Brain Involvement in Neuromyelitis Optica Spectrum Disorders

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Background: Neuromyelitis optica spectrum disorders (NMOSDs) are severe inflammatory demyelinating disorders of the central nervous system. Brain involvement is increasingly recognized.

Objective: To study brain involvement in NMOSDs among Hong Kong Chinese patients.

Design: Retrospective study of patients with NMOSDs.

Setting: Tertiary medical center in Hong Kong.

Patients: Thirty-four Hong Kong Chinese patients with NMOSDs of 2 years or longer were recruited.

Interventions: Brain and spinal cord magnetic resonance imaging was performed during NMOSD attacks and was repeated yearly for the first 3 years.

Main Outcome Measures: We evaluated clinical features of NMOSDs associated with brain involvement and brain lesions on magnetic resonance imaging.

Results: Among 34 patients with NMOSDs of 2 years or longer, 20 (59%) had brain involvement. The mean age at onset among these 20 patients was 45.6 years (age range, 19-67 years); 18 were women. Eleven patients (32%) of all the patients with NMOSDs had clinical manifestation of brain involvement, 19 patients (56%) had brain abnormalities on magnetic resonance imaging consistent with inflammatory demyelination, and 2 patients (6%) fulfilled criteria for multiple sclerosis. Clinical manifestation of brain involvement included the following: trigeminal neuralgia; vomiting, vertigo, ataxia, dysphagia, and tetraparesis from lesions around the third and fourth ventricles and aqueduct; homonymous hemianopia, aphasia, hemiparesis, and cognitive impairment from extensive hemispheric white matter lesions; and ataxia, diplopia, hiccups, facial sensory loss, internuclear ophthalmoplegia, hemisensory loss, and hemiparesis from other lesions in the midbrain, pons, cerebellar peduncles, and medulla. Eight patients (24%) developed brainstem encephalitis clinically, and brainstem encephalitis was the initial clinical manifestation in 6 patients (18%). Brain abnormalities on magnetic resonance imaging were detected in brainstem in 15 patients (44%), hemispheric periventricular white matter in 7 patients (21%), deep white matter in 7 patients (21%), corpus callosum in 4 patients (12%), subcortical white matter in 3 patients (9%), thalamus in 2 patients (6%), hypothalamus in 1 patient (3%), basal ganglia in 1 patient (3%), internal capsule in 1 patient (3%), periaqueductal gray matter in 1 patient (3%), and around the third and fourth ventricles in 1 patient (3%); large confluent lesions were detected in 2 patients (6%).

Conclusion: Brain involvement manifesting clinically as brainstem encephalitis is common among Hong Kong Chinese patients with NMOSDs.

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EUROMYELITIS OPTICA (NMO) is a severe central nervous system inflammatory demyelinating disorder characterized by monophasic or relapsing acute myelitis (AM) and optic neuritis (ON), with the relapsing form being predominant.\(^1\)\(^2\) A typical presentation of AM in NMO is longitudinally extensive transverse myelitis (LETM), manifesting as severe paraparesis or tetraparesis, sphincter disturbance, and sensory loss; potentially life-threatening respiratory failure may occur in high cervical myelitis associated with a hyperintense T2-weighted lesion on magnetic resonance (MR) imaging that extends over 3 or more vertebral segments.\(^7\)\(^8\) Optic neuritis in NMO can be bilateral or unilateral and tends to be severe, with frequent early permanent vision loss.\(^3\) Advancing our understanding of NMO pathogenesis was the discovery of NMO-IgG autoantibodies against aquaporin 4 (AQP4), the most abundant water channel protein in mammalian central nervous systems,\(^9\)\(^11\) which were detected in 60% to 90% of patients with NMO but not in patients with classic multiple sclerosis (MS).\(^7\)\(^12\)\(^18\) Neuromyelitis optica and classic MS are distinct entities, with differing immunopathogenetic mechanisms.\(^8\) Detection of AQP4
autoantibodies facilitates early diagnosis of NMO and distinction of relapsing NMO from relapsing-remitting MS. This is clinically useful because early frequent relapses with significant neurological disability are common in NMO and because long-term pharmacotherapies for NMO and relapsing-remitting MS differ. In addition, detection of AQP4 autoantibodies leads to recognition of a wider range of NMO spectrum disorders (NMOSDs), including patients having single or recurrent LETM without ON, as well as patients having recurrent ON without AM who are seropositive for AQP4 autoantibodies. In vitro and in vivo studies revealed that IgG from serum of AQP4 autoantibody–positive patients with NMO led to AQP4 loss, astrocytic necrosis via complement activation, and inflammation, supporting that AQP4 autoantibodies are directly pathogenic in NMO.

Lack of cerebral involvement was initially proposed for NMO, but accumulating evidence reveals that involvement of various regions of the brain, both symptomatic and asymptomatic, is common in NMOSDs. These findings have led to the revised criteria for diagnosis of NMO, which require the presence of AM, ON, and at least 2 of the following 3 supportive criteria: (1) MR imaging evidence of a contiguous spinal cord lesion (hyperintense T2-weighted) extending over 3 or more vertebral segments longitudinally in the context of AM, (2) initial brain MR imaging not diagnostic of MS at onset of disease, and (3) NMO-IgG seropositivity. We studied the clinical and MR imaging characteristics of Hong Kong Chinese patients having NMOSDs with brain involvement.

METHODS

PATIENTS

Patients with NMOSDs were diagnosed, treated, and assessed as described previously, and only patients with disease duration of 2 years or longer after clinical onset were recruited for this study. Patients having NMOSDs who were recruited into the study included those with the following characteristics: (1) NMO diagnosed using revised criteria by Wingerchuk et al., (2) a single attack or recurrent LETM with AQP4 autoantibody seropositivity, (3) a single attack of unilateral or bilateral ON or recurrent ON with AQP4 autoantibody seropositivity, and (4) a single attack or recurrent brainstem encephalitis (BE) with AQP4 autoantibody seropositivity. Brain and spine MR imaging with gadolinium contrast was performed within 2 weeks after onset of clinical features that were suggestive of inflammatory demyelination attacks and was repeated 2 to 3 months later to document neuroradiological improvement. In the first 3 years after clinical onset, brain MR imaging with gadolinium contrast was performed yearly even in the absence of clinical features that were suggestive of relapse. Since 2009, patients who were intolerant of or refractory to azathioprine therapy have been switched to mycophenolate mofetil therapy; patients who were intolerant of or refractory to mycophenolate mofetil, as well as those who had fulminating disease characterized by severe frequent attacks while awaiting onset of action of azathioprine or mycophenolate mofetil, were treated with rituximab. All MR images were reviewed by 2 of us (K.H.C. and C.T.T.) independently.

Table 1 summarizes the frequency of brain involvement in our 34 patients with NMOSDs who were followed up for 2 years or longer after clinical onset. Among these, 20 patients (59%) had brain involvement clinically or radiologically. Eleven patients (32%) had brain involvement clinically, whereas 19 patients (56%) had brain abnormalities on MR imaging consistent with inflammatory demyelination. The single patient with brain involvement but without detectable brain abnormalities on MR imaging was seen with trigeminal neuralgia years before onset of recurrent LETM and was seropositive for AQP4 autoantibodies; brainstem involvement was considered the cause of her trigeminal neuralgia, although this is uncertain. Two patients (6%) had brain abnormalities on MR imaging fulfilling criteria for MS by Barkhof. The detailed clinical, neuroradiological, and serological details of 20 patients having NMOSDs with brain involvement are given in eTable 1 and eTable 2. The 20 patients had NMO (9 patients), recurrent LETM with BE (5 patients), recurrent LETM (4 patients), recurrent ON with subclinical LETM (1 patient), and recurrent BE with subclinical LETM (1 patient). Their mean age at onset was 45.6 years (age range, 15-70 years) and median disease duration was 25.5 months (range, 2-144 months).

Table 1. Frequencies of Brain Involvement Clinically or Detected on Magnetic Resonance Imaging Among 34 Patients With Neuromyelitis Optica Spectrum Disorders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain involvement clinically or detected on MR imaging</td>
<td>25 (59)</td>
</tr>
<tr>
<td>Brain involvement clinically</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Cerebral hemisphere</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Subcortical white matter</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Diencephalon</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Periaqueductal region</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cerebral peduncle</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pons</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Medulla</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Cerebellar peduncles</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Clinical attack of brainstem encephalitis</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Brain involvement clinically as initial manifestation</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Cortical signs from large hemispheric white matter lesion</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Brain abnormalities on magnetic resonance imaging</td>
<td>19 (56)</td>
</tr>
</tbody>
</table>

a Both patients had extensive confluent lesions involving subcortical and deep white matter.
19-67 years), and 18 were women. Eighteen patients had LETM clinically; the remaining 2 patients (one with recurrent ON and the other with recurrent BE) had no myelitis attack clinically, but spine MR imaging detected extensive hyperintense T2-weighted lesions compatible with subclinical myelitis. Clinical manifestation of brain involvement included the following: (1) vomiting, vertigo, cerebellar ataxia, and dysphagia complicated by aspiration pneumonia and tetraparesis from involvement of regions around the third and fourth ventricles and peri-aqueductal region (Figure 1); (2) vomiting, hiccups, diplopia, facial sensory loss, and dysphagia from involvement of the midbrain, anterior pons, middle cerebellar peduncles (Figure 2), and medulla in continuity with high cervical myelitis complicated by respiratory insufficiency requiring assisted ventilation; (3) severe ataxia, diplopia, internuclear ophthalmoplegia, hemisensory loss, and hemiparesis from large lesions affecting the unilateral dorsolateral pons and superior cerebellar peduncle (Figure 3); (4) trigeminal neuralgia; (5) homonymous hemianopia from large parietal and occipital white matter lesions; and (6) aphasia, hemiparesis, and cognitive impairment from large confluent lesions in frontal and parietal subcortical white matter (Figure 4).

Eight patients (24%) had a history of acute or subacute attack of severe bulbar dysfunction that was compatible with BE clinically; in 6 patients (18%), the initial clinical BE attack was the first clinical manifestation. Among these 6 patients, 4 had vomiting on the initial presentation during the BE attack. Four of 6 were initially treated for brainstem infarction with aspirin and physiotherapy, 1 was treated for Bickerstaff encephalitis with intravenous immunoglobulin, and 1 having simultaneous high cervical myelitis was treated for Guillain-Barré syndrome with intravenous immunoglobulin, as she had areflexia in the spinal shock stage together with bulbar and respiratory weakness. Five patients (15%) had severe high cervical myelitis associated with respiratory insufficiency requiring assisted ventilation. Eight patients (24%) had cerebrospinal fluid pleocytosis, and 2 patients (6%) had cerebrospinal fluid analysis that was positive for oligoclonal bands. Eighteen of 20 patients with brain involvement were seropositive for AQP4 autoantibodies (7 patients with NMO and all 11 patients in eTable 2). Their mean Expanded Disability Status Scale score at the latest follow-up was 6.8 (score range, 3-10), with 19 patients having significant disability (score, ≥4) and 14 patients having severe disability (score, ≥6). Two died of NMOSDs (one death from severe high cervical myelitis and the other death from sudden cardiac arrest probably due to cardiac arrhythmia complicating BE with simultaneous high cervical myelitis).

Table 2 summarizes the frequencies, locations, and nature of brain abnormalities on MR imaging in our patients with NMOSDs. Fourteen of 19 patients had abnormalities detected on initial brain MR imaging; the other 5 had normal initial brain MR imaging, with abnormalities detected months to 1 year later. Abnormalities were detected most frequently in the brainstem among 15 patients (+4% of all 34 patients with NMOSDs), followed by hemispheric periventricular white matter in 7 patients (21%), deep white matter in 7 patients (21%), and corpus callosum in 4 patients (12%). In 2 patients (6%), large confluent lesions (>3 cm) were detected, manifesting clinically as homonymous hemianopia and expressive aphasia with cognitive impairment and as contralateral hemiparesis, respectively. Lesions in the thalamus, hypothalamus, internal capsule, periaqueduct-
tal gray matter, and regions around the third and fourth ventricles were detected in only 1 patient each (3%).

REPORT OF CASES

Brain involvement manifesting clinically as BE was common among our patients with NMOSDs. Case histories of 2 representative patients are given.

Patient 1

Patient 1 was a 59-year-old woman previously in good health who was seen with vertigo, diplopia, and vomiting for 3 days, followed by tetraparesis that progressed to tetraplegia 2 weeks later. Examination findings revealed vertical nystagmus, dysarthria, pharyngeal weakness, and tetraplegia. Brain computed tomographic images were normal, and she was treated for brainstem infarction with aspirin and physiotherapy at a regional hospital. She developed aspiration pneumonia and required mechanical ventilatory support and was transferred to Queen Mary Hospital, Hong Kong. Cerebral MR imaging that was performed 4 weeks after onset revealed hyperintense T2-weighted lesions at the midbrain and pons over periaqueductal and periventricular regions of the third and fourth ventricles (Figure 1). Vasculitis markers, viral serological testing (herpes simplex virus, herpes zoster virus, adenovirus, and Japanese encephalitis virus), and serum pp65 antigen for cytomegalovirus were negative. Cerebrospinal fluid analysis revealed normal protein and glucose levels without pleocytosis or oligoclonal bands. Bickerstaff encephalitis and central nervous system inflammatory demyelinating disorder causing BE were considered, but the patient's serum was negative for anti-GQ1b antibody. She was given intravenous immunoglobulin (0.4 g/kg/d for 5 days), which led to recovery. Three months later, she had minimal diplopia and nystagmus only. Seven months after the initial presentation, she developed severe paraparesis and sensory loss due to LETM affecting the T2-T6 levels. Her condition improved with intravenous methylprednisolone, and prednisolone (60 mg/d) with azathioprine was initiated, but LETM recurred 1 month and 3 months later. Therapy with rituximab was started. She gradually recovered ambulation using a walking stick and independent activities of daily living and remained stable on a regimen of rituximab every 6 months for 2 years. She was seropositive for AQP4 autoantibodies.

Patient 2

Patient 2 was a 24-year-old woman who was seen with intractable vomiting, hiccups, dysarthria, and dysphagia, followed by tetraparesis, sensory loss, and respiratory insufficiency developing over 5 days. Examination findings revealed pharyngeal weakness, absent gag reflex, and tetraparesis. Brain computed tomographic images were unremarkable. At a private hospital, she was treated for Guillain-Barré syndrome with mechanical ventilation, plasma exchange, and then intravenous immunoglobulin; she was transferred to our hospital 2 weeks later. Brain and spinal cord MR imaging revealed a hyperintense T2-weighted triangular lesion in the anterior pons around the midline extending to the medulla, as well as a lesion at C2-C3 consistent with BE and high cervical myelitis (Figure 2). Her condition gradually improved, with full recovery 12 weeks after onset. Eight years later, she relapsed with BE affecting the left cerebral peduncle and bilateral middle cerebellar peduncles and with coexisting myelitis affecting C2-C4, which responded to intravenous methylprednisolone therapy. Her visual evoked potential was prolonged, and she was seropositive for AQP4 autoantibodies. Combined corticosteroid and azathioprine (2 mg/kg/d) therapy was initiated. She was stable for 3 years on a regimen of azathioprine (2.5 mg/kg/d).

COMMENT

Lack of brain involvement was originally considered characteristic of NMO. However, brainstem lesions that are typically continuous with high cervical myelitis are recognized in NMO on MR imaging and confirmed by his-

Figure 3. Brain magnetic resonance image of a patient with recurrent brainstem encephalitis and subclinical myelitis who was seen initially with brainstem encephalitis. A T2-weighted image revealed a hyperintense lesion at the right dorsolateral pons involving the right superior cerebellar peduncle (A), which was also shown on a coronal fluid-attenuated inversion recovery image (B). The lesion was enhanced with gadolinium (C).
ological examination of affected brain tissues from patients who develop bulbar dysfunction manifesting as dizziness, vertigo, ataxia, diplopia, dysphagia, intractable hiccups, facial sensory impairment or paresthesia, nystagmus, or dysautonomia, which may cause sudden cardiac arrest. Patients with NMO may initially be seen with endocrinopathies and hypothalamic dysfunction, including hyperphagia with weight gain, amenorrhea, galactorrhea, diabetes insipidus, and hypothyroidism, with lesions seen in the hypophysis and hypothalamus on MR imaging. Recently, brain involvement in NMOSDs is increasingly recognized. At the Mayo Clinic, Pittock et al systematically studied brain involvement of patients with NMO and reported the following observations: up to 60% of patients had brain lesions on MR imaging, approximately 10% of patients had brain abnormalities on MR imaging that are typical of classic MS (usually asymptomatic), and 8% of patients, mostly children, had diencephalic, brainstem, and cerebral lesions that are atypical of classic MS. These investigators also noticed a pattern of abnormalities on MR imaging involving the hypothalamus, periaqueductal region, and periventricular region surrounding the third and fourth ventricles (periependymal regions) in 6 of 89 patients with NMO and in 2 of 31 relapsing patients with LETM, which was characteristic of NMOSDs. This is pathogenetically relevant because these sites are regions with a high level of AQP4 expression. Our findings that 59% (20 of 34) of patients with NMOSDs had brain involvement and that 56% (19 of 34) of patients had brain abnormalities on MR imaging, with 6% (2 of 34) of the latter fulfilling criteria by Barkhof for classic MS, were consistent with results reported by Pittock et al. However, 32% (11 of 34) of our patients had clinical manifestation of brain involvement, especially as BE with florid bulbar signs and symptoms of severe brainstem dysfunction in 24% (8 of 34) and as initial clinical presentation in 18% (6 of 34). This differed from the findings by Pittock et al in which most patients with brain lesions on MR imaging were asymptomatic or mildly symptomatic only. Among 88 pediatric patients with NMO who were seropositive for AQP4 autoantibodies, McKeon et al reported that

Figure 4. Brain magnetic resonance imaging of a patient with extensive hemispheric white matter involvement. An axial T2-weighted image revealed a large confluent white matter lesion over the left occipital region (A), which was also shown on a fluid-attenuated inversion recovery (FLAIR) image (B). Multiple white matter lesions in bilateral hemispheres were shown on a T2-weighted image (C) and a FLAIR image (D); some of the lesions were cystic (D). Gadolinium enhancement was noted in some hemispheric white matter lesions, which were compatible with cloud-like enhancement (E). The corpus callosum was involved, with an enhancing lesion shown on a sagittal T1-weighted image (F). This patient fulfilled Barkhof criteria for multiple sclerosis and was seropositive for aquaporin-4 autoantibodies.
Wang et al.45 studied 40 Chinese patients with NMO vomiting, hiccups, headache, and altered mental status. and 5 had atypical symptoms, including dysphonia, abnormalities on MR imaging, 5 had brainstem lesions reported that, among 6 patients having NMO with brain

manifestation of brain involvement in our patients is similar to that among these pediatric patients

including episodic encephalopathy, ophthalmoparesis, ataxia, seizures, intractable vomiting, or hiccups, and that

68% had brain abnormalities on MR imaging predominantly involving periventricular areas, including the medulla (34%), supratentorial (29%) and infratentorial (23%) white matter, midbrain (21%), cerebellum (18%), thalamus (13%), and hypothalamus (5%). Lotze et al.42 reported on 9 pediatric patients with NMO; all had brain abnormalities on MR imaging, and 5 were symptomatic, including encephalopathy, seizures, hemiparesis, aphasia, vomiting, or hiccups. The abnormalities were detected in periventricular regions (88%), brainstem (77%), juxtacortical (55%) and central (55%) white matter, corpus callosum (44%), and hypothalamus (44%). The frequent clinical manifestation of brain involvement in our patients is similar to that among these pediatric patients with NMO, but none of our patients had encephalopathy or seizures.

Kim et al.43 studied 78 Korean patients with NMOSDs and reported that brain abnormalities on MR imaging predominantly involving periventricular areas, including the medulla (51%), supratentorial (13%) and infratentorial (36%) regions around the third and fourth ventricles typical of NMO; and 5% had MS-like lesions. This frequency of brain abnormalities on MR imaging was lower than that among our patients. Among 61 Chinese patients with NMO, Wu et al.46 reported that brain abnormalities on MR imaging were detected in 64%, with the following observations: 51% had supratentorial lesions predominantly in juxtacortical, subcortical, deep white matter, and regions around lateral ventricles; 25% had infratentorial lesions predominantly in regions around the aqueduct and fourth ventricle; and 12% had supratentorial and infratentorial lesions simultaneously. This high frequency of brain abnormalities on MR imaging is consistent with findings in our patients, but their frequency of brainstem lesions is lower than that among our patients. Among 33 Chinese patients with NMO, Li et al.47 reported that brain abnormalities on MR imaging were detected in 85%, with the following observations: 15% had non-enhancing lesions in deep white matter not typical of MS; 10% had lesions in hypothalamus, brainstem, or regions around the third and fourth ventricles typical of NMO; and 5% had MS-like lesions. This frequency of brain abnormalities on MR imaging was lower than that among our patients.

Table 2. Frequencies, Locations, and Nature of Brain Abnormalities on Magnetic Resonance Imaging Among 34 Patients With Neuromyelitis Optica Spectrum Disorders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Patients</th>
<th>Detected &lt;1 y After Symptom Onset</th>
<th>Detected &gt;1 y After Symptom Onset</th>
<th>Abnormalities in Other Brain Regions</th>
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<tbody>
<tr>
<td>Brainstem lesion</td>
<td>15 (44)</td>
<td>12 (35)</td>
<td>3 (9)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Hemispheric periventricular white matter lesion</td>
<td>7 (21)</td>
<td>5 (15)</td>
<td>2 (6)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Deep white matter lesion</td>
<td>7 (21)</td>
<td>5 (15)</td>
<td>2 (6)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Corpus callosum lesion</td>
<td>4 (12)</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Subcortical white matter lesion</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Cerebellar white matter lesion</td>
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<td>2 (6)</td>
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<tr>
<td>Large confluent lesion &gt;3 cm</td>
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<tr>
<td>Thalamic lesion</td>
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<tr>
<td>Hypothalamic lesion</td>
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<td>1 (3)</td>
<td>1 (3)</td>
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<tr>
<td>Basal ganglia lesion</td>
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<tr>
<td>Internal capsule lesion</td>
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<td>1 (3)</td>
<td>...</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Periaqueductal gray matter lesion</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>...</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lesion in periventricular region of third and fourth ventricles</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>...</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cavitory lesion</td>
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<tr>
<td>Enhancing lesion</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>...</td>
</tr>
<tr>
<td>Brain abnormalities on magnetic resonance imaging fulfilling criteria for multiple sclerosis by Barkhof</td>
<td>2 (6)</td>
<td>...</td>
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</tbody>
</table>

Abbreviation: Ellipses, not applicable.
ACHE, and vision symptoms.55 We have not observed this syndrome in our patients with NMOSDs and manifests clinically as florid and explosive neuromyelitis optica.44,52 In some of our patients, similar large spheric confluent cavitary lesions, presumably due to a discrete demyelinating attack, have been observed in NMO.49-51 Matsushita et al51 reported on patients with NMOSDs and manifested clinically as subacute myelitis complicating optic neuritis.51

The authors estimated that approximately 12% of patients with NMOSDs had vomiting as the initial symptom and suggested that the AQP4-rich area postrema might be the site of the initial attack. The authors estimated that approximately 12% of patients with NMOSDs had vomiting as the initial symptom and suggested that the AQP4-rich area postrema might be the site of the initial attack in NMOSDs.49,50,52,53

Bythipanakul et al48 described 12 patients with NMOSDs and AQP4 autoantibody seropositivity whose initial symptom was intractable vomiting and some of whom showed lesions on MR imaging in the medulla affecting the bilateral area postrema. The authors estimated that approximately 12% of patients with NMOSDs had vomiting as the initial symptom and suggested that the AQP4-rich area postrema might be the site of the initial attack in these patients.48 These results are consistent with our observation that 12% (4 of 34) of patients with NMOSDs in our study had vomiting as an initial symptom and support our finding that brainstem involvement can be the initial site of attack in NMOSDs manifesting as BE.

Extensive hemispheric and corpus callosal lesions are observed in NMO.15,46 Matsushita et al41 reported on patients with AQP4 autoantibody seropositivity and NMOSDs who had extensive hemispheric lesions over white matter, basal ganglia, and corpus callosus manifesting as limbic encephalitis, parkinsonism, and coma. The authors suggested that the lesions were vasogenic edema associated with inflammation. Large hemispheric confluent cavitory lesions, presumably due to a large area of inflammation with necrosis, are also observed in NMO.14,52 In some of our patients, similar large confluent lesions in frontal, parietal, and occipital lobes were observed manifesting clinically as homonymous hemianopia, aphasia, and cognitive impairment. Ito et al53 reported that “cloud-like enhancement” consisting of multiple patchy areas of enhancement with blurred margins is characteristic of brain lesions on MR imaging in patients with NMO. This was observed in one of our patients. Patients with NMO may be predisposed to a higher frequency of posterior reversible encephalopathy syndrome when subjected to blood pressure fluctuations or therapies causing rapid fluid shifts, such as plasmapheresis and intravenous immunoglobulin.24 This syndrome manifests as reversible encephalopathy, seizures, headache, and vision symptoms.55 We have not observed this syndrome in our patients with NMOSDs.

In conclusion, brain involvement is common in patients with NMOSDs and manifests clinically as florid and diverse neurological signs and symptoms, sometimes as the initial clinical presentation. Brainstem involvement manifesting clinically as BE is common among Hong Kong Chinese patients with NMOSDs.

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