Medical Services

Multiple Sclerosis

Version 1 Final

Document control

Version history

Version	Date	Comments
1 Final	19 March 2007	Signed off by MSCMT
1e (draft)	1 March 2007	Comments
1d (draft)	22 January 2007	Formatting
1c (draft)	4 December 2006	External review by Dr A Jackson
1b (draft)	17 November 2006	Internal QA by Dr A Ferguson, Dr C Traquair and Dr G Buchanan
1a (draft)		Initial Draft

Changes since last version

Introduction

Definition

Multiple Sclerosis is a chronic inflammatory disease of the central nervous system characterised by plaques of demyelination at sites throughout the CNS. Diagnosis is clinical, and requires evidence of lesions that are separated in time and space, and the exclusion of other inflammatory, structural or hereditary conditions that might give a similar clinical picture.
The disease takes three main forms: -

Relapsing and remitting - characterised by episodes of neurological dysfunction interspersed with periods of stability.

Primary Progressive - in which progressive neurological disability occurs from the outset.

Secondary Progressive - in which progressive neurological disability occurs in the later stages of the disease. [1]

In 90% of people, early disease is relapsing/ remitting. Most develop secondary progressive disease, usually 6-10 years after onset. In 10% the disease is progressive from the outset however, as detailed later, the rate of progression appears similar and functional loss at any specific age is a factor of years with disease rather than actual age. [8] In the majority of patients life expectancy is not greatly affected.

Aetiology and Incidence

The cause is unknown but an immunological abnormality is suspected. One postulated cause is infection by a latent virus (possibly by a human herpes virus or retrovirus) in which virus activation and expression trigger a secondary immune response. An increased familial incidence and association with certain HLA allotypes suggest genetic susceptibility.

Environment may be a factor. MS is more common in temperate climates (1/2000) than in the tropics (1/10,000). It has been linked to the geographical area where the individual spent their first 15 years. Relocation after age 15 years does not alter the risk. In Europe and North America MS is the most common cause of neurological disability in young adults.

Age of onset is broad peaking between 20 and 40 years. [2]

Diagnosis

Symptoms and Signs

Physical

The disease is characterised by various symptoms and signs of CNS dysfunction, with remissions and recurring exacerbations. First presentations are usually monosymptomatic. The most common early presenting symptoms are :-

- Parasthesiae in one or more extremities, in the trunk, or on one side of the face.
- weakness or clumsiness of a leg or hand
- visual disturbances, e.g., partial blindness and pain in one eye (retrobulbar optic neuritis), dimness of vision, or scotomas.

Other early symptoms are:

- ocular palsy resulting in double vision (diplopia)
- transient weakness of one or more extremities
- slight stiffness or unusual fatiguability of a limb
- minor gait disturbances
- difficulty with bladder control
- vertigo
- mild emotional disturbances

These symptoms indicate scattered C.N.S. involvement and often occur months or years before the disease is recognized. Excess heat (e.g., warm weather, a hot bath, and a fever) may accentuate symptoms and signs.

Mental

- Apathy, lack of judgment, or inattention may occur.
- Other cognitive difficulties may manifest with problems in the ability to pay attention, learn and remember information, solve problems, and use language to express ideas. It is now estimated that 50% of people may have some degree of cognitive impairment rising to 80% if the most severe cases are included.
- Emotional lability is common and may suggest an incorrect initial impression of hysteria. Euphoria occurs in some patients.

- Reactive depression.
- Sudden weeping or forced laughter (concomitants of pseudobulbar palsy) indicates that corticobulbar pathways of emotional control are affected.
- Convulsive seizures seldom occur.
- Severe changes (e.g., mania or dementia) can occur late in the disease.
- Scanning speech (slow enunciation with a tendency to hesitate at the beginning of a word or syllable) is common in advanced disease and often associated with cerebellar involvement.
- Aphasia is rare.

Cranial Nerves

Optic neuritis is a broad term expressing inflammation, degeneration, or demyelination of the optic nerve. It includes:

- papillitis or anterior optic neuritis - the intraocular portion of the nerve is affected, and the optic disc is swollen
- retrobulbar neuritis - optic neuritis in which the disc is not swollen
- neuroretinitis - optic disc and adjacent temporal retina are affected

The majority of patients under the age of 45 years recover normal visual acuity within 2 months. Older patients recover less well and there may be evidence of optic atrophy. .Patients with MS may have recurrent episodes of optic neuritis. With each subsequent episode there is less recovery and there will be a degree of long term visual impairment.

Optic atrophy with temporal pallor can be seen on fundoscopy, and is associated with optic neuritis.

Internuclear ophthalmoplegia – this is weakness or paralysis of eye movements caused by damage to nerve fibres that give rise to cranial nerves III, IV and VI, which results in painless visual disturbance and diplopia on lateral gaze. There is nystagmus in the abducting eye.

Nystagmus is a common finding and may be due to cerebellar or vestibular nucleus damage.

Other evidence of cranial nerve involvement is uncommon, and when present, is usually due to brain stem injury in the area of the cranial nerve nuclei.
Deafness is rare, but vertigo is not.

Unilateral facial numbness or pain (resembling trigeminal neuralgia) occurs occasionally, as does hemifacial palsy or spasm.

Motor nerves

- Deep reflexes (e.g., knee and ankle jerks) are generally increased.
- Babinski's sign (upgoing plantar response) and clonus (sustained muscle contraction) may be present.
- Often, the patient complains of unilateral symptoms, but examination elicits signs of bilateral corticospinal tract involvement.
- Intention tremor due to cerebellar lesions is common, and continued purposeful effort accentuates it. The motion is ataxic, shaky, irregular, tremulous, and ineffective.
- Static tremor may occur. It is especially obvious when the head is unsupported.
- Muscular weakness and spasticity from corticospinal damage produce a stiff, imbalanced gait. Later, a combination of spasticity and cerebellar ataxia may become totally disabling. Cerebral lesions may result in hemiplegia, sometimes the presenting symptom.
- Painful flexor spasms in response to sensory stimuli (e.g., bedclothes) may occur in late stages.
- One pattern of disease includes acute optic neuritis, sometimes bilateral, with demyelination of the cervical or thoracic spinal cord (optic neuromyelitis), producing visual loss and paraparesis.
- Charcot's triad (nystagmus, intention tremor, and scanning speech) is a common cerebellar manifestation in advanced disease.
- Mild dysarthria may result from cerebellar damage, disturbance of cortical control, or injury to the bulbar nuclei.

Sensory nerves

- Complete loss of any form of cutaneous sensation is rare
- Parasthesiae, numbness, and blunting of sensation (e.g., reduced pain or temperature sense, disturbances of vibratory or position sense) may occur and are often localized, e.g., to the hands or legs. Objective changes are fleeting and are often elicited only with thorough testing. A range of painful sensory disturbances (e.g., burning, electrical, or paroxysmal pain) can occur, especially with spinal cord demyelination.

Autonomic nerves

Urinary urgency or hesitancy, partial retention of urine, or slight incontinence and constipation are common when the spinal cord is affected, as are erectile dysfunction in men and genital anaesthesia in women.

Urinary and faecal incontinence may occur in advanced disease.

Differential Diagnoses

The following is a list of conditions that may share some overlap with multiple sclerosis:

AIDS.

Amytrophic lateral sclerosis
A rare fatal progressive degenerative disease that affects pyramidal motor neurons, usually begins in middle age, and is characterized especially by increasing and spreading muscular weakness. (also known as Lou Gehrig's disease.)

Abnormalities of the spine or skull base.

Arthritis of the cervical spine.

Basilar Invagination (upward bulging of the occipital condyles)

CNS tumours, abscess or other mass lesions.

Guillain-Barre syndrome
A polyneuritis of unknown cause characterized especially by muscle weakness and paralysis.

Hereditary ataxias
Any of a group of inherited neurodegenerative disorders that are characterized by cerebellar dysfunction manifested especially by progressive ataxia.

Lyme disease

Pernicious Anaemia

Ruptured intervertebral disc

Small cerebral infarctions

Tertiary Syphilis

Syringomyelia
A chronic progressive disease of the spinal cord associated with sensory disturbances, muscle atrophy, and spasticity.

Systemic Lupus Erythematosus
An inflammatory connective tissue disease of unknown cause that can involve the CNS.

Transverse Myelitis
Inflammation of the spinal cord or of the bone marrow.

Vascular malformations of the brain or spinal cord

Investigations

No single investigation can reliably diagnose MS – diagnosis is a combination of clinical symptoms and signs supported by laboratory testing and brain imaging. Typical cases can usually be diagnosed confidently on clinical grounds. The diagnosis can be suspected after a first attack, especially in a young patient with sensory, motor or visual disturbance. Later, a history of remissions and exacerbations and clinical evidence of C.N.S. lesions disseminated in more than one area are highly suggestive. Other possibilities must be considered.

Magnetic Resonance Imaging (MRI), the most sensitive diagnostic imaging technique, may show plaques. It may also detect treatable non-demyelinating lesions at the junction of the spinal cord and medulla (e.g., subarachnoid cyst, foramen magnum tumours) that occasionally cause a variable and fluctuating spectrum of motor and sensory symptoms, mimicking MS. Gadolinium-contrast enhancement can distinguish areas of active inflammation from older brain plaques.

MS lesions may also be visible on contrast-enhanced CT scans; sensitivity may be increased by giving twice the iodine dose and delaying scanning (double-dose delayed CT scan).

CSF is abnormal in the majority of patients. IgG may be > 13%, and lymphocytes and protein content may be increased, but these findings are not pathognomonic.
Oligoclonal bands, which indicate IgG synthesis within the blood-brain barrier, may be detected by agarose electrophoresis of CSF in up to 90% of patients with MS, but absence of these bands does not rule out MS.

IgG levels correlate with disease severity.

Myelin basic protein may be elevated during active demyelination.

Evoked potentials are recorded electrical responses to stimulation of a sensory system. Pattern-shift visual, brain stem auditory, and somatosensory evoked potentials may be abnormally delayed early in the disease, because demyelination slows the conduction of electrical impulses in these sensory pathways.

Treatment

Pharmacological

Spontaneous remissions and fluctuating symptoms make treatments difficult to evaluate.

Corticosteroids (oral prednisolone 60mg to 100 mg/day tapered over 2 to 3 weeks or intravenous methylprednisolone 500mg to 1000 mg/day for 3 to 5 days) are the main form of therapy. They may shorten the symptomatic period during attacks, although they may not affect eventual long-term disability.

In patients presenting with acute severe optic neuritis the onset of MS may be delayed by using high-dose intravenous corticosteroids.

Long-term corticosteroid treatment is rarely justified and can cause numerous medical complications including osteoporosis, ulcers, and diabetes.

Alternatively, ACTH 40 u to 80 u/day intramuscularly for 5 days tapered over 2 to 3 weeks can be used but has been largely replaced by corticosteroid use.

Immunomodulatory therapy with Interferon-β reduces the frequency of relapses in relapsing remitting MS and may help delay eventual disability.

Glatiramer acetate may have similar benefits for early, mild MS.

Intravenous Gamma Globulins given monthly may help control relapsing MS refractory to conventional therapies.

Immunosuppressive drugs (Methotrexate, Azathioprine, Cyclophosphamide, Cladribine) for more severe progressive forms are not uniformly beneficial and have significant toxic risks.

Drugs for spasticity such as Baclofen and Tizanidine can be initiated at a low dosage and gradually increased until the patient responds.

Non Pharmacological

In debilitated patients prevention of bed sores and urinary tract infections is essential. The need for self catheterisation has to be carefully evaluated.

Studies have shown that the prevalence of depressive symptoms in a population based sample of people with M.S. is high. Given the serious nature of depression and its association with worse self reported functioning and weak sense of coherence, attention to, and treatment of mental health problems and depression are strongly indicated in the clinical management of Multiple Sclerosis. [3]

Multidisciplinary Rehabilitation.

Rehabilitation in MS is often driven by need rather than by the underlying severity of the disease. Persons with MS are often young and diagnosed usually in the third decade of their life. They have greater potential for neurospasticity and a longer survival time over which to maximise functional and financial independence than the brain injured population in general. Despite better education and advances in disease modifying drugs, persons with MS are unemployed at a rate of 70%-80% five years after diagnosis. This has adverse consequences for the individual and society.

MS has a fluctuating nature (unlike stroke or spinal cord injury) and is a dynamic process (as in relapsing/remitting form of MS). Rehabilitation is therefore an ongoing effort not limited to a finite time, and requires more frequent visits to health professionals compared with other neurological conditions. These persons may require different programs of rehabilitation at different stages of their illness.

As MS is progressive, rehabilitation professionals should anticipate future needs, services and equipment rather than when the situation reaches crisis point. In accordance with guidelines, multidisciplinary rehabilitation services and programs have been developed to serve the needs of the younger 'working age' adults with MS. These are individualized programs and encompass all aspects of care including personal, social and physical.

As the impact of MS extends to many aspects of a person’s life, an individualized, multidisciplinary approach is essential and often in-patient rehabilitation is the most appropriate setting to treat complex needs of these patients. Intensive in-patient rehabilitation has been advocated to improve patient function (mobility, transfer skills, gait).

Community and home based programs have broad outcomes that aim to reduce impairment and disability, facilitate social reintegration and return to work with financial independence, improved participation and psychosocial adjustments.

Persons with MS can present to rehabilitation services with various combinations of deficits, such as physical, cognitive, psychosocial, behavioural and environmental problems.

These include impairments (strength, coordination, balance, spasticity, memory, urinary urgency), which result in disability or functional limitation (mobility, self care, incontinence, pain, cognitive deficits) and limitation in performing their role in society (participation), in accordance with the international classification of functioning, disability and health (ICF) endorsed by the World Health Organization in 2001.

Therefore issues of progressive physical disability, psychosocial adjustment, social reintegration, financial strain and impact on driving, work and family occur over time.

Systematic reviews show that multidisciplinary rehabilitation is effective in stroke and traumatic brain injury populations, but the evidence base for the effectiveness of multidisciplinary rehabilitation in patients with multiple sclerosis (MS) is not yet

established. [4] [5]

A recent meta-analysis on the effectiveness of physical, functional and psychological interventions in MS suggests that occupational therapy (OT) was beneficial in treating deficits from MS. These findings may be biased as the final analysis included pre-experimental design with no control group.

Further, another systematic review could make no recommendations on the efficacy of individual OT interventions on functional ability, social participation and quality of life in MS, due to lack of randomized controlled trials.

More recently a systematic review reported the effectiveness of exercise therapy (alone), in terms of activities of daily living (ADLs) and positive outcomes related to mood, anxiety and depression in MS. There was however no evidence that specific exercise therapy programmes were more successful in improving ADLs than any other exercise treatments. [4][6][7]

Prognosis

The most commonly used scale to measure degrees of disability in patients with MS is the Expanded Disability Status Scale of Kurtze (EDSS) [Appendix 1]. This scale ranges from 0, equivalent to no disability, and rises in increments of 0.5 to 10, indicative of death from MS.

Studies indicate that the rate of progress through these disability milestones is time related.

It was shown that median ages at time of assignment of irreversible disability were 44.3 years for a score of EDDS 4, 54.7 years for EDDS 6 and 63.1 years for EDDS 7. [8]

These results were essentially similar whether the initial course of Multiple Sclerosis was exacerbating-remitting or progressive, and whatever the initial symptomatology. Females reached disability milestones at an older age than males.

The most influential clinical factor was age at clinical onset of multiple sclerosis: the younger the onset, the younger the age at assignment of disability milestones and vice versa. Therefore, prognosis in Multiple Sclerosis appears, at least to some extent, as duration dependent and not substantially affected by the initial course, be it exacerbating-remitting or progressive.

Aside of acute focal recurrent inflammation and diffuse chronic neurodegeneration, accelerated ageing-related mechanisms may operate in the central nervous system of multiple sclerosis patients [9]

There is convincing evidence that neurological relapses in Multiple Sclerosis (MS) are the clinical counterpart of acute focal inflammation of the central nervous system (CNS) whereas neurological progression is that of chronic diffuse neurodegeneration.

The classical view is to consider that MS is an organ-specific autoimmune disease, i.e. that inflammation is the cause of the neurodegeneration. The succession of relapses eventually leads to accumulation of disability and clinical progression results from subclinical relapses. A series of recent observations tends to challenge this classical concept.

Important observations have come from the study of the natural history of MS. In the Lyon MS cohort, [10] accumulation of irreversible disability appeared not to be affected by clinically detectable neurological relapses. This has also been shown to be "amnesic" for the early clinical characteristics of the disease, and essentially age-dependent.

Suppressing relapses by disease-modifying agents does not dramatically influence the progression of irreversible disability. Beta Interferon reduces the relapse rate by 30% and conventional MRI activity by more than 50%. In spite of this effect on inflammation, the effect on disability is only marginal and possibly relapse-reduction-dependent.

Administration of Campath-1h (Alemtuzumab) to patients with very active disease in terms of frequency of relapses, accumulation of disability and MRI activity, results in a profound, prolonged lymphopenia and the suppression of clinical and MRI activity, but in spite of this, clinical disability and cerebral atrophy still progress.

The same experience has been reported with Cladribine and Autologous Haematopoietic Stem Cell Transplantation.

All these observations give support to the fact that relapses do not essentially influence irreversible disability in the long term in MS. They are consistent with what has been shown at the individual level in the 1970s by performing serial quantitative neurological examinations over several years, and with what is currently emerging from early and serial structural brain MRI studies. These breakthroughs have immediate implications for the counselling of patients with MS. They suggest that MS is as much neurodegenerative as inflammatory, and should cause the modification of disease-modifying therapeutic strategies by focussing on the protection and repair of the nervous system and not only on the control of inflammation. [9][10]

Main Disabling Effects

The principle manifestations of MS are weakness of one or more limbs, spasticity, muscle fatigue, unsteadiness of gait and difficulties with speech.

Tremor sufficient to interfere with upper limb function may occur and loss of sensation may develop.

Difficulty in bladder control is common and may range from urge incontinence to full incontinence requiring catheterisation.

As the disease progresses mobility problems become apparent and sufferers may require the use of a walking aid. Difficulties may be due to weakness and spasticity or because of unsteadiness leading to falls. When walking the severity of muscle weakness may cause the person to have frequent falls.

Visual problems may also increase mobility problems and weakness or tremor of the upper limbs may cause difficulty using walking aids.

With further progression these manifestations will give rise to difficulty with self care. In addition the presence of depression or other mental health problem may cause additional difficulty for patients with MS coping with Activities of Daily Living.

Some of the specific cognitive deficits observed in people with MS are:

- Memory Dysfunction. This is the most commonly reported cognitive dysfunction in MS and occurs in 20 to 44% of people with MS. The type of memory deficit most often reported is free recall of recently learned material. Free recall is the ability to get to a memory instantly - MS rarely seems to affect a person's ability to get items into the memory banks however it often takes much longer to retrieve.
- Verbal fluency is affected in some people with MS whereas verbal comprehension appears undamaged. Verbal fluency deficits usually take the form of slowed free recall of words that describe concepts and less often words that name objects.
- Cognitive Fatigue. Continued attempts to remember names or finish sentences can lead to continual slowing of a successful outcome.
- Impaired planning skills. One study reported that 40% of people with ms are less able to plan things than healthy controls. This study was criticised because it was a timed test and may be influenced by recall slowness than outcome difficulty.

In relapsing remitting MS spontaneous remission is common in the early stages of the disease and indeed may be life long.

It is now considered that if symptoms resulting from relapse do not result in remission within 6 months they are likely to be permanent.

If the patient with MS becomes chair or bed bound then they will also require help to move frequently to prevent the development of bed sores. [11]

Appendix A - Expanded Disability Status Scale (EDSS) of Kurtzle for Patients with Multiple Sclerosis

Overview :

Kurtzke modified the Disability Status Scale (DSS) to allow for finer gradings of disability. It incorporates the functional system grades to help quantify the findings. The author is from Georgetown University in Washington, D.C.

Functional Systems:

(1) pyramidal functions (P)

(2) cerebellar functions (Cll)

(3) brain stem functions (BS)

(4) sensory functions (S)

(5) bowel and bladder functions (BB)

(6) visual or optic functions (V)

(7) cerebral or mental functions (Cb)

(8) other functions (O)

Functional Level	Functional System Score	EDSS
normal neurologic examination	cerebral grade 0 to 1, others 0	0
no disability	minimal signs in 1 system other than cerebral (one non-cerebral FS =1)	1.0
no disability	minimal signs in > 1 system other than cerebral (> 1 non-cerebral FS =1)	1.5
minimal disability in 1 system	1 FS grade 2, others 0 or 1	2.0
minimal disability in 2 systems	2 FS grade 2, others 0 or 1	2.5
moderate disability in 1 system, fully ambulatory	1 FS grade 3, others 0 or 1; or 3-4 FS grade 2, others 0 or 1	3.0
moderate disability in 1 system, fully ambulatory	1 FS grade 3 and 1-2 FS grade 2, or 2 FS grade 3, or 5 FS grade 2; others 0 or 1	3.5

fully ambulatory without aids; self-sufficient; up and about 12 hours a day; able to walk without aid or rest 500 meters	1 FS grade 4 alone, others 0 or 1; combination of lesser grades exceeding pattern 3.0	4.0
fully ambulatory without aids; self-sufficient; up and about most of the day; able to work full day but may have some limitations in full activity; may require minimal assistance; able to walk without aid or rest 300 meters	1 FS grade 4 alone, others 0 or 1; combination of lesser grades exceeding pattern 3.0	4.5
fully ambulatory without aids; unable to work full day without special provisions; able to walk without aid or rest 200 meters	1 FS grade 5 alone, others 0 or 1; combination of lesser grades exceeding pattern in step 4.0	5.0
fully ambulatory without aids; self-sufficient; unable to do full daily activities; able to walk without aid or rest 100 meters	1 FS grade 5 alone, others 0 or 1; combination of lesser grades exceeding pattern in step 4.0	5.5
intermittent or constant unilateral aid (cane, crutch, brace); can walk about 100 meters with or without resting	>= 3 FS >=3	6.0
constant bilateral walking aids (canes, crutches, braces); can walk about 20 meters without resting	>= 3 FS >=3	6.5
unable to walk more than 5 meters even with walking aid; essentially restricted to a wheelchair; can wheel self and perform transfers alone; can use standard wheelchair; up and about approximately 12 hours a day	rarely pyramidal grade 5 alone; more than 1 FS >= 4	7.0
unable to take more than a few steps; restricted to a wheelchair; may need aid in transfer; cannot carry on in standard wheelchair 12 hours; may require motorized wheelchair	more than 1 FS >= 4	7.5
restricted to bed or chair; may be out of bed much of the day; retains many self-care functions; generally has effective use of arms	several systems >= 4	8.0
essentially restricted to bed much of the day; has some effective use of the arms; some self-care functions	several systems >= 4	8.5

helpless in bed; can communicate and eat	most grades >= 4	9.0
totally helpless in bed; unable to communicate effectively; unable to eat or swallow	almost all grades >= 4	9.5
death due to MS		10.0

References:

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status index (EDSS). Neurology. 1983; 33: 1444-1452 (Appendix B, page 1451-1452).

References

[1] Clinical Evidence: Neurological Disorders: Multiple Sclerosis Web publication 01 october 2005

[2] The Merck Manual of Diagnosis and Therapy. Sec. 14, ch:180.

[3] Gottberg K, Einarsson U, Fredrikson S, von Koch L and Widén Holmqvist L. A population-based study of depressive symptoms in Multiple Sclerosis in Stockholm County. Association with functioning and sense of coherence. J. Neurol. Neurosurg. Psychiatry published online 17 Jul 2006; doi:10.1136

[4] Khan F, Turner-Stokes L, Ng L, Abrahamason S, Kilpatrick T. Multidisciplinary rehabilitation for adults with Multiple Sclerosis. (Protocol) Cochrane Database of Systematic Reviews 2006, issue 2.

[5] Management of Multiple Sclerosis in primary and secondary care National Institute for Clinical Excellence. Clinical guideline 8, Nov. 2003

[6] Steultjens EMJ, Dekker J, Bouter LM, Cardol M, van de Nes JCM, van den Ende CHM. Occupational therapy for Multiple Sclerosis (Cochrane Review). The Cochrane Database of Systematic Reviews 2003, issue 3. art. No.: CD003608.

[7] Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G. Exercise therapy for Multiple Sclerosis. Cochrane Database of Systematic Reviews 2004, issue 3. Art no.: CD003980

[8] Confavreux C, Vukusic S. Age at disability milestones in Multiple Sclerosis. Brain. 2006 Mar; 129 (pt. 3) : 561 – 563

[9] Confavreux C, Wertheimer P, Vukusic S. Accumulation of irreversible disability in Multiple Sclerosis – lessons from natural history studies and therapeutic trials. J R Coll. Physicians Edinb. 2004; 34:268 – 273

[10] Confavreux C, Vukusic S, Moreau T and Adeleine P. Relapses and progression of disability in Multiple Sclerosis. N Engl J Med. 2000 Nov 16;343(20):1430-8.

[11] Aylward M, Dewis P, Scott T (Eds). The Disability Handbook – a Handbook on the Care Needs and Mobility Requirements likely to arise from various Disabilities and Chronic Illnesses. HMSO 1992