS group (5.2%) (p<0.001). Only one MS patient had a positive AQP4-IgG status. A comparison of MRI findings between the MS and NMO patients showed that the MS group was significantly higher in fulfilling brain MRI 9 T2 or one gadolinium enhancing lesion, juxtacortical lesions (both p<0.001) and periventricular lesions (p=0.010), whereas the NMO group had more ≧3 segment spinal lesions (p=0.001).

The demographic data of AQP4-IgG positive NMO patients (NMO AQP4-IgG(+)) are shown in Table 1 right column, unveiling they had older age, age-of-onset, and longer symptom duration compared with MS group. More evidence of

Table 1. Demographic data of the multiple sclerosis (MS), neuromyelitis optica (NMO), and neuromyelitis optica with aquaporin-4 antibody (NMO AQP4-IgG(+))

	MS Mean (SD)	NMO Mean(SD)	NMO AQP4-IgG(+) Mean (SD)
	n=19	n=15	n=10
Age (years)	35.8(9.7)	43.1(13.8)	46.6(13.9)*
Sex (male/female)	6/13	0/15*	0/10*
AQP4-IgG positivity	1	10*	10*
Education (years)	12.6(3.5)	12.0(5.3)	11.0(6.2)
Age of onset	33.9(12.4)	36.4(14.5)	40.5(15.0)*
Symptom duration (months)	68.7(54.9)	98.3(75.3)	128.3(84.2)*
EDSS (mean)	1.5-7.0 (3.5)	1.5-7.5 (4.8)	1.5-7.0 (4.5)
Clinical symptoms			
Optic neuritis	10	15	10
Intranuclear opthalmoplegia	1	2	0
Motor symptoms	18	13	8
Sensory symptoms	17	14	9
Neurogenic bladder/bowel	5	7	4
Cerebellar symptoms	5	0	0
Brain MRI:			
9 T2/1 Gd(+)	16	3*	1*
1 Infratentorial	15	14	9
1 Juxtacortical	16	3*	1*
3 Periventricular	16	6*	5
Spine MRI:			
≧3 Vertebral segments	3	11*	7*

Abbreviations: SD=standard deviation

*p<0.05 compared with MS; symptom duration = the period between the patient's first symptom and the time of the study

myelitis ≧3 segment and less brain lesions, either 9 T2/1 enhanced or 1 juxtacortical ones, were noted on comparing of brain and spine images in MS patients.

Cognitive assessment

Table 2 shows the cognitive test results of the study groups. The MS group had lower scores in mini-mental state examination (MMSE), Chinese Version Verbal Learning Test (CVVLT)-T3, CVVLT-T4, CVVLT-total, CVVLT-30s, CVVLT-10m, CVVLT-recognition, CVVLT-cued correct, Delayed Rey-Osterrieth recall, pentagon copy, problem solving ability, abstract thinking, execution tasks, and pronounced perseveration response/error during Wisconsin Card Sorting

Table 2. General cognitive tests of the multiple sclerosis (MS), neuromyelitis optica (NMO), and neuromyelitis optica with aquaporin-4 antibody (NMO AQP4-IgG(+))

	MS Mean (SD)	NMO Mean (SD)	NMO AQP4-IgG(+) Mean (SD)
	n=19	n=15	n=10
Mini-Mental State Examination	24.8(5.9)*	27.3(3.5)	27.0(4.0)
Chinese Version Verbal Learning Test			
T1	4.7(2.6)	5.0(0.9)	4.7(1.0)
T2	6.1(2.5)	7.1(1.4)	6.9(1.4)
T3	6.3(2.8) *a	8.1(1.3)	7.8(1.4)
T4	6.4(2.9)*a	8.2(1.3)	8.0(1.5)
T1-T4 total	23.6(10.3) *	28.4(3.9)	27.4(4.2)
30 sec free recall	5.8(3.1)*a	7.8(1.5)	7.4(1.6)
10 min free recall	5.6(3.0) *a	7.5(2.0)	6.9(2.1)
Recognition hits	7.4(2.7) *	8.6(0.7)	8.6(0.7)
Cued correct	5.9(3.1) *	7.5(2.4)	6.8(2.7)
Visuospatial Functions			
Modified Rey-Osterrieth Copy (17)	15.2(5.4)	16.3(2.6)	17.0(0.0)
Delayed Rey-Osterrieth recall	10.3(7.0) *	12.9(4.8)	13.7(3.1)
Cube copy (2)	1.2(0.8)	1.1(1.0)	1.0(1.0)
Pentagon copy (1)	0.8(0.4)*	0.8(0.4) *	0.7(0.5) *
Visual Object and Space Perception (10)	7.6(2.9)	8.5(2.0)	9.0(1.2)
Abstract thinking (3)	1.7(1.2) *	2.1(1.2)	1.6(1.3)
Problem solving (3)	1.6(1.2)*	2.0(1.0)	2.1(1.1)
Executive function			
Digit backward	4.2(2.0)	4.7(1.9)	4.4(2.0)
Stroop interference correct	35.7(19.8)	45.6(15.8)	47.0(19.2)
Design fluency	6.9(4.1) *	9.5(3.6)	8.9(3.8)
Stroop error	2.1(3.6)	2.0(4.7)	0.6(0.8)
Trail making test time	63.9(43.7)*	54.8(37.1)	62.0(42.6)
Correct line in trail making (14)	11.5(4.6)	12.6(3.6)	11.9(4.5)
Semantic fluency-fruit (1 minute)	11.2(5.7) *	15.3(4.0)	15.0(4.5)
Wisconsin Card Sorting Test			
Perseveration response	39.1(34.7)*	33.4(26.0)*	38.6(30.8) *
Perseveration error	32.7(25.9)*	28.9(19.6)*	33.0(22.8) *
Non-perseveration error	25.1(19.7)*	19.3(13.5)	19.4(15.8)
Conceptual level response (%)	44.7(28.4)	48.9(24.1)	45.1(26.9)
Category achievement	2.5(2.6)	3.8(2.5)	3.3(2.6)
Unable to remember rule	1.3(2.4)	1.6(1.7)	1.5(1.9)

Abbreviations: SD=standard deviation
*p<0.05 compared with controls; ap<0.05 compared with the NMO group

Test as compared with the control group. The differences between the NMO and MS groups were the performances in CVVLT-T3, CVVLT-T4, CVVLT-30s, and CVVLT-10m. The retention rate of CVVLT (CVVLT-30s/CVVLT-T4 and CVVLT-10m/CVVLT-T4) is of no significant difference among NMO, MS, and the control.

On focusing cognitive deficits of NMO AQP4-IgG(+) (Table 2, right columns), they had lower achievement on pentagon copy and more pronounced perseveration response/error as compared with the control group. Their performance in neuropsychiatric testing showed no statistical differences as compared with the MS group. All three groups showed impaired pentagon copy and perseveration response/error in Wisconsin Card Sorting Test during comparison. No differences of cognitive assessment with regard to AQP4-IgG status were noted.

Behavioral assessment

On behavioral assessment, the total score of neuropsychiatric inventory (NPI) of MS group was significantly higher than the control group. Sub-domains of NPI included depression, apathy, and irritability scores were significantly higher in the MS group compared with the control, while irritability scores of NMO is intermediate to those observed from MS and control groups (Figure 2). There were no differences between the NMO and control groups or between the AQP4-IgG sero-groups in NPI total scores. Among cognitive tests discriminating between MS and NMO, only recognition scores of CVVLT correlated with NPI, and these were attributed as being incidental results during statistical analysis.

Comparison of ADC values among groups

The ADC values of GM and WM among MS, NMO and AQP4-IgG (+) NMO are shown in Table 3. The values in bilateral dorsolateral prefrontal and occipital GM and WM were significantly higher in MS than controls. In NMO, ADC level of bilateral dorsolateral prefrontal GM and parieto-occcipital WM were elevated as compared with the controls. On focusing ADC changes of NMO AQP4-IgG(+), ADC values on bilateral dorsolateral prefrontal GM, left dorsolateral prefrontal and bilateral parieto-occcipital WM were significantly higher than the control. For NMO, higher ADC values as compared with the controls were found in the WM of parietal, occipital, and posterior periventricular areas. In NMO, there were no ADC value differences with regard to AQP4-IgG status.

Correlation between ADC values with cognitive tests in NMO

Correlation between cognitive tests with ADC value of different region of interest (ROI) was analyzed. In NMO patients, ADC value in left temporal GM correlated with CVVLT-10m ($r=-0.638$, $p=0.026$) and cued correct ($r=-0.721$ $p=0.008$). Among execution tests, left dorsolateral prefrontal WM correlated with abstract thinking ($r=-0.785$, $p=0.002$), trail making test time($r=0.929$, $p<0.001$), while right dorsolateral prefrontal WM correlated with design fluency($r=-0.811$, $p=0.008$). Correlation between pentagon copying and left occipital GM ($r=-0.845$, $p=0.001$) and WM ($r=-0.941$, $p<0.001$) and bilateral temporal WM (right: $r= -0.787$, $p= 0.004$; left: $r= -0.747$, $p= 0.008$) was significant.

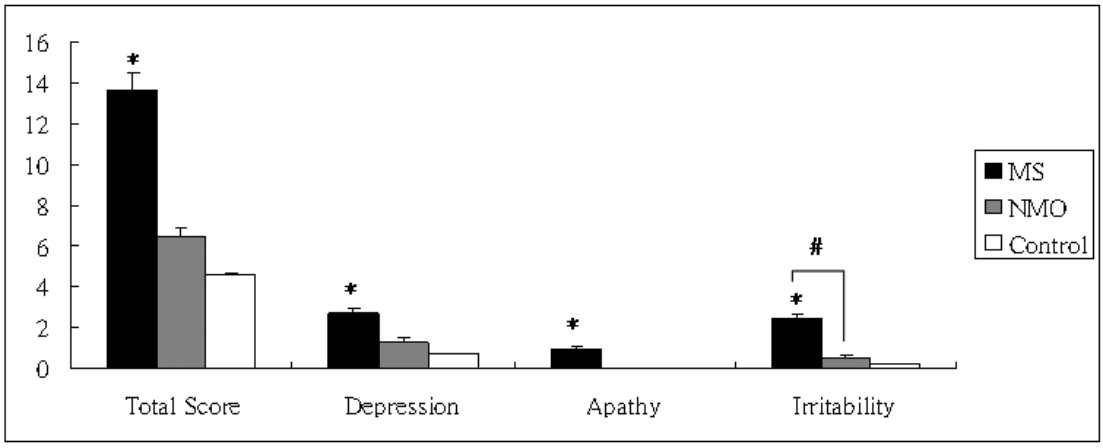

Figure 2. Neuropsychiatric inventory (NPI) scores in multiple sclerosis (MS), neuromyelitis optica (NMO) and control. Data were shown as mean+/- standard error *: $p<0.05$ compared with the control; #: $p<0.05$ compared with the NMO

Table 3. Apparent diffusion coefficient (ADC) value comparison of the multiple sclerosis (MS), neuromyelitis optica (NMO), and neuromyelitis optica with aquaporin-4 antibody (NMO AQP4-IgG(+))

Area	Control ADC value ($\times 10^{-6}$)	MS ADC value ($\times 10^{-6}$)	Difference with control		NMO ADC value ($\times 10^{-6}$)	Difference with control		NMO AQP4-IgG(+) ADC value ($\times 10^{-6}$)	Difference with control	
	Mean (SD)	Mean (SD)	%	p value	Mean (SD)	%	p value	Mean (SD)	%	p value
Gray Matter										
Rt dorsolateral prefrontal cortex	884(55.5)	1048(244.3)	19	0.010*	1034(201.7)	17	0.027*	1026(179.5)	16	0.014*
Lt dorsolateral prefrontal cortex	809(57.9)	1062(194.4)	31	0.000*	1041(194)	29	0.002*	1017(180.7)	26	<0.001*
Rt anterior cingulate cortex	887(44.7)	847(129.3)	-5	0.207	902(73.5)	2	0.413	901(66.5)	2	0.492
Lt anterior cingulate cortex	862(55.0)	888(175.4)	3	0.534	868(111.6)	1	0.858	885(102.9)	3	1.000
Rt parietal cortex	859(72)	895(120.6)	4	0.186	914(193)	6	0.359	970(237.0)	13	0.065
Lt parietal cortex	849(87.0)	843(132.8)	-1	0.833	872(99.1)	3	0.458	913(79.4)	8	0.262
Rt temporal cortex	838(77.5)	877(123.0)	5	0.166	859(68.6)	3	0.408	878(68.0)	5	0.626
Lt temporal cortex	794(60.3)	863(116.5)	9	0.024*	983(303.1)	24	0.055	979(355.9)	23	0.028*
Rt occipital cortex	793(63.5)	830(96.3)	5	0.103	808(78.6)	2	0.528	801(49.7)	1	1.000
Lt occipital cortex	769(54.0)	828(113.5)	8	0.046*	835(142.5)	9	0.143	873(174.6)	14	0.014*
White Matter										
Rt dorsolateral prefrontal area	798(42.7)	879(164.5)	10	0.048*	806(82.1)	1	0.754	822(88.2)	3	0.900
Lt dorsolateral prefrontal area	769(47.5)	908(161.1)	18	0.002*	839(116.2)	9	0.065	871(137.7)	13	0.003*
Rt corpus callosum	870(76)	927(250.4)	6	0.347	881(97.5)	13	0.680	884(85.8)	-2	0.275
Lt corpus callosum	862(67.5)	944(263.3)	9	0.200	865(138.3)	0	0.957	913(162.5)	6	0.510
Rt parietal lobe	760(53.0)	850(187.1)	11	0.053	921(209.5)	21	0.022*	883(88.3)	16	0.039*
Lt parietal lobe	749(56.8)	849(221.9)	13	0.068	929(264.0)	24	0.038*	972(318.6)	30	0.001*
Rt temporal lobe	791(60.7)	853(109.9)	8	0.012*	815(64.3)	3	0.251	826(77.5)	4	0.545
Lt temporal lobe	791(55.9)	884(197.2)	12	0.058	803(74.1)	2	0.550	820(81.7)	4	0.759
Rt occipital lobe	739(56.3)	856(142.7)	16	0.003*	878(146.2)	19	0.007*	857(120.3)	1	0.008*
Lt occipital lobe	732(59.0)	846(184.2)	16	0.016*	831(117.5)	13	0.016*	854(145.3)	17	0.002*
Anterior periventricular area	740(67.0)	947(201.3)	30	0.077	759(82.4)	3	0.117	946(134.8)	28	0.141
Posterior periventricular area	823(45.1)	1018(260.4)	24	0.004*	969(143.6)	18	0.005*	1009(162.8)	30	0.023*
Cerebral aqueduct area	739(67.0)	763(119.1)	3	0.438	758(82.4)	3	0.423	778(75.2)	5	0.186

Abbreviation: SD=Standard Deviation; Rt=Right; Lt=Left
*$p < 0.05$ compared with controls

In NMO AQP4-IgG(+) patients, ADC value in left temporal GM still correlated with CVVLT-10m (r=-0.865, p= 0.012) and cued correct (r=-0.890, p= 0.007). Trail making test time correlated left dorsolateral prefrontal WM (both r=0.979, p= 0.004). Pentagon copying correlated with value in left occipital WM(r= -0.980, p<0.001) and GM (r= -0.842, p= 0.018). We found no strong correlation of Wisconsin Card Sorting Test and NPI with all ROI.

DISCUSSION

In our study, although NMO AQP4-IgG (+) patients had older age at examination as compared with the MS patients, their cognitive deficits were not worse. This observation support the suggestion that clinical diagnosis (i.e. MS or NMO) rather than the AQP4-IgG status was more predictive with regards to cognitive performance; MS, in general, performed worse than NMO. Based on this study, cognitive deficits detected in the NMO groups regardless of the AQP4-IgG status suggested that although pathognomic, the clinical impact of AQP4-IgG on cognition should not be overemphasized. In hydrocephalus rat model[36], upregulation of AQP4-IgG was observed suggesting a possible protective role of AQP4-IgG. Whether AQP4-IgG actually exerted a protective role on NMO group or interact with other autoantibidies[37] coexisted in NMO were beyond the scope of this study.

Use of ADC was considered as a sensitive surrogate marker for demyelination in MS.[19,22] In our MS group, elevated ADC values were similarly observed either in the GM or WM. Both pathology[38] and neuroimaging study[39] in MS suggested the GM damages be related to inflammatory injury and Wallerian degeneration. In light of previous ADC studies measuring isolated WM[19,21,40] or GM[41,42] changes, the ADC patterns observed on dorsolateral prefrontal and occipital GM and WM areas suggested the parallel damages in the related networks.

In our study, anatomical regions with elevated ADC values were different in NMO and MS. NMO patients tended to have preferential WM involvement.[43,44] In addition, elevations of ADC in dorsolateral prefrontal GM were also observed in our NMO group, albeit of a lesser magnitude than MS. Only one study addressed the regions of ADC elevation in an Asian NMO population[45] and the results were in the parietal WM and optic radiation. Although their image processing methods were different from our study, the changes of ADC in the parietal WM were similarly observed in our NMO and NMO AQP4-IgG (+) group. In addition, we also observed the changes of occipital WM in the NMO group, suggesting that existence of optic neuritis in NMO patients with secondary degeneration as a plausible mechanism of such ADC patterns. Both our study and the study by Yu *et al*[45] were in contrast with the findings by Rocca *et al.*, where global WM diffusivity of NMO were not different from the control.[46] The discrepancies might be related to races, patient enrolment criteria and the ROI methods chosen. Due to lack of histology evidence in our study, the changes in GM in our NMO groups still warrant further confirmation.

Based on the knowledge that AQP4-IgG is also distributed in the ependymal lining, we also assessed the ADC changes on periventricular and periaqueductal areas.[47] Among these three ROIs, our study found that elevation in ADC values were only in the posterior periventricular area in the NMO, AQP4-IgG (+) NMO and MS group. Study by Tourdias *et al* [36] show that periventricular ADC elevation to be correlated with AQP4-IgG density and disease severity. Since our MS group also showed posterior periventricular area ADC elevation, our study could not conclude fully the linkage between AQP4-IgG and the changes of ADC.

It is worth pointing out that the comparison between the NMO and MS patients in our study was based on a similar EDSS while only verbal memory tests help to distinguish these two, especially in the late registration, early and delay recall scores. A previous study reported no differences between MS and NMO in selective reminding tests and word generation tests.[48] This might suggest that impairment in verbal memory tests in MS patients was related to a lower learning curve rather than retrieval problems. Since there were more demyelinating lesions in our MS patients, it would be plausible that more executive deficits were expected from our study. However, the results only showed more dysexecution in the MS group as compared with controls but not with the NMO group, which was similarly observed by Blanc *et al.*[48] using different executive batteries. In addition, both our MS and NMO patients had more perseveration responses and errors on the Wisconsin card sorting test. Based on our study results that elevated ADC values were found in bilateral dorsolateral prefrontal cortices and the high correlation between frontal lobe lesions with executive dysfunction[49], we considered the important role of prefrontal lobe in MS and NMO.

The scores of NPI in the MS patients were higher than the NMO and control groups. Behavioral changes in MS have been reported to be depression, sleep disturbance, irritability, liability, apathy, anxiety, and vulnerability to stress.[50] Due to the limited correlation between NPI sub-domain and neuropsychiatric test performance, we inferred that the cognitive deficits in the MS/NMO patients were independent from their behavioral or psychiatric problems.

Our AQP4-IgG positive rate, age of onset[5] and the female preponderance[51] in the NMO group were similar to previous reports, but the progression rate, in terms of EDSS, was slower. We consider this be related to the introduction of immunosuppressants or interferon-beta in the last decade. Though not thoroughly discussed in this study, the effect of disease-modifying agents on cognition merited future evaluation.

In conclusion, our study showed that influence of AQP4-IgG on cognitive performances was not detected, while cognition deficits between NMO and MS existed. Clinical diagnosis of MS or NMO may be more helpful on predicting cognitive deficit than solely depending on the AQP4-IgG status. Verbal memory tests, mainly late registration, early and delay recall scores, might be helpful in differentiating NMO and MS. ADC values in the GM and WM can be considered as a surrogate marker for these two diseases based on the correlation with cognitive test scores.

DISCLOSURE

Conflict of interest to declare: None

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