We reviewed and compared the neuropathology of multiple sclerosis (MS), neuromyelitis optica (NMO), neuromyelitis optica spectrum disorders (NMOSD) and acute disseminated encephalomyelitis (ADEM) in Japan. Demyelinating lesions of MS are well circumscribed as compared with the lesions of NMO and NMOSD, which reveal variable, irregularly shaped and ill-defined borders that extend longitudinally along vessels, causing destructive changes with poor gliosis. Although the optic nerves and chiasm, spinal cord, cerebral white matter, brainstem, and cerebellum are involved in both MS and NMO/NMOSDs, the formation patterns of demyelinating lesions appear to differ between MS and NMO/NMOSD. NMO/NMOSD preferentially exhibit central lesions of the spinal cord with strongly softening features. Furthermore, the expression of myelin basic protein (MBP) is strongly diminished in the demyelinating lesions of MS, without loss of aquaporin-4 (AQP4) or GFAP expression. However, AQP4 and GFAP expression is decreased in the demyelinating lesions of NMO/NMOSD. Therefore, AQP4 and MBP immunoreactivity may distinguish NMO/NMOSD from MS neuropathologically. Serial sections of the spinal cord demonstrate longitudinally extensive lesions in NMO/NMOSD, although some cases with MS also reveal similar longitudinally extensive lesions of the spinal cord. In ADEM, demyelinating lesions form primarily in small perivenous foci that differ from the lesions of MS and NMO/NMOSD. Therefore, the shape and formation patterns of demyelinating lesions appear to be disease specific, and it might be possible to distinguish among MS, NMO and ADEM; the immunoreactivity patterns of MBP, AQP4, and GFAP may also aid diagnosis.

ABBREVIATIONS

ADEM: Acute Disseminated Encephalomyelitis; AHL: Acute Hemorrhagic Leukoencephalopathy; MS: Multiple Sclerosis; NMO: Neuromyelitis Optica; NMOSD: Neuromyelitis Optica Spectrum Disorders; C: Cervical Cord; T: Thoracic Cord; L: Lumbar Cord

INTRODUCTION

The pathology of demyelination is defined as the destruction of normal myelin with relative preservation of axons. The term demyelination excludes diseases characterized by a loss of myelin due to an inherited defect of metabolism (leukodystrophies) or a loss of myelin as a result of axonal degeneration.

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system. NMO, also known as Dévick’s disease, is characterized by the acute development of optic neuritis and acut e transverse myelitis within weeks of each other [1-5]. Until relatively recently, NMO has been classified as a subtype of multiple sclerosis. There has long been controversy concerning whether NMO is a variant of MS, called optic-spinal multiple sclerosis (OSMS) in Asian countries, or a distinct disease [1-5]. After the identification of AQP4, which is the main water channel protein in the CNS and is densely expressed on astrocyte endfeet at the blood-brain barrier (BBB), the loss of AQP4 in NMO lesions revealed distinct pathogenesis and pathology, distinguishing it from MS [6,7].

The recognition of variable distributions of NMO lesions in regions other than the spinal cord and optic nerves has promoted the concept of NMO spectrum disorders (NMOSD) [8,9]. We use the term NMOSD as a comprehensive concept in this review. We reviewed the neuropathology of 27 autopsied cases with demyelinating diseases in Japan and demonstrated the characteristic features of MS, NMOSD and ADEM. These patients were chosen from the files of the Institute for Medical Science of Aging, Aichi Medical University, between 1980 and 2013. The demographic features of all of the included cases are summarized in the Table 1. The pathological diagnosis revealed 9 cases with MS, 14 cases with NMOSD, 3 cases with ADEM and 1 case with AHL (Table 1). In cases with NMOSD, 2 cases were combined with Sjögren syndrome. It is interesting that NMOSD cases were more frequent than MS cases in Japan, although this may be biased by...
the autopsied series. Some cases that were previously diagnosed as MS were reassessed and classified as NMOSD. We present the macroscopic and microscopic features of MS, NMOSD and ADEM and confirm the discriminations of these demyelinating disorders based on their neuropathologies.

**MULTIPLE SCLEROSIS**

The pathological hallmark of MS is the presence of focal demyelinated plaques with partial axonal preservation and reactive glial scar formation in the white and gray matter of the CNS [10,11]. In addition, there is considerable axonal loss in small nerve fibers [12,13] as well as diffuse damage throughout the normal-appearing white and gray matter [14-17]. With disease progression, these alterations are associated with increasing global brain atrophy.

**Macroscopic findings**

In fixed tissues, MS plaques in the acute stage appear as well-circumscribed pale regions. When acute stage plaques are large and extending, the spinal cord may show transverse edema and softening (Figure 1). Chronic lesions in the cerebral white matter appear as round well-defined plaques with discoloration (Figure 5A). Cavitated lesions are observed in longstanding severely damaged plaques (Figure 7A).

**Microscopic findings**

In the acute stage, well-circumscribed demyelination is observed using myelin staining in the optic nerves and chiasm, the cerebral peduncles of the midbrain, the pons, the medullary tegmentum and the spinal cord (Figure 2). Demyelination with marked edema and softening is observed in cases with a rapidly progressive fatal course, known as acute (Marburg-type) MS. Within the plaque, relative preservation of neurons and numerous foamy macrophages and perivascular lymphocytes are observed (Figure 3A,B). Immunohistochemistry for phosphorylated neurofilament indicates relative preservation of axons and loss of staining for MBP (Figures 3,4). The lesions show different stages in time as well as demyelination and remyelination. In inactive lesions, staining for myelin reveals a well-circumscribed, round demyelinating plaque associated with marked hypocellularity, obvious loss of oligodendroglia and gliosis (Figure 5). In contrast to the marked loss of staining for MBP, GFAP and AQP4 immunoreactivity are preserved (Figure 6). In longstanding MS, extensive demyelinating lesions and axonal loss are observed in the subcortical white matter and at the junction between

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**Table 1: Table Demographics of NMOSD, MS and ADEM patients.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/sex</th>
<th>Disease duration</th>
<th>Pathological diagnosis</th>
<th>ON</th>
<th>Spinal cord (LETM)</th>
<th>Pathological lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/F</td>
<td>7 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, cerebral white matter</td>
</tr>
<tr>
<td>2</td>
<td>23/M</td>
<td>4 years</td>
<td>MS</td>
<td>+</td>
<td>-</td>
<td>ON, brainstem, periventricular white matter</td>
</tr>
<tr>
<td>3</td>
<td>63/F</td>
<td>5 years</td>
<td>NMOSD</td>
<td>+</td>
<td>NE</td>
<td>ON, brainstem, thalamus</td>
</tr>
<tr>
<td>4</td>
<td>43/M</td>
<td>8 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, brainstem, cerebellum, cerebral white matter</td>
</tr>
<tr>
<td>5</td>
<td>59/M</td>
<td>3 months</td>
<td>MS</td>
<td>+</td>
<td>+ (-)</td>
<td>ON, spinal cord, cerebral white matter</td>
</tr>
<tr>
<td>6</td>
<td>54/F</td>
<td>27 years</td>
<td>MS</td>
<td>+</td>
<td>± (-)</td>
<td>ON, spinal cord, brainstem, cerebral white matter &amp; cortices</td>
</tr>
<tr>
<td>7</td>
<td>82/M</td>
<td>6 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord</td>
</tr>
<tr>
<td>8</td>
<td>64/M</td>
<td>38 days</td>
<td>ADEM</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, brainstem, cerebellum, cerebral white matter</td>
</tr>
<tr>
<td>9</td>
<td>74/F</td>
<td>11 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, brainstem, cerebellum, cerebral white matter</td>
</tr>
<tr>
<td>10</td>
<td>46/F</td>
<td>3 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, brainstem, cerebellum, cerebral white matter</td>
</tr>
<tr>
<td>11</td>
<td>68/F</td>
<td>2 months</td>
<td>MS</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, brainstem</td>
</tr>
<tr>
<td>12</td>
<td>29/M</td>
<td>14 days</td>
<td>AHL</td>
<td>–</td>
<td>+ (-)</td>
<td>Brainstem, basal ganglia, cerebral white matter</td>
</tr>
<tr>
<td>13</td>
<td>74/F</td>
<td>2 months</td>
<td>NMOSD</td>
<td>–</td>
<td>+ (+)</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>14</td>
<td>67/F</td>
<td>5 years</td>
<td>NMOSD</td>
<td>–</td>
<td>+ (+)</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>15</td>
<td>85/F</td>
<td>11 months</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>16</td>
<td>67/M</td>
<td>5 years</td>
<td>MS</td>
<td>+</td>
<td>+ (-)</td>
<td>ON, spinal cord, brainstem, basal ganglia</td>
</tr>
<tr>
<td>17</td>
<td>68/F</td>
<td>22 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord</td>
</tr>
<tr>
<td>18</td>
<td>57/M</td>
<td>8 months</td>
<td>NMOSD</td>
<td>–</td>
<td>+ (+)</td>
<td>Spinal cord, brainstem</td>
</tr>
<tr>
<td>19</td>
<td>73/F</td>
<td>17 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, cerebral white matter</td>
</tr>
<tr>
<td>20</td>
<td>66/M</td>
<td>10 years</td>
<td>MS</td>
<td>–</td>
<td>+ (-)</td>
<td>Spinal cord, cerebral white matter</td>
</tr>
<tr>
<td>21</td>
<td>71/F</td>
<td>14 years</td>
<td>NMOSD</td>
<td>+</td>
<td>–</td>
<td>ON, brainstem, cerebral white matter</td>
</tr>
<tr>
<td>22</td>
<td>66/F</td>
<td>4 years</td>
<td>MS</td>
<td>+</td>
<td>+ (-)</td>
<td>ON, spinal cord, cerebral white matter</td>
</tr>
<tr>
<td>23</td>
<td>63/M</td>
<td>5 months</td>
<td>ADEM</td>
<td>–</td>
<td>+ (+)</td>
<td>Spinal cord, brainstem, basal ganglia, thalamus</td>
</tr>
<tr>
<td>24</td>
<td>63/M</td>
<td>44 years</td>
<td>MS</td>
<td>+</td>
<td>+ (-)</td>
<td>ON, spinal cord, cerebral white matter</td>
</tr>
<tr>
<td>25</td>
<td>56/M</td>
<td>4 years</td>
<td>MS</td>
<td>–</td>
<td>+ (-)</td>
<td>Spinal cord, brainstem, basal ganglia, thalamus, cerebral white matter &amp; cortices</td>
</tr>
<tr>
<td>26</td>
<td>64/F</td>
<td>23 years</td>
<td>NMOSD</td>
<td>+</td>
<td>+ (+)</td>
<td>ON, spinal cord, brainstem, cerebellum, cerebral white matter</td>
</tr>
<tr>
<td>27</td>
<td>60/F</td>
<td>14 days</td>
<td>ADEM</td>
<td>–</td>
<td>+ (+)</td>
<td>Spinal cord, brainstem, cerebellum, cerebral white matter &amp; cortices</td>
</tr>
</tbody>
</table>

f: Female; m: Male; ADEM: Acute Disseminated Encephalomyelitis; MS: Multiple Sclerosis; NMOSD: Neuromyelitis Optica Spectrum Disorder; NE: Not Examined; LETM: Longitudinally Extensive Transverse Myelitis; ON: Optic Neuritis.
Figure 1  Macroscopic appearance of acute MS of 2 months' duration (case 11). Scattered pale plaques (arrows) in cerebral peduncles of midbrain (A). Transverse sections in the thoracic cord with remarkable edematous myelitis (B). The numbers indicate the level of thoracic cord and the seventh and lower thoracic cords show severe edema and softening.

Figure 2  Optic nerves and chiasm, brainstem and spinal cord in acute MS (case 11). Staining for myelin reveals well-circumscribed areas of demyelination in the optic nerves and chiasm, midbrain, pons and medulla (A). Well-circumscribed lesions in the cervical cord and extensive longitudinal transverse demyelination with edema in the thoracic cord (B). Klüver-Barrera stain. (Reproduced with permission from Igaku-Shoin [31])

Figure 3  Spinal cord of an acute MS case (case 11). Relative preservation of neurons in the cervical cord (A) and numerous foamy macrophages (B). Immunohistochemistry for phosphorylated neurofilament shows relative preservation of axons (C) and loss of staining for MBP (D).

Figure 4  Immunostaining for myelin basic protein (case 11). Multiple well-defined area of demyelinating plaques (arrows) in the midbrain (A) and medulla (B).

Figure 5  Chronic plaque in the cerebral white matter (case 20). Macroscopic appearance of a round, well-defined plaque with discoloration (arrow) in the cerebral white matter (A). Staining for myelin reveals a well-circumscribed, round demyelinating plaque (B). Markedly hypocellular, inactive plaque with obvious loss of oligodendroglia (C). Most of the cells within the plaque are astrocytes (D). (Reproduced with permission from Igaku-Shoin [31])

the cerebral cortex and white matter, resulting in global brain atrophy (Figure 7B) [14-17].

Neuromyelitis optica spectrum disorders (MINOSD)

NMO is characterized by the development of optic neuritis and transverse myelitis within weeks of each other [1,3]. Since the identification of AQP4, a diverse spectrum of AQP4-related demyelination has been recognized [6,7,18-24]. In this review,
of 14 cases with NMOSD, 8 cases had both optic neuritis and longitudinally extensive transverse myelitis pathologically; two cases had localized lesions only within optic neuritis and transverse myelitis (case 7 and 17); there were 3 cases (cases 13, 14 and 18) without optic neuritis; and one case (case 21) without transverse myelitis (Table 1).

**Macroscopic findings**

In the acute stage, the optic nerves and chiasm and affected regions show swollen edema and softening. In chronic stages of long duration, the macroscopic appearance of spinal cords with...
a typical NMOSD presentation shows marked and extensive longitudinal atrophy of the cord (Figures 8-10). Cerebral white matter lesions in NMOSDs show multiple irregular cystic lesions in the corpus callosum, temporal white matter and periventricular white matter (Figure 11).

**Microscopic findings**

In NMOSDs, demyelinating lesions show multiple irregularly shaped areas of softening, which differs substantially from the sharp margin of MS plaques (Figure 12). The transverse sections of the cord show extensive irregular demyelination and longitudinal softening from the cervical cord to the lower thoracic...
Figure 16 Macroscopic findings of ADEM (case 8).
Case of a 64-year-old man who developed transverse myelitis and visual disturbance 2 weeks after the onset of an atypical mycobacterial disease, which resulted in death after 38 days. The brain shows edematous softening in the white matter and multiple large, swollen, confluent demyelinating lesions with small perivascular foci of demyelination (A, B). The resemblance to acute MS is striking.

Figure 17 Basal ganglia in ADEM (case 23).
Small disseminated perivascular demyelination (arrows) of the basal ganglia in acute disseminated encephalomyelitis (ADEM) at the chronic stage (A-C). Perivascular infiltration of lymphocytes and macrophages is present (D).

Figure 18 Brainstem in ADEM (case 23).
Multiple small softening lesions (arrows) of the medulla (A). Disseminated perivascular demyelination (arrows) is present (B), as shown by Klüver-Barrera staining.

Figure 19 Microscopic appearance of brainstem lesions in ADEM (case 23).
Small irregular foci of perivenous demyelination, as shown by Klüver-Barrera staining, (A) with infiltration of lymphocytes and macrophages around vessels (B). Preservation of axons, as shown by phosphorylated neurofilament immunostaining (C) and infiltration of macrophages (D). T lymphocytes (E) and B lymphocytes (F).

Figure 20 Spinal cord lesions in ADEM (case 23).
A transverse section of thoracic cord showing multiple irregular foci of demyelination along vessels from the peripheral zone, as shown by Klüver-Barrera staining, with inflammatory cell infiltration (A-C). The preservation of MBP immunoreactivity distinguishes it from multiple sclerosis (D).

Figure 21 Different formation patterns in demyelinating lesions between MS and NMOSD.
Well-circumscribed plaques in MS (A-C) and perivascular longitudinally demyelinating lesions and lesions showing cystic destruction extending from the central portion of the spinal cord (D-E) in NMOSD.
cord, accompanied by Wallerian degeneration in the posterior column and the bilateral pyramidal tract (Figure 12). The irregular lesions on the spinal cord showing cystic destruction extend from the central portion to the adjacent gray and white matter.

The demyelinating lesions of NMOsDs tend to extend along the perivascular region longitudinally (Figure 13A). Axons are more severely decreased in NMOSD lesions than in those of MS (Figure 13B). Foamy macrophages and hyaline thickening of small vessels in the lesion are observed (Figure 13C, D).

AQP4 immunoreactivity is severely decreased in cystic lesions when compared with normal-looking lesions (Figure 14A-C) [18-23]. AQP4 is highly expressed in the astrocytic endfoot around blood vessels. GFAP immunoreactivity is decreased in cystic lesions exhibiting severe damage, whereas GFAP expression remains or may recover in areas showing mild demyelination (Figure 14D-F). Phagocytized corpora amylacea have been reported to be a characteristic feature in acute NMOSD lesions (Figure 15) [25]. The presence of different lesion types is reported to suggest diverse mechanisms of tissue injury in NMO [26].

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

ADEM is a multifocal inflammatory disorder of the central nervous system, presenting perivenous demyelinating lesions, postinfectious encephalomyelitis and post-vaccinal encephalomyelitis [27-31]. In the acute phase, swelling of the brainstem, spinal cord or cerebral white matter may be observed in severe cases and may resemble acute MS in some cases (Figure 16). In the chronic stage, small areas of disseminated perivenous demyelination and perivenous infiltration of lymphocytes and macrophages are visible microscopically (Figures 17-19). In the spinal cord, transverse sections show multiple irregular foci of demyelination along vessels from the peripheral zone and inflammatory cell infiltration (Figure 20). The formation patterns of demyelinating lesions in the spinal cord are characteristic of ADEM and different from those of MS and NMOsDs.

CONCLUSION

Different formation patterns in demyelinating lesions are pathologically evident in MS, NMOSD and ADEM. The characteristic pathological features include well-circumscribed plaques in MS and irregular lesions showing perivascular longitudinal demyelination combined with cystic destructive lesions in NMOSD (Figure 21). Additionally, the immunoreactivities of MBP and AQP4 differ between MS and NMOSDs, which may aid the pathological reevaluation of past cases diagnosed as MS, OSMS or NMO. These pathological images may contribute to understanding the neuroimaging features of demyelinating diseases. Further investigation is needed to determine the pathomechanism of demyelination.

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