Magnetic resonance imaging in primary progressive multiple sclerosis

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Abstract—Ten to fifteen percent of patients with multiple sclerosis (MS) have a condition that is progressive from onset without a preceding relapsing-remitting phase: this is known as primary progressive multiple sclerosis (PPMS). Patients with PPMS tend to be older, often present with motor symptoms and, in contrast to relapsing MS, are as likely to be male as female. The conventional magnetic resonance imaging (MRI) characteristics of PPMS include a tendency to lower lesion loads and lower rate of new lesion formation. In common with relapsing MS, the relation between conventional MRI abnormalities and clinical condition is poor. Studies using newer MRI techniques, such as magnetization transfer imaging (MTI), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI), have also been carried out. These techniques are sensitive to a wider range of abnormalities within tissue, and their increased patho- logical specificity may be helpful in clarifying the underlying pathology of the condition.

Key words: diffusion-weighted imaging, functional magnetic resonance imaging, magnetic resonance imaging, magnetic resonance spectroscopy, magnetization transfer imaging, primary progressive multiple sclerosis, spinal cord.

INTRODUCTION

Progressive disease from onset without relapses and remissions is seen in 10 to 15 percent of patients with multiple sclerosis (MS), and for these patients, the term primary progressive multiple sclerosis (PPMS) is now widely accepted (1). The progressive, nonepisodic nature and relative rarity of PPMS complicate its study, and patients routinely have been excluded from many MS clinical trials. Patients with PPMS differ in a number of ways from the general MS population; they are likely to be older, motor symptoms are prominent at presentation, and incidence in males and females is similar (2). However, how truly distinct PPMS is from relapsing-remitting MS (RRMS) remains a subject for speculation, and the issue is likely to remain unresolved until underlying pathological mechanisms are more clearly understood. It is important to understand these mechanisms because PPMS is a disabling condition for which no effective disease-modifying treatment exists yet. It seems likely that the development of such treatments will be aided by insights into disease mechanisms. More speculatively, the progressive element that often ultimately develops in other clinical forms of MS may have similarities to the process that is occurring from onset in PPMS. Potentially, understanding the nature of progression of disability in PPMS may be helpful in understanding progression in MS more generally.

Magnetic resonance (MR) imaging (MRI) provides a safe and noninvasive way to study nervous tissue without the use of ionizing radiation. The extent to which tissue...
can be characterized by means of MRI has increased in recent years. The resolution of structural imaging has improved, and it is now possible to use MRI to obtain information about nervous tissue, including its chemical composition and structure. This information previously was available only by direct examination of pathological material. Unfortunately, limitations remain with respect to resolution and pathological specificity of the newer MRI measures. This article will outline the findings to date on conventional and nonconventional MR in patients with PPMS, beginning with the earliest studies designed specifically to examine patients with this form of MS.

INITIAL OBSERVATIONS

The first study to specifically examine PPMS compared its MR appearances with those of secondary progressive multiple sclerosis (SPMS) and benign MS (3). Patients with PPMS had the fewest lesions on T2-weighted MRI of the brain, and those lesions that were present were small, with 85 percent being under 5 mm. By comparison, in SPMS, lesions tended to be large and confluent. Distribution of lesions did not differ between the groups although patients with PPMS tended to have fewer lesions in the periventricular area (Table 1). Cortical atrophy (qualitatively assessed) was seen in 1 of 13 patients with PPMS in comparison with 1 of 12 patients with benign MS and 5 of 16 with SPMS.

CEREBRAL T2 HYPERINTENSITY AND T1 HYPOINTENSITY

Quantitative T2 lesion and T1 hypointensity load data (calculated with computer-assisted visual or semi-automated algorithms) have been presented in several studies. These studies confirm that PPMS tends to have lower lesion loads (Tables 2 and 3) (4–9). Two earlier studies that used a scoring system based on lesion size are not included (10,11). In these studies, T2 load was greater in SPMS than PPMS with ratios of 1.0:1.6 and 1.0:2.2 (PPMS:SPMS). The study of Filippi et al. found that the areas where difference in lesion load was greatest between patients with PPMS and patients with SPMS were the frontal, occipital horn, and trigone areas and the parietal and temporal lobes (11).

Changes in lesion number and load over time in PPMS were studied by Stevenson et al., who found that 43.6 percent of patients with PPMS demonstrated one or more new brain lesions over a 1-year period (12). Over the same period, T2 lesion load increased by a median of 7.3 percent and T1 lesion load increased by a median of 12.6 percent. Image registration has been used to show precisely where new T2 load is occurring (13). Over 2 years, 91 percent of the total new T2 lesion load was seen to come from the enlargement of existing lesions and only 9 percent from new discrete lesions.

Table 1. Lesion distribution (mean numbers) in primary progressive and secondary progressive MS (PPMS, n = 14, and SPMS, n = 20) compared (10).

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>PPMS</th>
<th>SPMS</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular</td>
<td>19.2</td>
<td>34.9</td>
<td>( p = 0.003 )</td>
</tr>
<tr>
<td>Discrete cerebral</td>
<td>15.6</td>
<td>22.0</td>
<td>( p = 0.01 )</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>1.5</td>
<td>1.9</td>
<td>( p = 0.29 )</td>
</tr>
<tr>
<td>Brainstem</td>
<td>3.6</td>
<td>3.5</td>
<td>( p = 0.74 )</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.0</td>
<td>1.9</td>
<td>( p = 0.21 )</td>
</tr>
<tr>
<td>Total</td>
<td>39.4</td>
<td>62.3</td>
<td>( [ p ] = 0.028 )</td>
</tr>
</tbody>
</table>

Table 2. T2 hypointensity load in RRMS, SPMS, and PPMS in cm³.

<table>
<thead>
<tr>
<th>Study*</th>
<th>Year</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycklama á Nijeholt</td>
<td>1998</td>
<td>4.1</td>
<td>11.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Stevenson</td>
<td>1999</td>
<td>—</td>
<td>27.7</td>
<td>12.0</td>
</tr>
<tr>
<td>Filippi</td>
<td>1999</td>
<td>14.1</td>
<td>23.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Foong</td>
<td>2000</td>
<td>—</td>
<td>39.8</td>
<td>10.7</td>
</tr>
<tr>
<td>van Walderveen</td>
<td>2001</td>
<td>4.7</td>
<td>11.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Wolinsky</td>
<td>2001</td>
<td>15.4</td>
<td>16.5</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*See main text for reference note numbers.

Table 3. T1 load in RRMS, SPMS, and PPMS in cm³.

<table>
<thead>
<tr>
<th>Study*</th>
<th>Year</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lycklama á Nijeholt</td>
<td>1998</td>
<td>0.3</td>
<td>2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Stevenson</td>
<td>1999</td>
<td>—</td>
<td>7.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Filippi</td>
<td>1999</td>
<td>0.9</td>
<td>4.9</td>
<td>0.1</td>
</tr>
<tr>
<td>van Walderveen</td>
<td>2001</td>
<td>0.3</td>
<td>2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Wolinsky</td>
<td>2001</td>
<td>0.5</td>
<td>1.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*See main text for reference note numbers.
In addition to finding lower lesion loads in PPMS compared to SPMS, Lycklama à Nijeholt et al. reported a lower ratio of T1 hypointensity to T2 load in PPMS (14). This was seen too, although to a less marked extent, in the study of van Walderveen et al. (8). Patients with PPMS in this study were found to have a higher incidence of diffuse hyperintense brain abnormalities on proton-density-weighted images when compared to patients with SPMS (9 of 31 patients against 3 of 28 patients). These diffuse abnormalities were found mostly in the parietal periventricular white matter. An example of similar changes in a patient with PPMS is shown in Figure 1.

The relation between lesion load and clinical measures is poor in PPMS. For example, in the comparative study of van Walderveen et al., neither T1 hypointensity nor T2 lesion volume correlated with any clinical parameter in the PPMS group. Although associated with T1 hypointensity volume, expanded disability status scale (EDSS) score and disease duration were seen in RRMS and SPMS groups (8). In the multicenter study of Stevenson et al. lesion load, measures in the PPMS group did not correlate with either EDSS or disease duration (5). However, correlations were seen between T2 and T1 lesion load and nine-hole peg test score and a measure of cognitive impairment (15). When this study was extended to 2 years, no additional correlations were found between absolute or percentage change in clinical outcomes and MRI (16). Finally, differences in lesion load with clinical presentation have also been reported. In the study of Filippi et al., patients with a progressive spinal cord syndrome, the most common clinical presentation in PPMS, and without clinical evidence of cerebral or brainstem involvement had significantly lower cerebral lesion loads than those with evidence of these features (11). This difference was also observed by Stevenson et al. (5).

GADOLINIUM ENHANCEMENT

Single Dose

An early MR observation about PPMS was that in addition to having a low rate of new lesion formation, the frequency of lesion enhancement following administration of gadolinium (Gd)-diethylenetriamine pentaacetic acid (DTPA) (Gd-DTPA) was less than that of other subtypes (10). In the study of Thompson et al., which followed 12 patients with SPMS and 12 patients with PPMS monthly for 6 months, of 129 new lesions seen over a 6-month period, 109 were in 11 of the 12 patients with SPMS while only 20 new lesions were seen in 6 of the 12 patients with PPMS. The rate of development of new lesions was 3.3 lesions per patient per year in the PPMS group and 18.2 lesions per patient per year in the SPMS group. Of 105 new lesions scanned with Gd-DTPA in the SPMS group, 91 (87 percent) showed enhancement with Gd-DTPA compared to only 1 of 20 new lesions seen in the PPMS group. A low rate of MR activity in PPMS was also seen by Kidd et al. (17).

Additional data are available from a very large cohort of patients (946) with PPMS participating in an international clinical trial of glatiramer acetate (9). Baseline MR images of 541 patients with PPMS were compared with identically processed baseline images from 92 patients with RRMS and 626 patients with SPMS who had participated in a separate trial. A very low mean volume of Gd-enhancing lesions was seen. This volume was 0.03 mL on
average in PPMS compared to 0.4 mL in the RRMS group and 0.2 mL in the SPMS group.

**Triple Dose**

In RRMS, the use of triple dose Gd-DTPA (0.3 mM/kg rather than 0.1 mM/kg) increases the number of enhancing lesions seen. A study that found similar results in patients with PPMS was that of Filippi et al. (18). Ten patients with PPMS were examined over two sessions with early and delayed imaging after the administration of Gd-DTPA. In two patients, a total of four enhancing lesions were detected when the standard dose of Gd-DTPA was used. When triple-dose Gd-DTPA was used, the number of enhancing lesions increased to 13 and the number of patients with such lesions to 5. When in addition to a triple dose, there was a 1-hour delay before scanning, lesions increased to 14 and the number of patients to 6. The mean contrast ratio for enhancing lesions detected with triple-dose Gd-DTPA (scanned immediately) was higher than that for both the standard dose and triple dose with delayed scanning.

In the study of Silver et al., 50 patients were studied, including 16 with PPMS (19). Imaging was performed on two occasions with single- and triple-dose Gd-DTPA. Patients were imaged within early (0 to 20 min), short-delay (20 to 40 min), and long-delay (40 to 60 min) time windows. In this study, in contrast to that of Filippi et al. described above, triple dose and delay increased the yield of enhancing lesions in patients with RRMS and SPMS but not in patients with PPMS. However, when quantitative signal changes were measured in seven PPMS patients, in lesions conventionally regarded as nonenhancing, a significant signal increase was found. This suggests the presence of a low-grade degree of blood brain barrier (BBB) leakage. There was also a trend to increased signal in normal-appearing white matter (NAWM), raising the possibility of an even more diffuse BBB abnormality; however, more sensitive methods will be needed to definitively study this issue.

An unresolved issue is whether PPMS may have an early inflammatory phase. Given that it can take some time for the diagnosis of PPMS to become established, patients included in MR studies tend to have had symptoms for several years. A recent preliminary study of patients with disease duration of less than 5 years has shown a higher degree of enhancement (present in 55 percent of patients) (20).

**INVOLVEMENT OF NORMAL-APPEARING TISSUE: EVIDENCE FROM STUDIES USING CONVENTIONAL MR TECHNIQUES**

By definition, NAWM is normal in its appearance on conventional MR imaging, and the identification of subtle abnormalities has largely awaited the development of so-called nonconventional MR methods (discussed in more detail in subsequent paragraphs). In an early study, however, Thompson et al. showed that T1 relaxation times in an area of frontal NAWM were higher in SPMS than PPMS (where values were only slightly higher than those found in control subjects) (10). A relationship was found between NAWM T1 values and T2 lesion load. T2 relaxation times were similar in all groups.

**SPINAL CORD**

Patients with PPMS often have prominent spinal cord symptoms. A possible explanation for the disparity between apparently low levels of brain abnormality and high levels of disability is that there is a correspondingly greater degree of spinal cord abnormality. Kidd et al. observed that in PPMS, cord lesions make up a slightly greater percentage of total load than is seen in SPMS (11.8 to 8.2 percent) (21). For some patients with PPMS, conventional MR abnormalities may be almost entirely confined to the cord. Thorpe et al. studied 11 patients with PPMS with a normal or near-normal brain MRI (22). All patients had at least one lesion visible in the spinal cord. However, the finding of an entirely normal conventional brain MRI in PPMS is unusual and, in one retrospective study, was estimated to occur in less than 5 percent of cases (23).

Lycklama á Nijeholt et al. studied spinal cord appearances in 31 patients with PPMS, 28 with RRMS, and 32 with SPMS (14). The number of focal spinal T2 lesions was similar between clinical subtypes, but in PPMS, there was an increased likelihood of finding patients with diffuse signal change on proton-density-weighted images within the spinal cord. Diffuse abnormalities were seen mainly in SPMS and PPMS (10 of 32 and 19 of 31 patients, respectively). An example of diffuse change in a patient with PPMS is shown in Figure 2. By comparison,
diffuse abnormalities were present in only 6 out of 28 patients with RRMS. The presence of diffuse spinal cord abnormalities without focal lesions may be an even more specific feature of PPMS. It was seen in 10 of 31 patients with PPMS but in only 4 of 32 patients with SPMS and was entirely absent in 28 patients with RRMS.

Conventional MR appearances of the cervical cord were studied by Filippi et al. (24). Nine patients with PPMS were studied, together with forty-one with RRMS and thirty-one with SPMS. Of patients with PPMS, 81.8 percent had abnormal cervical cord scans compared to 78.8 percent of patients with RRMS and 94 percent of patients with SPMS. Patients with PPMS had a mean of 1.8 cervical cord lesions compared to a mean of 1.7 lesions in RRMS and 2.5 lesions in SPMS.

The extent of cord damage was assessed with the use of the mean number of cervical cord slices showing lesions. This was 3.2 for PPMS, 4.4 for SPMS, and 2.7 for RRMS. Patients with SPMS had a higher number of lesions and a greater number of slices involved than both other groups ($p = 0.04$ in each case).

The number of focal spinal lesions in PPMS was found to be lower than in SPMS in the study of Stevenson et al. (means 1.9 and 3.2, respectively, $p = 0.04$) (5). At baseline, there was no correlation between spinal cord lesion load and disability. Over 1 year, 25.5 percent of patients had one or more new cord lesions. Change in EDSS correlated with percentage increase in number and load of spinal cord lesions ($r = 0.19$, $p = 0.005$). No correlation was seen with the number of brain lesions. At baseline, when patients with PPMS who had presented with spinal cord symptoms were compared with those who had presented in other ways, they were not found to differ in terms of cord lesion load. Over 1 year, the number of new cord lesions was higher in the cord presentation group compared to the noncord presentation group, but this did not reach significance (12).

Further information about MR and histological abnormalities in the spinal cord in PPMS comes from a study that compared MR appearances of the cord at postmortem at two field strengths (4.7 T and 1.0 T) with histological appearances (25). Seven patients with PPMS were included in this study, and MR appearances suggested extensive involvement of the spinal cord. In comparison with SPMS cords, only a mild increase in signal intensity was seen and there was little involvement of gray matter. Interestingly, a greater degree of abnormality was present on the MR images than was detected histopathologically. Areas of high signal intensity on MR corresponded with areas of complete demyelination, identified histologically, while areas of mildly increased signal corresponded with areas of partial demyelination.

A requirement for MR abnormalities to be present in either brain or cord has been incorporated into recently published diagnostic criteria for PPMS (26). Given that spinal cord lesions are more specific than brain lesions and do not occur with aging, the presence of only two discrete spinal cord lesions is regarded as positive MRI evidence according to these criteria, even if brain MRI is normal. Nine lesions on a brain MRI are otherwise regarded as providing positive MRI evidence, but should one spinal cord lesion be present, only four brain lesions are required.
In summary, PPMS may show abnormalities in the cord when none is detectable in the brain, but a particularly high or extensive focal lesion load does not seem to exist compared to other MS subtypes. Some correlation may exist between lesion load and disability, and it has been suggested that a greater degree of diffuse abnormality (corresponding histologically to partial demyelination) may be a characteristic feature. Other evidence relating to cord changes in PPMS comes from studies of atrophy.

**ATROPHY MEASURES IN PPMS**

Measures of tissue volume and area can be made from a conventional MRI. These measures can be used to detect atrophy, either by comparing values in a single subject over time or by comparing a control population at a single time point. Atrophy measures reflect changes in central nervous system white and gray matter and, in theory, are relatively specific markers of pathological processes such as axonal loss. However, other processes are also likely to influence atrophy measures. For example, inflammation can cause increases in tissue volume through increased water and cellular content, and this might obscure atrophy caused by tissue loss.

A cross-sectional area of the spinal cord at four levels (C5, T2, T7, and T11) was studied by Kidd et al. in patients with PPMS and SPMS over a 1-year period (27). A reduction in cord area was seen in both groups that was most pronounced at the C5 level and was greatest in SPMS, with a median change of –5.39 mm² compared to –2.62 mm² in PPMS. In this study, there was no correlation between change in cord area at any of the four levels and change in EDSS. Although in those patients who changed more than one EDSS point compared to those who did not change, there was a trend toward a greater reduction in the C5 cord area. A larger median spinal cord area in PPMS compared to SPMS was also found by Lycklama á Nijeholt et al. (14). In this study, the authors also saw an association between the cross-sectional cord area and the number of spinal cord segments showing diffuse involvement in PPMS. Losseff et al. studied spinal cord area at C2 in 15 patients with PPMS (28). Their median cord area was 73.1 mm² compared to 61.2 mm² in SPMS, 85.6 mm² in RRMS, and 84.7 mm² in controls.

Stevenson et al. studied atrophy measures in both the spinal cord and brain (5,12). The authors measured the cervical cord area at the C2 level using the technique developed by Losseff et al. (28). The mean spinal cord area was 64.1 mm² in SPMS and 72.7 mm² in PPMS (although average EDSS was also greater in the SPMS group). Partial brain volume above the level of the third ventricle was used as a measure of partial cerebral atrophy (29). No differences were seen between groups at baseline. Over 1-year changes in both, measures were seen in PPMS with a median change of –2.3 percent in partial brain volume and –2.9 percent in cord area. There was no correlation with clinical measures, and patients presenting with cord syndromes did not differ from those presenting in other ways in terms of brain or cord atrophy.

Ventricular and cerebrospinal fluid (CSF) volumes can be used as measures of cerebral atrophy as they reflect loss of central white matter. Wolinsky et al. studied CSF volume normalized to total segmented intracranial contents (9). Average CSF volume in PPMS was 15.8 mL compared to 17.1 mL in RRMS and 17.8 mL in SPMS. Patients with higher EDSS were found to have larger CSF volumes. Ventricular volume was measured on T1-weighted images by Lycklama á Nijeholt et al. (14). They found that mean ventricular volume was greatest in SPMS at 31.9 mL in comparison to 21.3 mL in PPMS and 22.3 mL in RRMS. In PPMS, an association was seen between ventricular volume and pyramidal functional systems score.

**NEWER MRI MEASURES**

Within the last 10 years, new MR methods have been developed to provide better ways of characterizing brain tissue. These methods include magnetization transfer transfer imaging (MTI), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI). Results from some initial studies are presented in the following sections.

**Magnetization Transfer in PPMS**

The contribution of free water protons dominates the conventional MR image but another population of protons, bound to macromolecules, can also be visualized. This is done by measuring the amount of signal suppression following off-resonance irradiation. The resulting measure is known as the MT ratio (MTR) and reflects characteristics of the macromolecular environment.
Initially, it was hoped that MTR reduction would provide a specific MR marker of demyelination, but from subsequent histopathological correlation studies, this does not appear to be the case. Reductions in MTR in MS probably represent a combination of demyelination, matrix destruction, and axonal loss.

Leary et al. studied MTR in NAWM in 52 patients with PPMS and 26 healthy controls (30). Absolute values of MTR were obtained from a number of brain regions, including the genu of the corpus callosum and the pons. Mean values were calculated from bilateral regions in the centrum semiovale, frontal white matter, parieto-occipital white matter, and posterior limb of the internal capsule. Median MTR was significantly lower in the corpus callosum, frontal white matter, and centrum semiovale, providing further support for the existence of widespread abnormalities in normal-appearing tissues in PPMS.

A novel technique for the interpretation of MTR data involves the use of whole brain MTR histograms. Filippi et al. compared MT histogram peak height and position in MS subtypes and found that patients with PPMS had lower histogram peak height compared to control subjects (6). MTR histograms were used to study normal-appearing cerebral tissue by Tortorella et al. and lower histogram peak height and lower average histogram MTR were found (31). The relation between MTR histogram measures and disability was studied by Kalkers et al. (32). Associations between clinical and MTR parameters were not seen in PPMS, although they were seen in RRMS. In the study of Dehmeshki et al., 46 patients with PPMS were studied along with a number of normal controls and patients with MS of other types (33). Average MTR was found to differ in PPMS in comparison with controls, and an association with disability was found when a principal component analysis was done. The association with disability was stronger for other MS subtypes. An extension of this work investigated segmented histograms and revealed abnormality in both gray matter and NAWM (34). MTR has also been used to study the cervical spinal cord where PPMS patients were also seen to have lower average cord MTR and peak height (35).

**Diffusion-Weighted Imaging in PPMS**

DWI is based on the application of MR gradient pulses, which result in the dephasing of signal intensity caused by the Brownian motion of water protons. Randomly moving spins (in contrast to stationary spins) do not completely refocus and therefore attenuate the signal. Since water protons diffuse faster along myelinated fibers than across them, the apparent diffusion coefficient is directionally restricted, or anisotropic. By measuring the amount of anisotropy, DWI provides a measure of tissue integrity. Droogan et al. in 1999 studied diffusion measures in nine patients with PPMS, along with a number of other MS subtypes (36). In this study, the authors found no differences between the diffusion measures between subtypes and no association with disability. A later study confirmed this finding, although some diffusion measures were found to differ between patients with PPMS and controls in the corpus callosum and internal capsule regions, where this was not found in patients with RRMS or SPMS (37). In the study of Ciccarelli et al., an association was found between diffusion measures and disease duration in patients with PPMS (38). DWI histograms in PPMS, have been studied by Cercignani et al. (39,40). While whole-brain analysis did not show differences between subtypes, there were differences in diffusion measures in lesions between PPMS and SPMS. Further information about the use of MTR and DWI in PPMS will be found in the review by Rovaris et al. (41).

**Magnetic Resonance Spectroscopy in PPMS**

In MRS, the protons of the free water pool that are used to generate the conventional MR image are suppressed. This allows separation of resonances from various brain metabolites, including N-acetyl aspartate (NAA), creatinine, myo-inositol, lactate, choline-containing compounds, and mobile lipids. NAA as a substance is virtually exclusively present in neurons and axons and can therefore be used as a marker for neuroaxonal loss. Davie et al. in 1997 measured NAA in a number of MS subtypes, including PPMS (42). Reduced NAA was seen in areas in high-signal T2 lesions in PPMS and RRMS and in lesions in MR images. NAA was also seen in NAWM in PPMS, and there was a relation between reduced NAA and EDSS.

Leary et al. compared 24 patients with PPMS with 16 age-matched controls and found lower levels of NAA in NAWM (43). Similar results were found when 17 patients with PPMS were studied by Cucurella et al.: reduced NAA was seen in PPMS lesions and NAWM (44). Differences between patients with PPMS and SPMS were not found. Lesions and NAWM in patients with PPMS and RRMS were compared by Suhy et al. (45). Similar reductions in NAA were seen in NAWM and
lesions between patients with RRMS and PPMS, but creatine was higher in PPMS in both locations. Caramanos et al. has recently reviewed the use of MRS in PPMS (46).

**Functional MRI in PPMS**

Functional MRI is a relatively new technique that uses signal changes associated with blood oxygenation to detect localized brain activity when stimuli are presented or tasks performed. Two studies looking specifically at patients with PPMS have been published to date. In the first study, 26 patients with PPMS performed a task consisting of flexion and extension of the last four fingers of the right hand (47). These patients had no clinical involvement of the right upper limb. In comparison with control subjects, patients with PPMS had greater activation bilaterally in the superior temporal gyrus, ipsilaterally in the middle frontal gyrus, and contralaterally in the claustrum. Associations were also seen between relative activation of cortical areas and both diffusion and MT measures in the normal-appearing brain. There was also an association between activation and MT measures in the cervical cord. In the second study, a strong correlation was found between T2 lesion load and the extent of activation in 30 patients with PPMS (48). In comparison with control subjects, there was also increased activation in “nonmotor” areas when a simple motor task was performed.

**CONCLUSIONS: MRI IN PPMS**

More recent studies have supported the original observations that patients with PPMS develop fewer T2 lesions in the brain, have less T1 hypointensity, and have a lower frequency of inflammatory lesions than patients with SPMS, despite comparable levels of disability. Conventional MR studies also suggest that PPMS has less focal inflammatory activity in comparison to other MS subtypes, and this is supported by histopathological studies (49). A summary, adapted from Lycklama á Nijeholt et al., is shown in Table 4 (14).

Table 4.
Summary of conventional MR features of PPMS (adapted from study by Lycklama á Nijeholt et al. (14)).

<table>
<thead>
<tr>
<th>Measure</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal T2 lesions</td>
<td>Many</td>
<td>Many</td>
<td>Moderate or few</td>
</tr>
<tr>
<td>Enhancing lesions</td>
<td>Often</td>
<td>Often (if also relapsing)</td>
<td>Seldom</td>
</tr>
<tr>
<td>Focal T1 lesions</td>
<td>Few or moderate</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Diffuse abnormalities</td>
<td>Seldom</td>
<td>Variable</td>
<td>Frequent</td>
</tr>
<tr>
<td>Ventricular enlargement</td>
<td>Mild</td>
<td>Moderate or marked</td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
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<td></td>
<td></td>
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<td>Focal T2 lesions</td>
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<td>Never</td>
</tr>
<tr>
<td>Diffuse abnormalities</td>
<td>Seldom</td>
<td>Variable</td>
<td>Frequent</td>
</tr>
<tr>
<td>Spinal cord atrophy</td>
<td>Mild</td>
<td>Marked</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

that only a weak correlation exists between conventional MR measures and disability. This is likely due to the poor pathological specificity of conventional MRI measures. At present, the approaches adopted for the use of conventional MRI to monitor clinical trials in PPMS have mirrored those used in trials in RRMS and SPMS (50). Further natural history studies, particularly when performed over extended periods, are likely to be helpful when interpreting treatment effects.

Although the extent of visible MR abnormality is usually lower in PPMS than other subtypes, an entirely normal conventional MR appearance is unusual, occurring in fewer than 5 percent of cases (23). This is acknowledged in recently published diagnostic criteria for PPMS (26). A diagnosis of definite PPMS, according to this consensus statement, requires the presence of nine brain lesions or two spinal lesions or four to eight brain lesions and one spinal lesion.

Administration of Gd-DTPA at either a single or triple dose is an important adjunct to conventional MR techniques. Lower levels of lesion enhancement in PPMS have been shown in several studies, but it is currently less clear whether this is also true for the earliest stages of the condition. Preliminary analysis of a cohort of patients with PPMS and short disease duration has shown a
higher-than-expected frequency of enhancing lesions. The finding of subtle quantitative signal alterations after gadolinium injection suggests that low-grade BBB leakage may exist in visibly nonenhancing PPMS; it is not clear whether this is pathologically significant.

The newer MR techniques, such as MTR, DWI, MRS, are functional MRI, have shown that there are widespread abnormalities in normal-appearing tissues in PPMS. Some measures derived from these techniques have been shown to correlate, albeit modestly, with clinical measures.

In summary, although newer MR techniques offer the possibility of greater pathological specificity, conventional MR measures seem likely to retain an important place in the assessment of patients with PPMS, both for diagnosis and for the monitoring of treatment. An important challenge for newer techniques is to clarify the underlying pathological processes that lead to progressive disability in the condition.

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