Enhancing Brain Lesions during Acute Optic Neuritis and/or Longitudinally Extensive Transverse Myelitis May Portend a Higher Relapse Rate in Neuromyelitis Optica Spectrum Disorders

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ABSTRACT

BACKGROUND AND PURPOSE: Neuromyelitis optica spectrum disorders are inflammatory demyelinating disorders with optic neuritis and/or longitudinally extensive transverse myelitis episodes. We now know that neuromyelitis optica spectrum disorders are associated with antibodies to aquaporin-4, which are highly concentrated on astrocytic end-feet at the blood-brain barrier. Immune-mediated disruption of the blood-brain barrier may manifest as contrast enhancement on brain MR imaging. We aimed to delineate the extent and frequency of contrast enhancement on brain MR imaging within 1 month of optic neuritis and/or longitudinally extensive transverse myelitis attacks and to correlate contrast enhancement with outcome measures.

MATERIALS AND METHODS: Brain MRIs of patients with neuromyelitis optica spectrum disorder were evaluated for patterns of contrast enhancement (periependymal, cloudlike, leptomeningeal, and so forth). The Fisher exact test was used to evaluate differences between the proportion of contrast enhancement in patients who were seropositive and seronegative for aquaporin-4 antibodies. The Mann-Whitney test was used to compare the annualized relapse rate and disease duration between patients with and without contrast enhancement and with and without seropositivity.

RESULTS: Brain MRIs of 77 patients were evaluated; 59 patients (10 males, 49 females) were scanned within 1 month of optic neuritis and/or longitudinally extensive transverse myelitis attacks and were included in the analysis. Forty-eight patients were seropositive, 9 were seronegative, and 2 were not tested for aquaporin-4 antibodies. Having brain contrast enhancement of any type during an acute attack was significantly associated with higher annualized relapse rates (P = .03) and marginally associated with shorter disease duration (P = .05). Having periependymal contrast enhancement was significantly associated with higher annualized relapse rates (P = .03).

CONCLUSIONS: Brain MRIs of patients with neuromyelitis optica spectrum disorders with contrast enhancement during an acute relapse of optic neuritis and/or longitudinally extensive transverse myelitis are associated with increased annual relapse rates.

ABBREVIATIONS: AQP4 = aquaporin-4; ARR = annualized relapse rate; CE = contrast enhancement; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; NMO = neuromyelitis optica; NMOSD = NMO spectrum disorders; ON = optic neuritis

Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder of the central nervous system, characterized by recurrent episodes of longitudinally extensive transverse myelitis (LETM) and/or optic neuritis (ON). Discovery of an NMO-specific autoantibody, NMO–immunoglobulin G (IgG), and its target autoantigen, aquaporin-4 (AQP4), have differentiated NMO from multiple sclerosis as a distinct disease entity. Moreover, given the high specificity of AQP4-IgG serology for clinically diagnosed NMO, such seropositivity was incorporated into the revised diagnostic criteria for NMO in 2006. The term “NMO spectrum disorders” (NMOSD) was introduced in 2007 to encompass broader phenotypes, including seropositive patients with coexisting autoimmune disorders and patients with limited or inaugural presentation of optic neuritis or longitudinally extensive transverse myelitis.

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In contrast, no MR imaging parameters have been shown to be associated with disease outcome.

In the current study, we aimed to delineate the extent and frequency of CE in the brain during acute attacks of ON and/or LETM. We also sought to determine whether detection of brain CE was associated with specific outcome measures, including disease duration and the annualized relapse rate (ARR).

**MATERIALS AND METHODS**

**Patients**

A retrospective chart review was performed to identify patients with contrast-enhancing brain lesions between September 2001 and November 2013 at the Johns Hopkins NMO center. All patients identified were diagnosed with NMO or NMOSD based on the Wingerchuk et al 2006 or 2007 revised criteria, respectively. Institutional review board approval was obtained for the study. Electronic patient records were reviewed for demographic information, history of relapse, AQP4-IgG status, age at diagnosis, age at last follow-up, and the number of relapses.

**Neuroimaging**

MR imaging examinations were performed by using either 1.5T or 3T scanners (Philips Healthcare, Best, the Netherlands; GE Healthcare, Milwaukee, Wisconsin; and Siemens, Erlangen, Germany). T1WI, fast spin-echo T2WI, fast spin-echo FLAIR, and postgadolinium T1WIs were performed. A gadolinium contrast agent of 0.1 mL/kg was intravenously administered followed by a 20-mL saline injection. T1-weighted axial and coronal images were acquired without any delay after intravenous injection. The sagittal T1WIs were obtained with the following parameters: TR range = 520–696 ms, TE range = 4.6–14 ms, matrix size range = 192 × 192 to 512 × 196, FOV range = 190 × 190 mm to 240 × 240 mm, section thickness/spacing range = 1/1 to 5/7 mm. Axial T2WI was performed with the following parameters: TR range = 2500–7000 ms, TE range = 83–112 ms, matrix size range = 236 × 184 to 448 × 335, FOV range = 159 × 200 mm to 240 × 240 mm, section thickness/spacing range = 2/2 to 5/5 mm. A FLAIR sequence was obtained with the following parameters: TR = 6000 ms, TE = 120 ms, TI = 2000 ms, section thickness = 5 mm, FOV = 23 cm, matrix size = 256 × 256.

All brain MRIs were evaluated in consensus by 2 radiologists, a
This study demonstrates that approximately 63% of patients during an acute attack of ON and/or LETM may also show CE within the brain parenchyma. CE of periependymal contrast enhancement remains to be determined.

Table 1: Association between the proportion of patients with CE and the presence of AQP4-IgG seropositivity

| AQP4-IgG  | CE Present | CE Absent | No. of Patients (Total) |
|-----------|------------|-----------|-------------------------|
| Positive  | 31 (64.6%) | 17 (35.4%) | 48                      |
| Negative  | 4 (55.6%)  | 5 (44.4%)  | 9                       |
| Total     | 36 (63.2%) | 21 (36.8%) | 57 (not tested)         |

* Fisher exact test, \( P = .7 \).
* One patient was not tested.

Table 2: Comparison of disease duration and ARR between patients with and without CE during an acute attack

| Disease duration (mean) (yr) | CE Present | CE Absent | \( P \) Value |
|------------------------------|------------|-----------|---------------|
| 4.76 ± 4.81 (n = 21)         | 7.26 ± 5.75 (n = 38) | .05       |
| ARR (mean)                   | 1.15 ± 0.73 (n = 21) | 0.73 ± 0.52 (n = 38) | .03          |

* \( P < .05 \), based on Mann-Whitney test.

Statistical Analysis

The Fisher exact test was used to evaluate the difference between the proportions of patients with CE who were seropositive versus seronegative. A nonparametric Mann-Whitney test was used to compare the ARR and disease duration between those with and without CE. Regression analyses of the ARR with and without CE were also performed, with and without adjusting for age, sex, race, and AQP4 status. \( P \) values < .05 were considered statistically significant and were not adjusted for multiple analyses.

RESULTS

Brain MRIs of 77 patients (11 males, 66 females) were evaluated for contrast enhancement. Fifty-nine patients (10 males, 49 females) underwent brain MR imaging within 1 month of the onset ON and/or LETM attack and were included in the final analysis. The mean age of patients was 47.8 years (range, 6–78 years). There were 35 African-American, 18 white, and 6 Hispanic (individuals from Mexico) individuals. Forty-eight patients were AQP4-IgG seropositive, 9 were seronegative, and the AQP4-IgG status was not checked in 2 of them. The ARR was not available for 1 patient.

Table 1 depicts the proportions of patients with CE in those with or without AQP4-IgG seropositivity during acute attacks. The Fisher exact test did not demonstrate significantly different proportions of CE in patients with or without AQP4-IgG seropositivity during acute attacks \( (P = .7) \). No significantly different proportions were noted when stratified by specific enhancement patterns \( (P = .7 \), data not shown).

Tables 2 and 3 depict the association between the detection of CE during an acute phase and either disease duration or ARR. When imaged during the acute phase, patients demonstrating periependymal CE had significantly higher ARRs compared with those without periependymal CE \( (P = .03) \). More over, patients demonstrating any type of CE during the acute phase had significantly higher ARRs \( (P = .03) \) than those without.

On the basis of the regression analyses, the unadjusted difference in ARRs between those with periependymal CE and those without it was 0.56 (95% CI, 0.07–1.05; \( P = .03 \)). After we adjusted for age, sex, race, and AQP4 status, the difference was 0.60 (95% CI, 0.08–1.13; \( P = .03 \)). The unadjusted difference in ARRs between those with any CE and without was 0.42 (95% CI, 0.04–0.80; \( P = .03 \)). After we adjusted for age, sex, race, and AQP4 status, the difference was 0.41 (95% CI, 0.02–0.81; \( P = .04 \)).

Table 4 shows the distribution of brain CE patterns among 59 patients who were scanned within 1 month of an ON and/or LETM attack. Brain CE was categorized and evaluated in 6 specific patterns of enhancement: periependymal, clouddike, leptomeningeal, isolated, ring, or other (Figs 1 and 2). After excluding MRIs that were not obtained within 1 month of ON and/or LETM attack from the final analysis, we regrouped MRIs into 2 groups: a group with periependymal CE and a group with any type of CE. MRIs of 14 patients showed periependymal CE, and 21 patients showed any type of CE within 1 month of ON and/or LETM attacks.

DISCUSSION

The current literature on NMO is limited in its description of neuroimaging features that may predict the outcome of disease.\(^{24} \) Most asymptomatic NMO brain lesions have not been shown to demonstrate enhancement, and the frequency of acute lesion-associated enhancement remains to be determined.\(^{23} \) This study demonstrates that approximately 63% of patients during an acute attack of ON and/or LETM may also show CE within the brain parenchyma. CE within the brain, when identified during an acute phase, is associated with a significantly increased ARR. The relapse rate during the first 2 years of the disease strongly determines the risk of an unfavorable outcome as defined by severe disability or death.\(^{25} \) Brain enhancement in patients during an acute ON and/or LETM may reflect a more severe underlying disease process compared with those without brain CE.

We found no significant difference in the propensity for CE in patients who were AQP4-IgG seropositive (64.6%) and seronegative (55.6%) \( (P = .7 \), Table 1). CE patterns of brain lesions in the
Our study revealed a female and AQP4-IgG seropositivity. Moreover, the amount of CSF AQP4-IgG is correlated with clinical severity. For example, longer intervals between the first and second attack, older age at onset, and factors that have been described in the literature associated with outcomes such as seropositivity status, sex, race, and age at onset may be potential confounders and were not accounted for. There is a possible selection bias based on a group of patients with NMOSD who required brain MR imaging, which may reflect a different subgroup than that not requiring brain MRIs. The threshold of 1 month as the criterion for an acute attack may be arbitrary, given the lack of information in records available to more accurately assess the patients’ clinical statuses and may thus misrepresent these statuses in the current study. Furthermore, the current study was originally conducted before the introduction of the more inclusive revised diagnostic criteria for NMOSD of 2015. Rather, included patients were based on the 2006 diagnostic criteria; therefore, the current study does not account for patients who may now qualify as diagnostic for NMOSD under the 2015 criteria.

### CONCLUSIONS

Detection of CE in postgadolinium T1-weighted brain imaging within 1 month of onset of an acute ON and/or LETM is associated with higher ARRs. CE is an important marker reflecting the underlying pathogenic process of NMOSD. Although no significant association was found between CE and AQP4-IgG serostatus, the strong interplay among the BBB disruption, AQP4-IgG deposition, and CE warrants further investigation with a larger multicenter cohort to determine the prognostic role that CE may play as a predictor of outcome and its correlation with clinical severity.

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