Disruption of the leptomeningeal blood barrier in neuromyelitis optica spectrum disorder

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ABSTRACT

Objective: To describe leptomeningeal blood-barrier impairment reflected by MRI gadolinium-enhanced lesions in patients with aquaporin-4 immunoglobulin G (AQP4-IgG)-positive neuromyelitis optica spectrum disorder (NMOSD).

Methods: A retrospective case series of 11 AQP4-IgG-positive NMOSD patients with leptomeningeal enhancement (LME) were collected from 5 centers. External neuroradiologists, blinded to the clinical details, evaluated MRIs.

Results: LME was demonstrated on postcontrast T1-weighted and fluid-attenuated inversion recovery images as a sign of leptomeningeal blood-barrier disruption and transient leakage of contrast agent into the subarachnoid space in 11 patients, 6 in the brain and 6 in the spinal cord. The patterns of LME were linear or extensive and were accompanied by periependymal enhancement in 5 cases and intraparenchymal enhancement in all cases. The location of LME in the spinal cord was adjacent to intraparenchymal contrast enhancement with involvement of a median number of 12 (range 5–17) vertebral segments. At the time of LME on MRI, all patients had a clinical attack such as encephalopathy (36%) and/or myelopathy (70%) with median interval between symptom onset and LME of 12 days (range 2–30). LME occurred in association with an initial area postrema attack (44%), signs of systemic infection (33%), or AQP4-IgG in CSF (22%) followed by clinical progression. LME was found at initial clinical presentation in 5 cases and at clinical relapses leading to a diagnosis of NMOSD in 6 cases.

Conclusion: This study suggests that altered leptomeningeal blood barrier may be accompanied by intraparenchymal blood-brain barrier breakdown in patients with AQP4-IgG-positive NMOSD during relapses. Neuro Neuroimmunol Neuroinflamm 2017;4:e343; doi: 10.1212/NXI.0000000000000343

GLOSSARY

AP = area postrema syndrome/lesion; AQP4 = aquaporin-4; BBB = blood-brain barrier; CS = cerebral syndromes; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium; IVMP = IV methylprednisolone; LETM = longitudinally extensive transverse myelitis; LME = leptomeningeal enhancement; MNL = mononuclear leukocyte; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; PLEX = plasma exchange; PMNL = polymorphonuclear leukocyte; STIR = short tau inversion recovery; T1W = T1 weighted.

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory, autoimmune disease of the CNS that follows a relapsing course in the majority of patients. NMOSD-related neurologic disability frequently occurs as a consequence of cumulative attacks. The inflammation of NMOSD is often associated with blood-brain barrier (BBB) leakage, reflected by MRI
Neurology: Neuroimmunology & Neuroinflammation

Criteria or/and the International Panel for NMO Diagnosis IgG patients were included if they met the following criteria: (1) AQP4-IgG (Japan, South Korea, United States, France, and Denmark). Patients were included if they were positive for the following criteria: (1) AQP4-IgG in the CSF to get access to its junctions in ependymal cells may allow a basement membrane and expression of tight junctions in ependymal cells may allow AQP4-IgG in the CSF to get access to its target. AQP4-IgG may exert pathologic effects by binding selectively to AQP4 on CNS astrocytes, inducing complement-dependent astrocyte damage and inflammation.

MRI-detected leptomeningeal enhancement (LME), which reflects the leptomeningeal blood-barrier disruption, has been reported in patients with NMOSD. LME refers to an enhancement pattern that follows the pial surface of the CNS and fills the subarachnoid spaces of sulci and cisterns. The LME pattern depends on the extent and intensity of the involved inflammatory area and may provide useful clues to the diagnosis of, e.g., neurosarcoidosis.

In this retrospective case study, we investigated whether compromised integrity of the intraparenchymal BBB occurs concurrently with LME and whether such an alteration of BBB is associated with disease activity in patients with AQP4-IgG–positive NMOSD.

METHODS
Study design and population. The study was designed as a retrospective case series with clinical and radiologic follow-up and collected by a multicenter study group in 5 centers (Japan, South Korea, United States, France, and Denmark). Patients were included if they met the following criteria: (1) AQP4-IgG–positive NMOSD, qualifying for the 2006 Wingerchuk criteria or/and the International Panel for NMO Diagnosis (IPND) 2015 criteria and (2) LME as visualized by MRI following the standard protocols. Patients were excluded if they had (1) systemic inflammatory disease, e.g., sarcoidosis or (2) neoplastic disease. The information was obtained by review of medical records and reevaluation of previous MRIs of the CNS by local neuroradiologists. In addition, 2 expert neuroradiologists not involved in patient management evaluated images and were blinded to the clinical details (H.P.S. and J.W.).

Neuroimaging. Because the study was retrospective, several types of 1.5T MRI scanners were used. T2-weighted (T2W) and T1-weighted (T1W) images with or without Gd, diffusion-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) sequences were available for analysis for all brain scans. T2W and T1W with or without Gd and short tau inversion recovery (STIR) sequences were available for analysis for all brain scans. Precontrast and postcontrast images were evaluated to determine the presence of abnormal contrast enhancement on T1W and/or FLAIR sequences according to the criteria previously reported. If performed, postcontrast FLAIR sequences obtained at least 10 minutes after a single dose of contrast were also used for evaluation.

Standard protocol approvals, registrations, and patient consents. All patients provided oral and written informed consent for publication.

RESULTS
Retrospective MRI and clinical data from 11 AQP4-IgG–positive (measured either in a cell-based assay or ELISA) NMOSD patients with leptomeningeal enhancement (LME) were obtained for review (table 1). The female: male ratio was 9:2, and the median age at onset of disease was 40.8 years (range 15–71 years). Seven patients were East Asian, 1 African American, 1 of mixed ancestry, and 2 whites.

Radiologic characteristics. LME localization. Contrast enhancement in the leptomeningeal space was evaluated by precontrast and postcontrast T1W and/or FLAIR images and observed in all 11 patients, 6 in the brain and 6 in the spinal cord; 1 patient had both brain and spinal cord LME.

In the brain, T1W contrast-enhanced images revealed a linear or thick and extensive leptomeningeal and pial enhancement with localization in both cerebral hemispheres (2 patients), bilateral medial surfaces of the cerebral hemispheres (1), bilateral frontal, medial parietal lobe (1), right parietal lobe (1), and bilateral parieto-occipital lobes (1) (figure 1, A.a and b, C.a and b). FLAIR (figure 1, A.c and d, B.c and D.c and FLAIR postcontrast (figure 1B.a) sequences revealed similar leptomeningeal signal intensity changes.

In the spinal cord, T1W contrast-enhanced images showed LME in 6 patients, conus to cauda equina (2), multifocal spinal cord (1), and thoracic segments (3) (figure 2, A.a and b, B.a and C, figure 3B, figure 4, A and D, figure e-1, H1 and H3 at Neurology.org/nn).

Follow-up MRI demonstrated resolution of LME within 1–4 weeks in 9 patients. In one other case, the next MRI was performed after 72 days when the LME had disappeared. One patient did not have a follow-up MRI.

LME in association with parenchymal enhancement. LME in all cases spatially corresponded to intraparenchymal T1W contrast enhancement or/and FLAIR image abnormalities in the brain (figure 1, A.c, B.c, C.b and c). Periependymal linear T1W contrast enhancement was localized at the lateral ventricles (3 patients) (figure 1B.b, figure 3D) and adjacent to the third and fourth ventricles (2) (figure 3F). Intracerebral cloud-like enhancement (3 patients) (figure 1C.c), enhancement of hypothalamus (2) (figure 3G), and optic...
Spinal cord MRI demonstrated intraparenchymal T1W contrast enhancement in the underlying parenchyma adjacent to the LME (figure 2, A.a and B.a, figure 3B, figure 4B, figure e-1H1), involving cervical, thoracic, and lumbar cords. Spinal cord lesions expanded over a median of 12 segments (range 5–17) as demonstrated on contrast-enhanced T1W (figure 2, A.a and B.a, figure 3B, figure 4B, figure e-1H1) and T2W and STIR images (figure 2, A.b and d, B. b and d, figure 3, A and C, figure 4, C and E, figure e-1, H2 and H4).

**CSF abnormalities.** Lumbar puncture was performed after MRI investigation in all patients, and complete CSF analysis was available at the time of the LME for 6 of the 11 patients. CSF examination showed pleocytosis >50 mL (mm³) in all cases; 2 cases with increased polymorphonuclear leukocytes (PMNLs) had 80% (PMNL 166 and mononuclear leucocyte [MNL] 41/mm³) and 98% (PMNL 212 and MNL 4/mm³) PMNL, respectively. The combination of LME and pleocytosis in all cases, especially in the 2 cases with increased CSF-PMNL and fever, led to extensive virologic and bacteriologic workup, which proved negative both in blood and CSF. The median CSF protein concentration was 169 (range 54–322) (mg/dL), and CSF glucose level was normal in all cases. CSF-restricted oligoclonal bands or elevated IgG CSF-serum ratio were absent, except in 1 patient. AQP4-IgG in CSF was only measured in 2 patients, and it was positive in both patients.

**LME and clinical disease activity.** When LME was visible on MRI, all patients had experienced attacks with subacute onset and progressive neurologic deficits over a few weeks (7 patients) or with acute onset and rapid progression within a few days (4 patients). Median interval between symptom onset and MRI scans displaying LME was 12 days (range 2–30 days). Seven patients had longitudinally extensive transverse myelitis (LETM) (4 subacute and 3 acute onset) and 4 had cerebral syndromes (CS) (3 with subacute and 1 with acute onset) as the clinical presentation associated with LME (table e-1).

**Spinal cord involvement.** In the LETM group, 3 of the 4 patients with subacute onset initially had experienced an area postrema syndrome/lesion (episodes of nausea, vomiting, and hiccups) (figure 3, A–C) followed a few days later by extremity weakness, which progressed to tetraplegia (1 patient) or paraplegia (2) over 7, 12, and 30 days. MRI of the spinal cord at this time revealed LETM with LME adjacent to LETM. Another patient with a subacute onset of LETM had atypical chest pain as the initial symptom, which after 7 days progressed to paraplegia and MRI of the spinal cord revealed LME and LETM (figure 4, A–E).
In the remaining 3 patients with acute onset of LETM, 2 developed symptom/signs after an upper respiratory tract infection, by 2 and 4 days respectively (without the identification of an infectious agent) and 1 occurred 2 days after an induced abortion. One presented with tetraplegia and 2 with paraplegia. MRI of spinal cord revealed LETM with LME adjacent to the intramedullary lesion (H1-H4).

Brain involvement. In the CS group, 1 patient initially experienced an area postrema syndrome followed 10 days later by altered consciousness and recurrent generalized seizures. Brain MRI performed 17 days after onset of symptoms revealed LME (figure 1, A.a–c). Another patient experienced dizziness and was treated with corticosteroids. A third patient had nonspecific symptoms such as drowsy mental state, dysarthria, and recurrent episode of myelitis and optic neuritis (ON). LME were in those 2 cases who demonstrated on MRI 24 and 21 days after symptom onset, respectively. The one patient with acute symptom onset had a generalized seizure followed by tetraparesis from TM. LME was in this case demonstrated on MRI 5 days after symptom onset (table e-1).
Acute and long-term immunotherapy. In all patients, acute attacks were initially treated with IV methylprednisolone (IVMP), which were administered between the first and the follow-up MRI. The 7 patients with LETM did not clinically respond to IVMP therapy and were subsequently treated by plasma exchange.

Various immunosuppressive drugs as listed in table 1 were used as preventive therapy after the follow-up MRI, which showed resolution of LME; one received azathioprine before the attack and follow-up MRI examination.

LME and NMOSD diagnosis. LME was found at the initial attack of NMOSD in 5 (3: LETM, 2: area postrema syndrome) of the 11 patients (table 1). In the remaining 6 patients, symptoms at first attack were ON (2 patients), TM (1), AP (1), and CS (2).

A total of 6 patients, including all patients who had LME at the initial attack, qualified for the diagnosis of NMOSD except one, with area postrema syndrome, who received the NMOSD diagnosis 2 years later at testing for AQP4-IgG. Of the 6 patients, 2 had a history of TM and ON, respectively, and received the diagnosis of NMOSD in association with LME and acute attack, 1 with LETM, and 1 with a generalized seizure followed by TM (table 1).

Three patients with previous attacks received the NMOSD diagnosis at median 20 months (range 12–24) after attack with LME on MRI, with disease duration of median 116 months (range 108–132). They were suspected for MS and treated with interferon-β previously, relapses occurred and treatment was discontinued. One patient was diagnosed with NMOSD 2 years before an attack with LME on MRI. She was treated with azathioprine. For all patients, median follow-up after onset of attack and LME on MRI was 79.6 months (range 2–186).

DISCUSSION In this retrospective case series comprising 11 patients with AQP4-IgG–positive NMOSD, we observed contrast enhancement of the leptomeningeal structures during clinical attacks accompanied by intraparenchymal contrast enhancement spatially corresponding to the LME. LME was observed in association with either an initial area postrema attack, with precedent signs of systemic infection or with detectable AQP4-IgG in CSF.
followed by secondary worsening of symptoms/signs and lesions on MRI (figure e-2). These findings suggest that, in some cases, entry of serum-derived AQP4-IgG to the subarachnoid space may be facilitated by primary inflammation at area postrema by systemic infection or by blood-CSF barrier dysfunction (figure e-2). It could be speculated that AQP4-IgG may be deposited at the astrocytic foot processes at pial vessels and cause astrocytic damage. The resultant dysfunction of AQP4 water channels in the pial and subpial surfaces could lead to impairment of leptomeningeal vessel barrier, which may be involved in the development of NMOSD lesions.

In line with this study, pronounced meningeal inflammation has been reported in autopsy findings of patients with NMOSD. Our recent experimental study of intrathecal injection of AQP4-IgG may corroborate these findings, as pronounced deposition of AQP4-IgG was observed in the leptomeningeal area, including where pial vessels penetrate the brain parenchyma and form perivascular spaces into the brain parenchyma, the so-called paravascular pathway. Furthermore, AQP4-IgG initiated perivascular astrocyte-destructive lesions and consequently breakdown of the BBB. A significant proportion of subarachnoid CSF circulates through the parenchyma within these paravascular spaces which surround penetrating and cerebral surface vessels and is completely ensheathed by astrocyte end-feet. Of interest, experimental data have suggested that the flow of fluid along this paravascular route is mediated by astrocytic AQP4.

Although direct inferences from an animal study are not possible, our observations suggest that intraparenchymal contrast enhancement lesions may form in anatomical proximity to regions where LME is visible. LME was spatially associated with periependymal enhancement and with intraparenchymal enhancement in the brain, brainstem, hypothalamus, optic chiasm, and spinal cord. These CNS MRI abnormalities in patients with AQP4-IgG–positive NMOSD are believed to be common and typical of the disease with regards to localization and configuration. Conversely, LME has been reported in few patients only and is presumably more common during NMOSD relapses and in AQP4-IgG–positive patients. However, the frequency of LME is likely to be underestimated given that most MRIs are performed subsequently at onset of clinical symptoms and thus at a time point where lesion formation is probably completed and LME may have vanished. Timing of MRI may be important for the demonstration of LME, and evaluation of MRI should consider the interval between symptom onset and MRI scan. Last, LME may be suppressed by steroid treatment as immunosuppressive therapy probably decreases BBB permeability. It has previously been reported that corticosteroid treatment before MRI may lead to the improvement or resolution of LME as part of the treatment response. In this study, patients received treatment with IV corticosteroid before follow-up MRI, and this may have led to the

Figure 3 An area postrema lesion in association with leptomeningeal enhancement and intraparenchymal BBB breakdown

| Days after onset of area postrema syndrome (n=30, with relapses) |
|------------------|------------------|
| Leptomeningeal   | Intraparenchymal |

Spinal cord MRI (A–C) and brain MRI (D–G) from an AQP4-IgG–positive patient with NMOSD who presented with recurrent myelopathy of 1 month duration and area postrema lesion, which progressed into LETM. Images were obtained during acute attacks. An area postrema lesion (A) in association with subacute progression to LETM with leptomeningeal and intraparenchymal T1W contrast enhancement (arrows, B). The spinal cord lesions were also demonstrated on T2W and STIR images (C). Cerebral MRI during another attack with periependymal enhancement on T1W images at the lateral (D) and third ventricles (F). FLAIR images showing lesions along lateral ventricle (E), thalamus, and hypothalamus (G). (B) Used with permission of the publisher from Flanagan EP, Weinshenker BG. Neuromyelitis optica spectrum disorders. Curr Neurol Neurosci Rep 2014;14:483. Copyright © 2014, Springer Science+Business Media New York. AQP4-IgG = aquaporin-4 immunoglobulin G; BBB = blood-brain barrier; FLAIR = fluid-attenuated inversion recovery; LETM = longitudinally extensive transverse myelitis; NMOSD = neuromyelitis optica spectrum disorder; T1W = T1 weighted; T2W = T2 weighted.
The temporal evolution of alterations to the BBB permeability is difficult to determine and will require a kinetic study with sequential and frequent MRI images that analyze the dynamic changes of enhancement in newly appearing active lesions. The localization of the LME at the spinal cord in 70% of cases was associated with extremely long acute LETM lesions, and the patients were resistant to steroid therapy. This may on MRI reflect the severity of attacks in the spinal cord at the time of LME. However, such determination of an association between the leptomeningeal blood-barrier disruption and BBB breakdown sites and severity of attacks require larger and prospective studies.

In this study, all cases were associated with disease activity at the time of LME on MRI, and LME was accompanied by other characteristic findings such as LETM, area postrema lesion etc.\textsuperscript{11} In 7 of the 11 patients, the attacks occurred subacutely with a dynamic progression of symptoms/signs. Four of the seven patients had an initial area postrema syndrome. The dynamic formation of an LETM was previously reported with initial involvement of the area postrema during 12 days from the onset of symptoms as visualized on sequential brainstem/spinal cord MRI.\textsuperscript{26} These findings support the concept that area postrema, a circumventricular area which has incomplete BBB, may serve as entry route to the CNS for circulating AQP4-IgG.\textsuperscript{20,26,27}

In NMOSD, the presence of AQP4-IgG in CSF has been reported to be associated with high titers of AQP4-IgG in serum,\textsuperscript{28–30} and to be strongly correlated with astrocyte damage, as reflected in elevated levels of glial fibrillary acidic protein in the CSF and BBB disruption during disease attacks.\textsuperscript{30,31} In this small retrospective study, titers of AQP4-IgG in serum were not determined and AQP4-IgG in CSF was only measured in 2 patients, both of whom had positive results.

Infections may result in events that alter the BBB and thus permit access of AQP4-IgG to the CNS.\textsuperscript{32,33} Three cases with LETM were preceded acutely by symptoms suggestive of systemic infection. Cases of infectious or parainfectious events before the onset of neurologic symptoms and NMOSD have been reported, adding to the etiological diversity in NMOSD.\textsuperscript{32–36} It is possible that infection may act as a precipitating factor in the development of NMOSD with the presence of AQP4-IgG.

We observed that leptomeningeal blood-barrier integrity was compromised during relapses and was accompanied by intraparenchymal BBB breakdown in patients with AQP4-IgG–positive NMOSD. Although our data are too preliminary to allow for a firm statement on the putative mechanism of lesion formation in human NMOSD, they suggest in conjunction with previous animal experiments that the question of how pathogenic AQP4-IgG gains access to its CNS target deserves further attention. Moreover, future imaging studies may inform us about the relevance of LME for attack severity and clinical course in NMOSD.

**AUTHOR CONTRIBUTIONS**

N.A.: study concept and design, acquisition of data, interpretation of results, drafting, and revising of the manuscript. E.P.F., K.F., and H.J.K.: acquisition of data, interpretation of results, revising of the manuscript, and approving the final version. H.P.S. and J.W.: MRI reevaluation.
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