Cognitive Functions in Neuromyelitis Optica

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Background: Neuromyelitis optica (NMO) is characterized by optic neuritis and longitudinally extensive acute transverse myelitis. The brain is generally considered healthy in NMO, though very recent studies have demonstrated that magnetic resonance imaging abnormalities may be observed in various brain regions of NMO patients. To date, cognitive functions have never been investigated in NMO.

Objective: To investigate cognitive functions in a cohort of 30 patients with NMO.

Design: Observational, prospective study.

Patients: We studied 30 patients with NMO and compared them with 30 patients with multiple sclerosis and 30 healthy controls matched for age, sex, and educational level.

Main Outcome Measure: We applied a French translation of the Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis and 3 additional tests.

Results: Cognitive performance was significantly lower in the NMO and multiple sclerosis groups than in healthy controls for the 2-second \((P<.001)\) and 3-second \((P=.001)\) Paced Auditory Serial Addition Test, the digit symbol modality test \((P=.005)\), word generation \((P=.02)\), and forward \((P=.002)\) and backward \((P=.007)\) digit span test. We did not observe any difference in test performance between NMO and multiple sclerosis patients. We found no differences between the 3 groups for the other tests. We did not find any correlation between clinical, biological, or magnetic resonance imaging results and cognitive dysfunction.

Conclusions: This study confirms the recent concept of a possible brain involvement in NMO. Additional studies are needed to confirm these initial results and to better understand the mechanisms of such abnormalities.

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EUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is characterized by optic neuritis and longitudinally extensive transverse myelitis, which are usually relapsing diseases but may also be monophasic. In the past, NMO was often considered a form of multiple sclerosis (MS), but now there is a lot of evidence showing that they are different diseases. A serum autoantibody, called NMO antibody, which binds specifically to aquaporin 4, the dominant central nervous system water channel protein, was recently discovered.\(^1\)\(^2\) About 70% of NMO patients are positive for NMO antibody.\(^1\)

Aquaporin 4 is found throughout the central nervous system but in the optic nerve and spinal cord in particular.\(^3\)\(^4\) In the brain, aquaporin 4 is preferentially expressed in periventricular organs.\(^5\)

Generally, the brain has been considered to be without disease in NMO patients, though very recent studies have demonstrated that T2-weighted abnormalities may be observed in various brain regions, prevailing in the diencephalon and brainstem.\(^6\) A recent study found strong correlations between brain magnetic resonance imaging (MRI) abnormalities and aquaporin 4 localizations in periependymal regions.\(^7\)

All these findings have helped to define a larger spectrum for NMO disease, leading to a revision of the criteria first published in 1999.\(^8\) These new criteria require optic neuritis and myelitis as absolute criteria and at least 2 of the following 3 criteria: positive NMO antibody test results, normal brain MRI results, and presence of an extensive spinal cord lesion (\(>2\) vertebral segments on spinal cord MRI).\(^9\)

These new criteria allow diagnosis in NMO patients with clinical brain abnormalities or abnormalities shown on MRI but nevertheless remain highly specific.\(^10\)

During the past 10 years, numerous studies have revealed frequent and early cognitive impairment in MS. Cognitive deficiency chiefly involves attention, executive, and visuospatial functions. An internationally recognized battery of tests...
called the Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis\(^{11}\) has revealed that about 40% of MS patients have significant cognitive impairment. In a recent study validating a French adaptation of this battery,\(^{12}\) we found that 20% to 30% of patients during the first years of MS had cognitive impairment.

To date, cognitive functions have never been investigated in NMO. In light of both the confirmed frequent cognitive impairment in MS and the possible brain abnormalities in NMO, we aimed to investigate whether or not there is cognitive impairment in NMO. We examined a cohort of 30 patients (24 with diagnosed NMO and 6 with a high risk of conversion to NMO after optic neuritis or myelitis and an NMO antibody–positive test result) to determine whether cognitive impairment occurs in NMO and, if so, its frequency and the spectrum of cognitive dysfunction compared with that reported in MS.

### METHODS

#### NMO CHARACTERISTICS

We prospectively investigated 30 patients in 4 neurology departments that specialize in inflammatory diseases of the central nervous system. We only included patients with an Expanded Disability Status Scale (EDSS) score of 7 or lower because of the difficulty of applying cognitive tests in patients with more severe disabilities. Twenty-four patients had NMO according to the recently revised criteria.\(^{2}\) The remaining 6 patients were considered to be at a high risk for NMO, as they had recurrent optic neuritis (\(n = 2\)) or transverse myelitis (\(n = 4\)) and a positive NMO antibody test. Testing for NMO antibodies was conducted using a previously described method\(^{13}\) and results were positive in 17 of the 30 patients (56.7%). The mean (SD) age of the patients (23 women and 7 men) at the time of the study was 42.3 (12.3) years (range, 21-63 years). The presenting symptoms were optic neuritis in 12 cases, myelitis in 15 cases, and both optic neuritis and myelitis in 3 cases. Neuromyelitis optica was monophasic in 3 cases and multiphasic in the other cases, with a mean (SD) number of relapses of 4.2 (2.9; range, 0-11). The mean (SD) number of relapses per year was 0.8 (0.5; range, 0.1-2). Two patients were blind. The mean (SD) follow-up of NMO was 7.3 (5.4) years (range, 1-23 years). The mean EDSS score was 4.6 (SD, 2.4; range, 0-7). Four patients had other autoimmune diseases (Sjögren syndrome, \(n = 1\); systemic lupus erythematosus, \(n = 1\); Sjögren syndrome and systemic lupus erythematosus, \(n = 1\); Sjögren syndrome and myasthenia gravis, \(n = 1\)) and 2 patients had endocrinopathy (diabetes mellitus and thyroiditis).

All patients had brain and spinal cord MRI with conventional sequences in a 1.5-T machine (T1-weighted images before and after gadolinium infusion and T2-weighted, fluid-attenuated inversion recovery images). Brain MRI results were abnormal in 6 cases showing unspecific periventricular T2-weighted hyperintensities (\(n = 2\)), numerous brain lesions corresponding to MS criteria (\(n = 3\)), and periaqueductal lesion (\(n = 1\)). Spinal cord MRI results showed an extended lesion (>2 vertebral segments) on T2-weighted images in all patients except 2 and were normal in 2 cases (the 2 patients with recurrent optic neuritis and a positive NMO antibody test). We compared these 30 NMO patients with 30 MS patients and 30 healthy controls selected from a previous study who were matched for age, sex, and educational level.\(^{12}\) Characteristics of these populations are summarized in Table 1.

### COGNITIVE ASSESSMENT

The Batterie Courte d’évaluation Cognitive destinée aux patients souffrant de Sclérose en Plaques (BBCogSEP)\(^{12}\) and the Beck Depression Inventory\(^{13}\) were administered to each participant during one test session. The BBCogSEP is a battery of tests specially designed for MS patients to evaluate cognitive functions. It is based on the Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis proposed by Rao et al\(^{11}\) and comprises the French translation of the 5 following Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis tests:

1. The Selective Reminding Test, which evaluates verbal episodic memory. Performance was assessed by the mean number of words (of 15) correctly recalled at the free recall trials, a list learning index, and the number of words correctly recalled at the delayed recall.
2. The 10/36 Spatial Recall Test evaluating visuospatial episodic memory. Performance was assessed in terms of the mean number of localizations (of 10) correctly recalled at the immediate and delayed free recall trials.
3. The Paced Auditory Serial Addition Test (PASAT), which evaluates speed of information processing and sustained attention. Series of 61 numbers from 1 to 9 were randomly delivered at presentation rates of one number every 2 seconds and every 3 seconds. Participants were instructed to add each number to the one immediately preceding it. Performance was assessed by percentage of correct additions.
4. A word generation test evaluating verbal initiation. Participants were required to produce as many words as they could

### Table 1. Characteristics of NMO and MS Patients and Healthy Controls\(^{a}\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With NMO ((n = 30))</th>
<th>Patients With MS ((n = 30))</th>
<th>Controls ((n = 30))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M, No.</td>
<td>23/7</td>
<td>23/7</td>
<td>23/7</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.5 (12.3)</td>
<td>43.4 (12.1)</td>
<td>43.5 (12.3)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>12.8 (2.8)</td>
<td>13.3 (2.5)</td>
<td>12.8 (2.8)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Positive for NMO antibodies, No. (%)</td>
<td>17 (56.7)</td>
<td>0 NA</td>
<td>NA</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>7.3 (5.4)</td>
<td>9.7 (4.9)</td>
<td>9.4 (4.9)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>EDSS score</td>
<td>4.6 (2.4)</td>
<td>2.4 (1.4)</td>
<td>NA</td>
<td>.007</td>
</tr>
<tr>
<td>Brain MRI (Barkhof criteria), No. (%)</td>
<td>3 (10)</td>
<td>30 (100)</td>
<td>NA</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; NMO, neuromyelitis optica.

\(^{a}\)Values are mean (SD) unless otherwise indicated.
starting with the letter P and then as many animal names as they could. Each trial was limited to 1 minute. Performance was assessed by the number of different words generated.

5. The symbol digit modalities test of the Wechsler Adult Intelligence Scale–Revised, which evaluates information processing speed. Participants had to match (as quickly as possible and without error) symbols and numbers according to a key code. The task lasted 90 seconds and performance was assessed in terms of the number of symbols correctly coded.

The following 3 tasks were added to provide additional information about working memory and executive functions:

1. A cross-tapping test evaluating set-shifting abilities and resistance to interference. Participants were given a stick and were instructed to listen to a sound recording. When they heard a single brief sound they had to tap twice on the table with the stick; when they heard 2 consecutive brief sounds they had to tap once. Ten practice trials were run before starting the actual task, which comprised 40 trials. Performance was assessed in terms of the number of errors.

2. The go/no-go test evaluating inhibition. Participants were given a stick and were instructed to listen to a sound recording. When they heard a single brief sound they had to tap twice on the table with the stick; when they heard 2 consecutive brief sounds they had to do nothing. Ten practice trials were run before starting the actual task, which comprised 40 trials. Performance was assessed in terms of the number of errors.

3. The Wechsler Adult Intelligence Scale–Revised, digit span subtest evaluating audio-verbal working memory.

For the 2 blind patients, the 10/36 Spatial Recall Test and the digit symbol tests were omitted. We also evaluated the main mental functions by regrouping the following categories: long-term memory (Selective Reminding and 10/36 Spatial Recall tests), short-term memory (direct and indirect span number), speed of information processing (digit symbol), executive functions (PASAT, cross-tapping, and go/no-go test), and language (phonemic and semantic fluencies).

Table 2. Results of Cognitive Tests in NMO and Patients With MS

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Patients With NMO (n = 30)</th>
<th>Patients With MS (n = 30)</th>
<th>Controls (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Reminding Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of words</td>
<td>11.1 (1.8)</td>
<td>11.1 (1.7)</td>
<td>11.7 (1.4)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Learning</td>
<td>61.7 (19)</td>
<td>65.8 (18.5)</td>
<td>72.5 (17.4)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Deferred recall</td>
<td>12.2 (2.5)</td>
<td>13.1 (3)</td>
<td>13.8 (1.9)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>10/36 Spatial Recall Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>16.6 (6.6)</td>
<td>17.4 (4.6)</td>
<td>17.7 (6.1)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>6.4 (2.8)</td>
<td>6.7 (2.3)</td>
<td>6.8 (2.7)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Digit span</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>6.6 (1.4)</td>
<td>6.6 (0.9)</td>
<td>7.7 (1.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Indirect</td>
<td>5.8 (2.2)</td>
<td>5.6 (1.5)</td>
<td>7.3 (2.5)</td>
<td>.007</td>
</tr>
<tr>
<td>WAIS-R symbol digit modalities test</td>
<td>54.8 (19.5)</td>
<td>53.8 (14.9)</td>
<td>66.1 (12.6)</td>
<td>.005</td>
</tr>
<tr>
<td>Paced Auditory Serial Addition Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 s</td>
<td>28.5 (12.7)</td>
<td>25.6 (15.4)</td>
<td>36.5 (10.5)</td>
<td>.001</td>
</tr>
<tr>
<td>3 s</td>
<td>38.9 (12.7)</td>
<td>37.8 (21.9)</td>
<td>47.6 (8.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cross tapping</td>
<td>1.1 (1.8)</td>
<td>1.1 (1.6)</td>
<td>0.7 (0.9)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Go/no-go</td>
<td>1.4 (2.5)</td>
<td>0.6 (1.2)</td>
<td>0.6 (0.8)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Fluencies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonemic</td>
<td>14.3 (5.2)</td>
<td>13.5 (5.5)</td>
<td>16.9 (4.9)</td>
<td>.02</td>
</tr>
<tr>
<td>Semantic</td>
<td>22.1 (5.7)</td>
<td>20.4 (4.8)</td>
<td>21.7 (3.5)</td>
<td>&gt; .05</td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica; WAIS-R, Wechsler Adult Intelligence Scale–Revised.

DATA ANALYSIS

Results were expressed as mean (SD). We performed analysis of variance to compare the 3 subgroups. We looked for correlation between cognitive dysfunction and the following parameters: age, sex, disease duration, NMO antibodies, and presence of brain MRI abnormalities. For this statistical analysis we performed Wilcoxon and Pearson tests. P < .05 was considered significant. We considered patients to have abnormal mental functioning if their test results differed by more than 2 SDs from those of healthy controls.

RESULTS

The main demographic, clinical, and laboratory results are summarized in Table 1. The results of the cognitive tests are summarized in Table 2. Patients with NMO and MS showed significant impairment compared with healthy controls in the following tests: the 2-second PASAT (P < .001), the 3-second PASAT (P = .001), the symbol digit modalities test of the Wechsler Adult Intelligence Scale–Revised (P = .005), phonemic fluencies (P = .02), and the direct (P = .002) and indirect (P = .007) digit span test. When we compared NMO and MS patients’ performances for these tests, we did not observe any differences. We did not find any differences between the 3 groups for the Selective Reminding Test, the go/no-go test, the 10/36 Spatial Recall Test, the cross-tapping test, or the semantic fluencies evaluation. The Beck depression scores did not differ between the 3 groups. Symptomatic treatments did not differ between the NMO and MS groups.

Seventeen NMO patients (56.7%) and 11 MS patients (36.7%) had at least one result that differed by more than 2 SDs from that of healthy controls. The main cog-
Cognitive impairments are detailed in the Figure. Nine NMO patients (30%) had abnormal long-term memory impairment, 1 patient (3.3%) had abnormal short-term memory, 6 patients (20%) had abnormal information-processing speed, 8 patients (26.7%) had executive function dysfunction, and 4 patients (13.3%) had language dysfunctions. We did not find a significant difference between NMO and MS patients concerning the main cognitive dysfunctions (Figure). Five of the 6 patients with only a high-risk syndrome had at least one abnormal cognitive test. We did not find any correlations between cognitive dysfunctions and the various clinical parameters, especially Beck depression score, disease duration, and visual acuity. The only correlation we found was between the EDSS and symbol digit modalities test of the Wechsler Adult Intelligence Scale–Revised, scores ($P = .02$). We did not find any correlations between cognitive dysfunctions and brain abnormalities on MRI or NMO antibody status.

COMMENT

To our knowledge, this is the first study to have evaluated cognitive functions in NMO. In these patients, we found an unexpectedly high frequency of cognitive impairment and the results of the cognitive evaluation in our NMO cohort were very similar to those of the MS group, as we did not find any differences between these 2 groups for any of the subtests. Although these results could be considered surprising in a disease considered to be restricted to the optic nerve and spinal cord, recent MRI and immunopathologic findings suggest that tissue damage in NMO is more extensive than previously thought, including damage in the brainstem or brain. The results could be explained in part by the difference of disease severity between NMO and MS demonstrated by the EDSS scores (4.6 and 2.4, respectively). As NMO is a more severe disease than MS, the difference in EDSS score is not surprising.

Visual dysfunctions could also influence the results, but only 6 of the 8 subtests imply visual functions and we did not observe any correlation between visual function and cognitive tests. Cognitive tests could also be influenced by symptomatic medications (for urinary functions and mood disorders and antispastic treatments, etc.). This was not taken into account in our study, but classically symptomatic treatments are not different in NMO and MS.

The new, recently published criteria for NMO allow for brain involvement but maintain specificity by requiring, in addition to the absolute criteria of optic neuritis and myelitis, the presence of at least 2 of the following 3 additional criteria: (1) brain MRI results negative or nondiagnostic for MS at onset, (2) MRI evidence of a spinal cord T2 lesion of 3 or more vertebral segments, and (3) a serological test result positive for NMO antibodies. New NMO cohort is in very close concordance with those of recent NMO studies in terms of clinical and radiological parameters. It is now clear that trying to define “pure NMO,” though useful in defining the core elements of the disease, limits the understanding of the spectrum and should be abandoned. Recent MRI and neuropathologic studies argue for the concept of a disease that mainly involves the optic nerve and spinal cord but that also can extend to all central nervous system regions. Furthermore, a recent study on brain MRI of NMO patients with magnetic transfer and diffusion tensor MRI found abnormalities in normal-appearing gray matter. Our patients were investigated only with routine MRI techniques and it would therefore be interesting to apply these new techniques and also functional imaging in conjunction with the evaluation of cognitive performance.

Because aquaporin 4 is ubiquitous in the central nervous system, it is not really surprising to observe these results. However, our knowledge of the pathologic role of aquaporin 4 in NMO remains sparse and a better understanding is needed before any conclusions can be drawn. One might suspect a direct toxicity of NMO antibodies via IgG and complement deposits, as suggested in a previous neuropathologic study. As in 4 of our cases, NMO is frequently associated with other autoimmune diseases, such as Sjögren syndrome and systemic lupus erythematosus. Brain damage and cognitive impairment are described in these autoimmune diseases, but their exact mechanism remains unknown. New neuropathologic studies on NMO are warranted to try to improve our knowledge of these mechanisms. The frequency of each cognitive defect is near to that generally found in MS, including the speed of information processing and executive functions.

We also found a long-term memory impairment in about 30% of our NMO patients. Surprisingly, we did not find any correlation between the results of the cognitive tests and disease duration. In contrast, 5 of 6 patients with only high-risk syndromes for NMO had cognitive defects. A similar result was also found in previous studies on MS patients, where cognitive dysfunctions did not correlate with disease duration. We did not find any cor-
relation with MRI lesions, but T2-weighted hyperintensities were observed in only 6 patients, 3 of whom met the criteria for MS. This lack of correlation is also observed in MS, in which cognitive dysfunctions are rarely correlated with the MS lesion load or localization.22-24

Our findings may have therapeutic implications as both immunomodulatory and immunosuppressive drugs have been shown to be effective in treating cognitive dysfunction in MS. Recent studies argue in favor of using immunosuppressive drugs in NMO rather than immunomodulatory drugs.25,26 Owing to the large panel of immunomodulatory and immunosuppressive drugs have been shown to be effective in treating cognitive dysfunctions were observed in only 6 patients, 3 of whom met the criteria for MS. This lack of correlation is also observed in NMO patients, we cannot draw any conclusion concerning immunosuppressive drugs’ influence on cognitive dysfunction, but it would be of interest to propose systematic cognitive testing in further prospective studies on NMO.

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