**Case Study**

**Introduction:**

There are two main types of tissue found within the human brain: white matter and grey matter (See Appendix One). White matter can be affected by a number of diseases, including multiple sclerosis (MS) (Lassmann et al, 2007). The intention of this report is to present a fictitious case study which examines the diagnoses and treatment of MS disease.

**Background:**

This case study focuses on a 35-year-old female who had been suffering from headaches, blurred vision and muscle weakness. Investigation into her family history revealed no similar symptoms. The patient made the decision to organise an appointment with her doctor. After asking her how she felt, the doctor supposed that the symptoms were signs of multiple sclerosis disease and referred her to a specialist for further diagnostic tests and imaging.

**Multiple sclerosis disease:**

**Aetiology:**

MS is thought to be due to an autoimmune process; however, its exact origin is not fully comprehended and is probably caused by a multitude of factors (Cosh & Carslaw, 2014). The majority of professionals in the field agree that MS is likely due to a blend of genetic and environmental factors (Cosh & Carslaw, 2014). Evidence for the genetic component is that a fifth of all patients with MS will have a family member who also has the disease, while environmental factors, such as diet or chemical exposure, may also pose a risk in causing the development of MS (Cosh & Carslaw, 2014).

Though a large number of symptoms exist, some of the most common include extreme tiredness, pain, sensory disturbance with numbness, issues with mobility and balance, visual disturbance, muscle weakness and sexual dysfunction (Cosh & Carslaw, 2014).

In 2014, according to NICE, there were an estimated 100,000 people in the United Kingdom who suffer with MS. It has been reported that in the 20–40 age group, MS is three times as likely to occur in women as in men (Parizel et al, 2010).

Many risk factors have been identified in the development of MS. In 2014, NICE mentioned the possibility of the involvement of a virus. Other reasons include smoking and low exposure to sunlight, which gives rise to a Vitamin D deficiency.

**Diagnosis:**

As reported by Cosh and Carslaw, MS is a clinically diagnosed disease; however, it is problematic because no single laboratory test can categorically diagnose it (2014). As a result, paraclinical tests that form part of the diagnostic criteria include MRI, cerebrospinal fluid (CSF) analysis and evoked potentials (Cosh & Carslaw, 2014). These investigations are at the behest of specialist evaluation teams for the diagnosis of MS (Cosh & Carslaw, 2014). In lieu of a comprehensive explanation, the diagnosis is based on the dissemination in time and space of a disease that is adaptable with central nervous system demyelination. In 2010, Parizel et al also showed that the presence of MS lesions show demyelinating lesions in the brain and spinal cord. The diagnosis of MS is clinical, and MRI results may contribute to the determination of dissemination in time and space (Sahraian & Eshaghi, 2010).

Early stage assessment of a patient who may have MS begins with the use of MRI, as the technique is extremely sensitive in revealing abnormalities in white matter and clinically silent lesions (Sahraian & Eshaghi, 2010). Software used in modern MRI scanners allows the simultaneous positioning of slices on three image planes:

1. Sagittal: the left–right sides of the brain.

2. Axial: the superior–inferior portions of the brain.

3. Coronal: the posterior–anterior areas of the brain (Parizel et al, 2010) (See Appendix Two).

The use of conventional MRI has become an important tool in evaluating patients suspected of having MS over the past 15 years (Filippi & Rocca, 2011, 2007). Typical MRI protocols for the diagnosis of MS using conventional MRI techniques include the use of T1/T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequences. More modern MRI techniques, such as diffusion tensor, magnetisation transfer, MR Spectroscopy and functional MRI, have altered our comprehension about the fundamental mechanisms and pathophysiology of the disease (Filippi & Rocca, 2011, 2007).

Firstly, to detect demyelinating lesions in white matter, the MRI sequence should be optimised and provide the following: (1) high contrast between lesions and cerebrospinal fluid (CSF); (2) high contrast between lesions and normal white matter (Parizel et al, 2010). T2-weighted images are ideal as they are highly sensitive in detecting MS lesions, as reported by (Sahraian & Eshaghi, 2010) T2-weighted images are particularly useful in evaluating periventricular lesions, something associated with multiple sclerosis, because the hyperintense lesions are contrasted against the CSF (Brown & Semelka, 2011). The axial plane is often used because it reveals more information about the anatomy (Brown & Semelka, 2011). Although MS lesions are not always typical, they are often small, round or oval in shape (Sahraian & Eshaghi, 2010). Despite these advantages, in 1997 it was reported by Gawne-Cain et al, that T2-weighted images do have a number of limitations such as a lack of specificity to the heterogeneous pathologic substrates of MS lesions, and an inability to detect subtle abnormalities in the normal appearing white matter (NAWM) (Gawne-Cain et al, 1997).

Secondly, Fluid-attenuated inversion recovery (FLAIR) imaging has been used in the last few years and shows quick brain imaging acquisition sequences that produce heavily T2-weighted images with signal suppression from CSF (Sahraian & Eshaghi, 2010; Parizel et al, 2010; Filippi & Rocca, 2007). It does this by utilising an inversion time that commonly ranges from 1800 to 2500 ms (Parizel et al, 2010; Sahraian & Eshaghi, 2010). For MS studies, the primary advantages of FLAIR are that it detects more MS lesions, especially in changes in the white matter (WM), and that it shows higher reproducibility for the quantitative assessment of brain lesion volumes (Filippi & Rocca, 2007). However, a disadvantage of FLAIR images are a lower sensitivity in the depiction of plaques that involve the brainstem and cerebellum, meaning that lesion load may be underestimated in the posterior fossa (Parizel et al, 2010).

Thirdly, for the diagnosis of MS, T1-weighted imaging (without the addition of a gadolinium-based contrast agent) provides important information. Despite this, there is a low level of specificity for heterogeneous pathologic substrates of individual lesions, especially oedema, inflammation, demyelination and gliosis (Filippi & Rocca, 2011). As a result, the addition of a gadolinium-based contrast agent allows T1-weighted images to discern between active and inactive lesions.

This is because of an increased blood brain barrier permeability which is related to the areas of persistent inflammation (Sbardella & Tomassini, 2014; Filippi & Rocca, 2011) (See Appendix Three).

In conclusion, the use of conventional MRI (T2-weighted, pre- and post-contrast T1-weighted scans) has had a remarkable effect by enabling earlier diagnosis of MS. It has provided markers which show the response to current treatments and nascent experimental agents. Although it is prominent in scientific analysis and clinical management of MS has increased, conventional MRI shows low pathological specificity and low sensitivity to diffuse damage in normal-appearing white matter (NAWM) and grey matter (NAGM), and it has only limited associations with clinical status (Inglese & Bester, 2010).

The limits of conventional MRI have been addressed by advanced MRI methods which are able to improve the ability to evaluate, observe and define the pathophysiology of the disease (Inglese & Bester, 2010; Bakshi, 2008). Diffusion-weighted imaging (DWI) is an inherent physical process that is completely independent of the MRI effect or the magnetic field (Le Bihan et al, 2001). The technique utilises the random motion of water molecules in tissues. It allows for this molecular movement in tissue matter to be measured quantitatively.

In diseases of the central nervous system (CNS), cell structures become damaged or impaired due to the pathological process. DWI may be able to provide some insight into the nature and severity of pathological damage that occurs in these diseases (Bakshi, 2008). This requires the provision of markers that are related to the underlying pathologic substrates and that are more sensitive to the full range of ‘occult’ brain tissue damage in MS patients (Inglese & Bester, 2010) (Seen Appendix Four).

Another technique which uses DWI is diffusion tensor imaging (DTI). DTI is able to delineate the axonal organisation of the brain, which is useful for highly ordered cell structures, such as in the axonal ‘fibres’ within white matter. This would not be possible with conventional MRI (Horsfield & Jones, 2002; Mori & Zhang, 2006).

**Magnetisation transfer imaging (MTI):**

For large molecules such as myelin, MTI provides an enhanced pathologic specificity. It quantifies MT effects by calculating the magnetisation transfer ratio (MTR), which gives a distinctive imaging marker for myelin disorders. Under normal circumstances, white matter has a larger MTR than grey matter due to the greater amount of myelin. A reduction in MTR is an indicator of pathologic and/or structural tissue damage. As a result, MS lesions usually have a lower MTR compared with ischemic lesions in small-vessel diseases. The main advantages of MTI may be its increased specificity in terms of MR imaging and a more accurate assessment of the degree of demyelination or residual myelination of MS lesions (Ge, 2006).

**MR Spectroscopy:**

The natural history of MS and its pathogenesis have been re-examined as a result of the use of MRI. A large part of this has been due to the results shown in studies involving proton magnetic resonance spectroscopy (1H-MRS). The use of MRS has shown the importance of assessing myelin damage and repair. Analyses using MRS have shown the possibility of providing an up-to-date and essential understanding of the pathogenesis and natural history of MS. However, the data provided by this technique are not used routinely in examining MS patients, despite the high pathological specificity of MRS and the comparatively large number of clinical studies on MS. This is because of the technical issues and limitations which are currently not resolved (De Stefano & Filippi, 2007).

**Functional MRI:**

Functional magnetic resonance imaging (fMRI) is a technique which is largely used to study the functioning mechanisms of the CNS and which is able to highlight irregular brain activation patterns that occur as a result of the disease (Rocca & Filippi, 2007).

The technique is used to investigate both normal and abnormal brain function. Specifically, fMRI examines localised alterations in blood flow to denote increased neuronal activity in different areas of the brain in reaction to different stimuli, such as motor, visual, sensory, cognitive or auditory signals. It has been reported that the technique can be used to examine cortical activation in people with MS (Bakshi, 2008; Rocca & Filippi, 2007) (See Appendix Five).

**High-Field MR Imaging and MS:**

The quality of an image is related to the strength of the magnet. Filippi and Rocca (2007) stated that a field strength of 3T or higher would show great potential in clinical practice. An evident advantage of imaging at a high field strength is the greater signal-intensity-to-noise ratio (SNR). A higher value SNR permits thinner sections and higher-resolution matrices, parameters which can advance the detection of lesions (Ge, 2006). It was reported by both Ge (2006) and Filippi and Rocca (2007) that the number of detected lesions can be 45% greater for a 4T magnet compared to a 1.5T magnet. High field strength provides both greater resolution and contrast and can detect cortical lesions, which are often not visible at lower field strengths. For patients who are clinically suspected of having MS, these advancements may allow for an earlier diagnosis of MS (Ge, 2006; Filippi & Rocca, 2007).

In summary, the primary advantage of MRI is in the scanning and detection of irregularities in soft organs such as the brain, as well as its benign nature, allowing it to be used in people who are at potential risk to the effects of radiation, such as pregnant women or babies. The main disadvantage of an MRI scan is that it is performed in an enclosed space, so it could adversely affect people who suffer from claustrophobia. Another important consideration is that MRI scanners are usually expensive and not widely available.

**Prognosis:**

The National Institute for Health and Care Excellence (NICE, 2014) categorises MS according to the course of the disease. Of all MS sufferers, about 85% undergo a relapsing-remitting (RR) clinical course, which is defined by a regular onset of symptoms followed by lasting problems, or they undergo a full recovery, particularly in the early stages of the disease. In a 25-year period, most untreated RRMS patients evolve into a secondary progressive (SP) phase with a chronic and steady decline. A fifth of RRMS patients stay clinically stable for 20 years and are categorised as having benign MS (BMS). Lastly, 10%–15% of MS patients will undergo a primary progressive (PP) course at the onset of the disease, with an absence of relapses (Inglese & Bester, 2010; Tsang & Macdonell, 2011).

**Treatment:**

Despite there being no current cure for MS, the long-term outcome of patients can be improved due to the constructive actions of healthcare workers and the use of positive treatment options. These include attempting to suppress disease progression, making the correct diagnosis, and helping patients have fewer symptoms and functional problems as possible. The main aim in MS therapy, therefore, is to reduce the incidences of relapse and to improve and maintain patients’ long-term health. Without this, the majority of patients would deteriorate over time (Hedley, 2012; Pandit, 2013).

**Case:**

The patient in this study showed that she was suffering from headaches, blurred vision, muscle weakness and issues with balance. These issues led the patient to see her GP.

Before referral to a neurologist, a number of steps had to be taken to provide an MS diagnosis. It is not routine to think that a patient has MS if the main symptoms are fatigue, depression or dizziness, unless they have a family history or evidence of focal neurological symptoms. People with MS commonly show symptoms as stated above and are often under the age of 50 (NICE, 2014). Therefore, the first step in excluding another diagnosis is to perform blood tests; these include a full blood count and tests for liver function, renal function, calcium and vitamin B12. The second step is then to refer the patient to a consultant neurologist and have them speak about the symptoms and pain. The third step is to make a diagnosis. A consultant neurologist should make the diagnosis of MS based on reputable and up-to-date information, as outlined in the [revised 2010 McDonald criteria](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084507/), after:

* Excluding of alternative diagnoses.
* Establishing (for a diagnosis of relapsing–remitting MS) that lesions have advanced at different times and are in different parts of the anatomy.
* Establishing (for a diagnosis of primary progressive MS) a status of progressive neurological deterioration over one or more years.

In the McDonald Criteria for the diagnosis of MS, the employment of imaging for showing the dissemination of CNS lesions in space and time has been simplified to the point that dissemination can be demonstrated by a single scan in some circumstances. Part of the criteria for diagnosing multiple sclerosis (MS) and excluding other diagnoses is to use clinical and paraclinical laboratory assessments which stress the need to show the dissemination of lesions in space (DIS) and time (DIT). A diagnosis can be made with just a clinical assessment, but MRI of the CNS can supplement or even replace some clinical criteria. This was recently highlighted by the International Panel on Diagnosis of MS, which mentioned the important role of the McDonald Criteria. This set of standards has resulted in earlier diagnoses of MS with a greater amount of specificity and sensitivity. In 2011, Polman et al reported that these standards had enabled enhanced counselling of patients and allowed for the provision of earlier treatment.

As part of the diagnosis process, the consultant neurologist should offer the patient, with agreement by the patient and family members, both verbal and written information. This should explain any possible treatments, including disease-modifying therapies, what MS actually is, and how to manage symptoms. Part of the discussion with the family should also address whether the patient has social care needs; if this is the case, then referral to social services for assessment should be carried out. After the diagnosis is established, the patient should have a follow-up appointment within six weeks with a professional who has expertise in MS. A final provision for post-diagnosis is to provide information and support about MS management. MS patients and their family members should be provided with a management plan that includes a contact point should the symptoms alter drastically. An explanation should be offered as to the possible causes of symptom changes, such as an infection. Lifestyle advice should be offered, and regular exercise should be emphasised, as this will not adversely affect the condition and may have beneficial effects. This follows a protocol written by NICE in 2014 (See Appendix Six).

**Conclusion:**

To conclude this case study, after the diagnosis was made, the doctor stated that the patient had early-stage MS, which was relapsing-remitting MS (PRMS). The doctor advised regular exercises to avoid stress and to have a follow-up appointment within six weeks.

**References:**

Bakshi, R. 2008, MRI in multiple sclerosis: Current status and future prospects, *Lancet Neurol,* 7, (7), 615–625.

Brown, M.A. & Semelka, R.C. 2011, *MRI: Basic principles and applications,* John Wiley & Sons.

Butler, P., Mitchell, A.W.M. & Healy, J.C. 2012, *Applied radiological anatomy*,ed. P. Butler, A. Mitchell & J. C. Healy,Cambridge University Press.

Catani, M. & de Schotten, M.T. 2012, *Atlas of human brain connections*,Oxford University Press.

Cosh, A. & Carslaw, H. 2014, Multiple sclerosis: Symptoms and diagnosis, *InnovAiT,* 7(11), 651–657.

De Stefano, N. & Filippi, M. 2007, MR spectroscopy in multiple sclerosis, *Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging*,17(1), 31S–35S.

Filippi, M. & Rocca, M.A. 2011, MR imaging of multiple sclerosis, *Radiology,* 259(3), 659–681.

Filippi, M. & Rocca, M.A. 2007, Conventional MRI in multiple sclerosis, *Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging*,17(1), 3S–9S.

Gawne-Cain, M.L., O'Riordan, J.I., Thompson, A.J., Moseley, I.F. & Miller, D.H. 1997, Multiple sclerosis lesion detection in the brain: A comparison of fast fluid-attenuated inversion recovery and conventional T2-weighted dual spin echo, *Neurology*,49(2), 364–370.

Ge, Y. 2006, Multiple sclerosis: The role of MR imaging, *American Journal of Neuroradiology*,27(6), 1165.

Hedley, L. 2012, Multiple sclerosis treatment options, *Pharmaceutical Journal*,288(7694), 247.

Horsfield, M.A. & Jones, D.K. 2002, Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases - a review, *NMR in Biomedicine*,15,(7–8), 570–577.

Inglese, M. & Bester, M. 2010, Diffusion imaging in multiple sclerosis: Research and clinical implications, *NMR in Biomedicine*,23(7), 865–872.

Lassmann, H., Brück, W. & Lucchinetti, C.F. 2007, The immunopathology of multiple sclerosis: An overview, *Brain Pathology*,17(2), 210–218.

Le Bihan, D., Mangin, J., Poupon, C., Clark, C.A., Pappata, S., Molko, N., et al, 2001, Diffusion tensor imaging: Concepts and applications, *Journal of Magnetic Resonance Imaging*,13(4), 534–546.

Mori, S. & Zhang, J. 2006, Principles of diffusion tensor imaging and its applications to basic neuroscience research, *Neuron*,51(5), 527–539.

Moritani, T., Ekholm, S. & Westesson, P. 2005, Diffusion-weighted MR imaging of the brain.

NICE, 2014. NICE. [online]. Available from: https://www.nice.org.uk/guidance/cg186/chapter/introduction [Accessed 23 November. 2014].

NICE pathways, 2014. [online]. Available from: http://pathways.nice.org.uk/pathways/multiple-sclerosis#path=view%3A/pathways/multiple-sclerosis/diagnosing-multiple-sclerosis.xml&content=view-index [Accessed 5 Dec. 2014].

Pandit, L. 2013, Multiple sclerosis: Treatment options, *Progress in Clinical Neurosciences*,62.

Parizel, P.M., van den Hauwe, L., De Belder, F., Van Goethem, J., Venstermans, C., Salgado, R., Voormolen, M. & Van Hecke, W. 2010, "Magnetic resonance imaging of the brain." in: *Clinical MR imaging*, Springer, pp. 107–195.

Polman, C.H., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., et al, 2011, Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria, *Annals of Neurology*,69(2), 292–-302.

Rocca, M.A. & Filippi, M. 2007, Functional MRI in multiple sclerosis, *Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging*,17(1), 36S–41S.

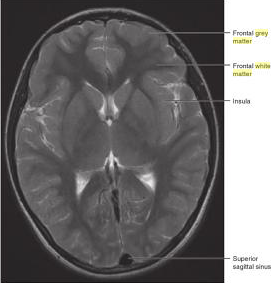
Sahraian, M.A. & Eshaghi, A. 2010, Role of MRI in diagnosis and treatment of multiple sclerosis, *Clinical Neurology and Neurosurgery*,112(7), 609–615.

Sbardella, E. & Tomassini, V. 2014, Applications of conventional MRI in multiple sclerosis: Highlights from the latest articles, *Future Neurology*,9(3), 261.

Tsang, B.K. & Macdonell, R. 2011, Multiple sclerosis – diagnosis, management and prognosis, *Australian Family Physician*, 40(12), 948–955.

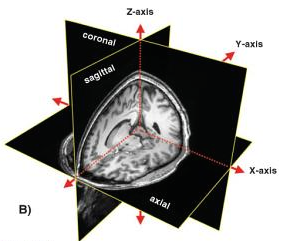
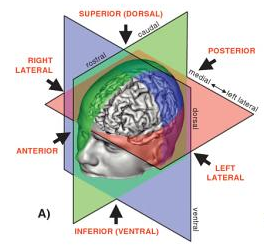
**Appendix One:**

MRI Image for white matter and grey matter. Adapted from Butler et al (2012).

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**Appendix Two:**

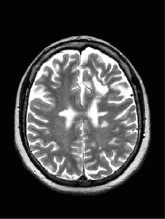
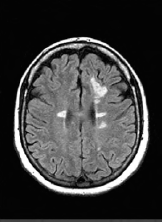
Brain planes. Adapted from Catani and de Schotten (2012).

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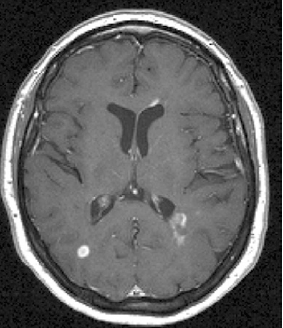
Brain orientation in A: surface B: sectional

**Appendix Three:**

MRI images with different sequences of a patient with RRMS demonstrating multiple hyperintense lesions. Adapted from Sahraian and Eshaghi (2010) and Filippi and Rocca, (2011).

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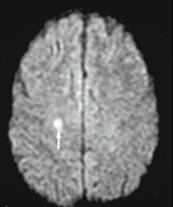
Axial, T2-weighted Axial, FLAIR images



T1-weighted with gadolinium-enhanced

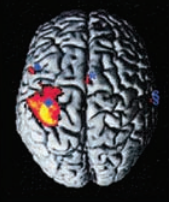
**Appendix Four:**

Diffusion Image. Adapted from Moritani et al (2005).

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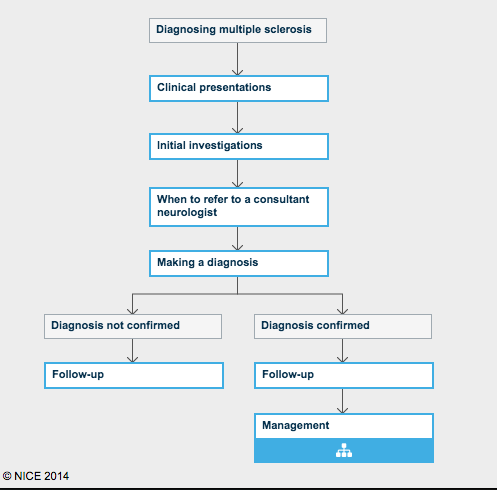
**Appendix Five:**

Functional MRI. Adapted from Rocca and Filippi (2007).



**Appendix Six:**

Diagnosing multiple sclerosis. Adapted from NICE (2014).

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