Multiple sclerosis: Managing shades of grey

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) resulting in neurological deficits, which can take a variable course. Peak onset occurs between age 20 and 40 years.[1] MS should be diagnosed definitively by a Neurologist, following clinical assessment combined with MRI evidence of typical lesions occurring on separate occasions, in different locations within the CNS. Chronic disability is a feature of MS. The primary care team will co-ordinate care with the patient's partner/family, carer and specialist health professionals, to reduce MS-associated complications and to assist with personal and family adjustment. Disease-modifying medicines may reduce the number of relapses a person with MS experiences, but there is no treatment which is effective at slowing the disease once in the progressive phase.

Prevalence and patterns of multiple sclerosis

Multiple sclerosis (MS) is the most prevalent non-injury related cause of long-term neurological disability in younger adults.[2] The underlying cause of MS has not been established but it is widely considered to be an autoimmune disease, possibly precipitated by an infectious agent priming the immune system against myelin antigens.[3] The factors influencing the prognosis of a person with MS are poorly understood. However, chronic disability is a frequent outcome and this can be devastating as it threatens independence, employment and lifestyle. The condition itself is not usually directly fatal, but death in people with MS is often due to a complication of the condition, e.g. pneumonia or a urinary tract infection (UTI).[1] On average, the life expectancy of people with MS is reduced by six to 11 years.[1]

Epidemiology

In New Zealand in 2006, there were almost 3000 people identified as having MS.[4] Approximately 2700 of these people were European, 90 identified as Māori, and 15 of Pacific Island or Asian descent.[4]

MS has a peak age of onset between 20 and 40 years and like other autoimmune diseases it is 2.5 times more prevalent among females than males.[3] However, males who develop MS will often be more severely affected by disability.[3]

MS is generally more common with increasing distance from the equator. This effect has been observed in both northern and southern hemispheres.[4] In New Zealand there is a three-fold increase in prevalence from 35°S (North) to 48°S (South).[4] This effect is approximately three times stronger in females than males.[4] The reason for this is unknown, however, there is increasing evidence that low vitamin D levels in regions with less sunshine exposure may be one of several contributing factors.[5]

One in five people who develop MS has an affected relative and 4% of people with a first-degree relative with MS will develop the disease.[1]

Smoking and exposure to the Epstein-Barr virus later in life are also associated with increased incidence of MS.[6]

Patterns of multiple sclerosis

MS is characterised by inflammatory demyelination (damage to the myelin sheath of the neuron), which occurs within the white and grey matter of the CNS.[6] The peripheral nervous system is unaffected. Inflammation causes a loss of myelin and neuronal/axonal injury. Over time, remyelination can repair some of this damage. Plaques are formed from dense clusters of supporting cells (gliosis) surrounded by fibrous material. The location, frequency and balance of injury versus repair determines the pattern of MS and its associated disability.

MS has a highly unpredictable course and prognosis. Communicating this uncertainty can be a challenge for clinicians and result in anxiety for patients and their families. After a period of months to years a cycle of recurrent symptoms may develop that allows a pattern of MS to be identified. The pattern of MS that a person has will affect their prognosis and may influence the treatment of their condition.

MS typically begins with a sudden episode of neurological symptoms. For example, the patient may report blurring of vision in one eye (optic neuritis), double-vision (diplopia), unsteadiness, sensory impairment spreading upwards from the legs or dysfunction in the limbs.[3] The symptoms are characterised by increasing severity over days, then stabilisation over days to weeks, followed by gradual resolution which will be complete or partial after several weeks.[7] The first episode is often referred to as a "clinically isolated syndrome".[7] Later, following a second clinical episode, or subclinical changes on MRI (see: "The McDonald Criteria". Page 42), the patient may be diagnosed with relapsing-remitting MS.

Relapsing-remitting MS is the pattern seen in 85% of people with early-stage MS.[1] This is characterised by recurrent acute neurological episodes, referred to as relapses, with residual symptoms suddenly increasing, or new symptoms developing. Recovery is gradual although residual symptoms will often remain.[7] Overall, people with MS have approximately one relapse every two years, however, the frequency and severity vary widely.[8] A high frequency of attacks during the first two years of MS is linked to and increased likelihood of people with relapsing-remitting MS developing secondary progressive MS and long-term disability.[8]

Secondary progressive MS develops in two-thirds of people with relapsing-remitting MS, within 15 years of diagnosis.[1] This is a gradual, progressive worsening of neurological function that is independent of acute relapses and due to a low-grade degenerative process which leads to most of the long-term disability in people with MS. However, acute attacks may still occur during this phase.[1]

"Benign MS" occurs in approximately one in ten people with MS.[1] This is diagnosed following a period of ten to 20 years without significant disability.[1, 7] However, many patients do still develop disability and the value of this diagnosis is controversial.

Primary progressive MS occurs in one in ten people with MS.[1] Neurological symptoms develop insidiously and progressively from the outset, usually with slowly increasing spastic lower limb weakness (paraparesis).[6]

Diagnosing multiple sclerosis

General Practitioners should consider MS as a possible diagnosis when a person aged 20 – 50 years presents with symptoms and signs suggestive of a focal CNS deficit. In this situation, a neurological referral should be considered. Diagnosis of MS is confirmed by the presence of characteristic lesions on MRI (see: "The McDonald criteria").

A focused clinical history should be taken whenever MS is suspected. Transient neurological symptoms in the past may assist in diagnosis. Clinical features are also likely to vary between patients.[1]

People who develop MS may report positive and/or negative symptoms. Positive symptoms include muscle spasm, and one in five people with MS will have various forms of neuralgia (e.g. tingling/burning/pruritic sensations), in the skin of the limbs, trunk or face.[3, 7] An electric shock sensation down the spine when the neck is flexed (Lhermitte's symptom) is characteristic, but not specific, for MS.[3] Negative symptoms include visual disturbances (e.g. decreased visual acuity or diplopia), numbness, motor dysfunction (e.g. weakness, gait disturbances and ataxia), bladder dysfunction, bowel or erectile problems.[6]

People with MS may experience a transient worsening of symptoms due to heat, e.g. when exercising, bathing or when in a heightened emotional state; this is known as Uhthoff's symptom.[7]

Optic neuritis and MS are closely linked. Visual impairment due to optic neuritis is the reason why one-quarter of people with MS present to a clinician, and more than half of people who present with optic neuritis will eventually develop MS.[1] Like MS, optic neuritis is more prevalent among younger women, Europeans and in people who live further from the equator.[9] However, there are alternative diagnoses that should also be considered, and people with optic neuritis will not necessarily develop MS.

The clinical features of optic neuritis are impairment of visual acuity, usually with reduced colour vision and eye pain, especially on eye movement.[9] Swelling of the optic disc (papilloedema) may also be observed. An important sign is a relative afferent pupillary defect. This can be detected with the "swinging light test". When a light is shone into the unaffected eye, both pupils constrict. However, when the light is swung to the affected eye, both pupils appear to dilate (also known as paradoxical dilation). This is because damage to the optic nerve on the affected side impairs reflexive pupillary

constriction. Loss of colour vision out of proportion to the visual acuity loss is also a characteristic feature of optic neuritis. To detect red desaturation, ask the patient to compare the intensity of a bright red object between each eye. Ishihara plates (images used to test red-green colour deficiencies with coloured numbers within patterns), if available, can detect a reduction in colour perception in 88% of patients with optic neuritis.[9]

After an attack of optic neuritis the optic disc may appear pale, compared to the unaffected eye, suggesting optic atrophy. Typically, vision will improve over time which helps to differentiate the episode from a progressive cause of impaired visual acuity, e.g. glaucoma.

The differential diagnosis for optic neuritis includes ischaemic optic neuropathy, inflammatory optic neuropathies due to infection, e.g. syphilis, cat scratch disease, or non-infectious conditions, e.g. sarcoidosis, and compressive optic neuropathies, e.g. tumours, thyroid eye disease.[9] Ischaemic optic neuropathy usually occurs in people aged older than 50 years, pain is usually absent and loss of vision may be more acute and profound.[9]

Internuclear ophthalmoplegia in MS is caused by damage to neuronal connections in the brainstem between the abducens (VI) and oculomotor (III) cranial nerve nuclei.[10] This prevents the eyes working as a single functioning unit and affects horizontal gaze. When the patient looks laterally to the unaffected side there is impairment of adduction observed in the affected eye, which lags behind the unaffected eye, as shown in Figure 1.[11] Fast involuntary movements (nystagmus) of the unaffected abducting eye are also often seen.

An extensor plantar (Babinski) response may be seen in people with MS without other major signs of upper motor neurone dysfunction.[7]

Differential diagnosis of MS

People with MS often receive an alternative diagnosis before the correct one is established; most frequently a musculoskeletal injury for males or a psychiatric cause for females.[7] Conditions that may need to be considered, depending on the presenting features, include:[7]

- Psychiatric disorders/functional syndromes
- Other causes of visual impairment
- Sciatica and musculoskeletal injury
- Carpal tunnel syndrome and other peripheral nerve disorders
- Intrinsic or expanding lesions of the CNS, e.g. tumour, syringomyelia
- Motor neurone disease
- Infections, e.g. syphilis, HIV or spinal abscess
- Systemic inflammatory disorders, e.g. systemic lupus erythematosus
- Stroke
- Paraneoplastic syndromes

MS only affects the upper neurone pathways in the CNS therefore absent reflexes or muscle wasting are not usually seen in patients with MS.[7]

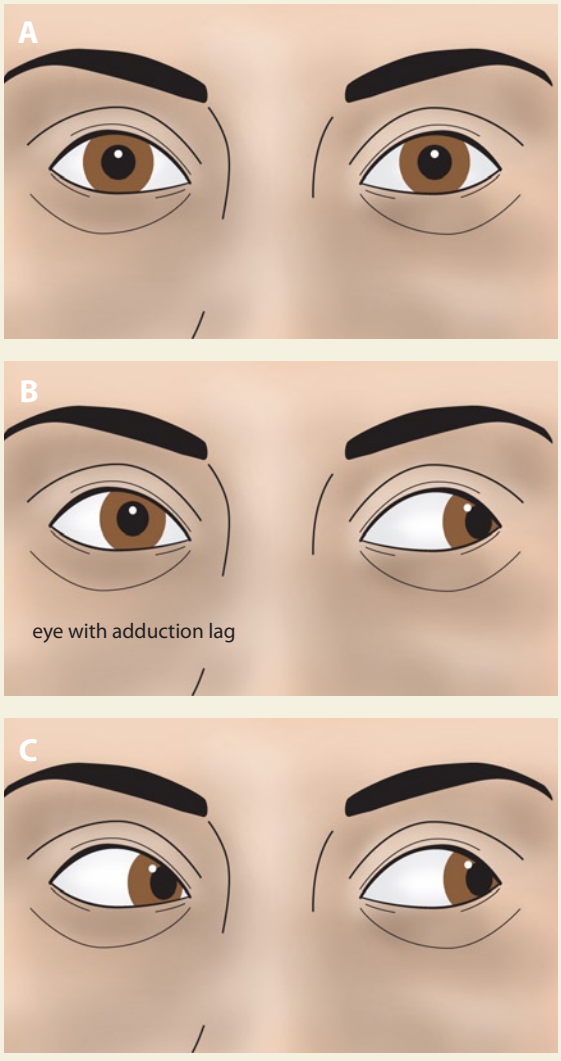

Figure 1: Adduction lag in unilateral internuclear opthalmoplegia on rapid left gaze. Starting at position A, adduction lag can be seen at position B, virtual complete adduction can be seen at position C. Adapted from Prasad and Galetta, 2010.[10]

The McDonald criteria

The McDonald clinical criteria state that a diagnosis of MS requires two or more episodes of inflammatory demyelination to occur on separate occasions, at least 30 days apart, in different locations within the CNS.[12] However, in some patients separation in time and space can be established with a single MRI scan when there is reasonable historical evidence of a prior attack.[12] An important aspect of the criteria is that alternative explanations for the lesions have been reasonably excluded.[12]

Multiple sclerosis and pregnancy

Females diagnosed with MS are often of childbearing age and may therefore have questions relating to their ability to have children. MS does not affect fertility.[1] Relapses are less likely to occur during pregnancy, but are more common in the three to six months following delivery.[1] Overall, pregnancy does not have any effect on the course of MS. Disease-modifying medicines should be avoided during pregnancy and ideally, for at least three months prior to conception.[13]

Confirmatory investigations are usually performed in secondary care

Primary care plays a key role in identifying people suspected of having MS. Confirmatory investigations are usually undertaken by a Neurologist. An MRI of the brain is the investigation of choice. Additional testing is generally only requested when there is uncertainty about the diagnosis.[3]

MRI is reported to have a sensitivity of 95% for detecting clinically confirmed MS.[6] The number of lesions found on MRI may also be the most accurate predictor of clinical outcome.[3] The patient's history often underestimates disease severity and other asymptomatic CNS lesions will be detected on MRI in approximately 80% of people with MS after they experience their first clinical episode.[3] People with spinal and brainstem lesions are at greater risk of permanent disability.[3]

Visual evoked potentials may identify subclinical demyelination of the optic nerve.[7] However, these findings can be non-specific and may be normal in half of people with MS.[3]

Oligoclonal IgG bands in cerebrospinal fluid present on protein electrophoresis are found in up to 95% of people with well established MS. [7] However, protein electrophoresis of the cerebrospinal fluid is rarely required where a characteristic clinical history and MRI changes are present.

Disease-modifying treatment of multiple sclerosis

Patients with active relapsing-remitting MS may be treated with disease-modifying medicines. There are three such medicines for MS available in New Zealand under Special Authority; glatiramer acetate, interferon beta-1a and interferon beta-1b. Subsidy for these medicines requires application from a Neurologist to the Multiple Sclerosis Treatment Assessments Committee. The subsidy approval criteria include that the patient has frequent relapses and significant residual disability. The medicines are sent by courier directly to patients or clinicians (i.e. not dispensed from a pharmacy). General Practitioners may assist in monitoring for adverse effects in patients taking these medicines.

The medicines have complex actions on immune function and their mechanism in MS is uncertain. They are considered to be immune-modulators, rather than general immune-suppressors. All three medicines have similar, limited effects on the course of relapsing-remitting MS: an approximate one-third reduction in the frequency of relapses, with a

greater effect on the reduction of new lesions and a less consistent effect on slowing the progression of disability.[14, 15] None of these medicines appear to be effective in people with secondary progressive MS.[15, 16]

Glatiramer acetate (Copaxone) is available in 20 mg prefilled syringes which are injected subcutaneously, once daily. Adverse effects of treatment include hypersensitivity reactions within minutes of injection, nausea, constipation, syncope, depression, headache, tremor and back pain.[13]

Interferon beta-1a (Avonex) is available in 30 micrograms vials and prefilled syringes and pens which are injected intramuscularly, once a week.[13] **Interferon beta-1b** (Betaferon) is available in 250 micrograms vials, with a reconstituting solvent, and is injected subcutaneously, every second day.[17] Beta-interferon may cause influenza-like symptoms and occasionally vomiting.[13] Less common adverse effects include anaphylaxis, urticaria, personality changes and suicidality, convulsions, hepatitis and thyroid dysfunction.[13] Dose titration may be necessary to improve tolerability.

Managing relapses and symptoms of multiple sclerosis

People with MS require the care of a multidisciplinary team. This is usually co-ordinated by primary care and supported in some regions by specialist nurses. The goals of treatment are to improve the quality of life, reduce symptoms and to minimise any adverse effects of treatment. Where possible, people with MS are encouraged to manage their own well-being.[19] The closest adult family member of a person with MS is often their main carer and supporting this relationship is an important role of the multidisciplinary team. The rate of divorce is nine times higher among couples where one person has MS.[7]

The Multiple Sclerosis Society of New Zealand is a non-profit organisation that provides support, education and advocacy for people and families with MS. For further information see: **www.msnz.org.nz**

Acute relapses are managed with methylprednisolone

Relapses are more common in people with MS who have viral infections or who are undergoing major life events causing stress.[7] Influenza vaccination of both the person with MS and their carer may reduce the likelihood of MS relapses and minimise the risk of respiratory complications.[7]

MS relapses can be treated in primary care with oral methylprednisolone in doses up to 200 mg, daily, following

New disease-modifying medicines for multiple sclerosis

Monoclonal antibodies which target specific surface molecules of immune cells have been trialled as MS-modifying injectable medicines. **Natalizumab** is available in New Zealand for the treatment of relapsing-remitting MS. It is not currently subsidised on the Pharmaceutical Schedule. One 300 mg intravenous infusion is given every four weeks.[13] Natalizumab reduces relapses by approximately two-thirds and new MRI lesions by 90%, with a small risk of serious viral neurological disease (progressive multifocal leukoencephalopathy) due to reactivation of John Cunningham virus (a common polyomavirus).[18]

There are four other monoclonal antibodies, mainly indicated for the treatment of leukaemia or prevention of organ transplant rejection, that have been trialled in the United States as disease-modifying medicines for MS; alemtuzumab, daclizumab, ocrelizumab and ofatumumab.[18] However, evidence of effectiveness for the treatment of MS is inconclusive and some of these medicines have been withdrawn from clinical use.

Fingolimod, teriflunomide, dimethylfumarate and laquinimod are oral medicines that have been investigated for the treatment of relapsing-remitting MS.[18] Fingolimod (Gilenya) is the only one of these medicines approved for use in New Zealand, and none are subsidised. Fingolimod is available in 0.5 mg capsules, taken once daily.[13] Fingolimod is contraindicated in people who are immunosuppressed, or have active infections or malignancies.[13] Adverse effects include; transient bradycardias and heart block, hypertension, diarrhoea, weight loss and a range of respiratory and neurological adverse effects.[13]

consultation with a Neurologist.[13] However, higher intravenous or oral doses (500 mg – 1 g, once daily, for three to five days) of methylprednisolone may be recommended if the patient is severely debilitated.[19] The treatment regimen will be guided by the Neurologist, and may also include a tapering period over 10 – 12 days.[13] Using corticosteroids more than three times a year or for periods longer than three weeks should be avoided.[19]

Symptomatic control of multiple sclerosis involves a multi-disciplinary approach

If the condition or needs of a patient with MS change, consider the following points:[1]

- Is there an alternative explanation? e.g. tiredness could also be explained by anaemia, hypothyroidism or depression
- Could a virus or other infection be the trigger?
- Are the symptoms an adverse effect of treatment?
- Are the symptoms explained by the gradual progression of MS?

Management of symptoms usually involves consultation with other members of the multi-disciplinary team. Check the New Zealand Formulary for medicines information and subsidy status.

Fatigue is experienced by 85% of people with MS.[1] Muscle weakness and ataxia may also be present. Depression, poor sleep, inadequate nutrition and pain should all be considered as possible contributing factors. Exercise, e.g. walking, should be encouraged. Physiotherapy will often improve motor control after two or three sessions and may allow exercise goals to be increased.[1] Both aspirin and amantadine (an antiviral and antiparkinson medicine) have been shown to provide some benefit for treating fatigue in patients with MS, however, further trials are required before the extent of any clinical effect can be established.[20, 21]

Pain affects up to two-thirds of people with MS.[1] Musculoskeletal pain can be caused by restricted movement or muscle spasms.[1] Peripheral pain can be managed with analgesics and physiotherapy. CNS lesions may also cause pain, especially if there are lesions affecting sensory pathways, e.g. trigeminal neuralgia may occur due to brainstem inflammation.[1] Table 1 lists medicines for the treatment of chronic pain.

Bowel dysfunction, e.g. constipation and/or faecal incontinence affects over 60% of people with MS.[1] This can be highly detrimental to the patient-carer relationship and is a common reason why people with MS are admitted to residential care.[1] Fluid and fibre intake should be increased before a laxative is considered.[1] Overflow incontinence, secondary to constipation, should also be considered as a possible cause.

Patients with MS may have difficulty initiating their bowel movement. Digital rotatory stimulation of the anorectum can be performed by a carer to provoke rectal contraction and bowel emptying.[22] If digital stimulation is ineffective then suppositories, e.g. bisacodyl (10 mg) or glycerol (3.6 g) in the morning, are recommended.[22]

Loperamide is the first-line treatment for faecal incontinence in patients with MS. For example, begin with 4 mg, daily, then adjust until control is achieved - the maintenance dose is 2 – 12 mg, daily, in one to three divided doses.[13, 22] Anal plugs can also be effective in patients with faecal incontinence.[22]

Table 1: Medicines that may be considered for chronic pain

Medicine	Dose
Amitriptyline or nortriptyline	10 – 75 mg, once daily
Carbamazepine (especially for trigeminal neuralgia)	100 mg, once or twice daily, increased gradually according to response, with a usual dose of 200 mg, three or four times daily, and up to 1.6 g daily in divided doses in some patients
Gabapentin	Titrate in 300 mg steps to a maximum of 3.6 g daily in three divided doses; a common dose in patients with MS is 600 mg, three times daily (do not withdraw abruptly)

Bladder problems, e.g. urgency, nocturia, incontinence and UTIs are common in people with MS. Anti-cholinergics, e.g. oxybutinin, 5 mg, three times daily, reduce urinary urgency and frequency.[1] However, these medicines can cause incomplete bladder emptying and urinary self-catheterisation may be required if there is significant post-voiding urine remaining.[1] If oxybutinin is ineffective or not tolerated, tolterodine (2 mg, twice daily) or solifenacin (5mg, once daily, increased to 10 mg, once daily, if necessary) may also be considered (under Special Authority).[13]

Nocturia can be treated with desmopressin.[1] The nasal spray is subsidised if prescribed by a Neurologist and injections are available on Special Authority. Tablets are available, but unsubsidised. Desmopressin can be taken at bedtime for nocturia, but can also be used during the day, e.g. for long journeys, however, it should only be taken once in a 24 hour period.[1]

Spasticity and spasms frequently occur in people with MS and affect mobility. Physiotherapy in combination with passive exercise is used to prevent permanent muscle shortening. Table 2 lists medicines for the treatment of severe spasticity.

Cannabidiol plus tetrahydrocannabinol oromucosal spray is an adjunctive treatment for moderate to severe spasticity in adults with MS.[13] This medicine is not subsidised and requires Ministerial approval as it is a controlled drug. Cannabidiol is contraindicated in people with a personal or family history of psychosis or a history of other severe psychiatric disorder.[13]

Managing disability and wider affects of MS

Managing disability is central to the care for a person with MS. An important component is to ensure that the patient feels that their needs are being met. Walking sticks and walking frames reduce the risk of falls and devices such as an hinged ankle-foot braces can improve dorsiflexion and improve movement.[3] Agreed goals are important in managing disability; these should be ambitious and challenging, yet achievable.[19]

Cognitive impairment occurs in approximately half of all people with MS, e.g. reduced ability to learn, plan or concentrate.[1] This is related to brain atrophy, particularly in areas near the cortex or in association fibres that link different brain areas.[1] A medicine review should be conducted to ensure adverse effects are not a contributing factor and the patient

Table 2: Medicines that may be considered for severe spasticity

Medicine	Dose
Baclofen	5 mg, three times daily, increased at three day intervals by 5 mg, three times daily. The maintenance dose is 30 – 80 mg daily, in three divided doses.
Orphenadrine citrate (for acute muscle spasm)	100 mg, twice daily
Dantrolene	25 mg, once daily, increased after four to seven days to 25 mg, two to four times daily. Doses can be increased further by 25 mg, every four to seven days, to a maximum of 100 mg, four times daily.
Diazepam	2 – 15 mg, daily, in divided doses, increased to 60 mg, daily, according to response
Fampridine*	10 mg, orally, twice daily, approximately every 12 hours, with treatment reviewed after eight weeks
Tizanidine (unapproved medicine)	2 mg, once daily, increased by 2 mg, daily, according to response, at intervals of at least three to four days, to a maximum daily dose of 36 mg, daily, in three to four divided doses

* Fampridine (Fampyra) is a potassium channel blocker indicated for improving walking in adults with MS. One month free trial is available in New Zealand, however, ongoing treatment is expensive and not subsidised in New Zealand.

Driving a motor vehicle

Driving ability should be considered once a person with MS has residual disability. Patients should be assessed for vision, limb strength, accuracy of rapid foot movements and joint proprioception.[23] Driving should cease if there are doubts regarding a person's ability to control a vehicle.[23]

Where there is uncertainty regarding a person's ability to drive, it may be appropriate to seek the assistance of an occupational therapist with experience in driver assessments. MS has a variable and intermittent progression, so it may be necessary to restrict people from driving during periods of relapse, while allowing them to drive during periods of remission.[23] License conditions may include regular assessments, such as an annual medical report.[23]

The New Zealand Transport Agency has a "Medical aspects of fitness to drive" website available from: **www.nzta.govt.nz/resources/medical-aspects/2.html**

assessed for sleep disturbances and depression. Restless leg syndrome is more common in people with MS and a sleep study may be useful in identifying causes of daytime fatigue.[1]

Depression and/or anxiety are likely to be experienced by people with MS, and also carers or family members.[1] Over half of people with MS will have a major depressive episode and the rate of suicide is reported to be 7.5 times higher in people with MS.[1] The patient, their carer and family require opportunities to talk about the impact MS is having on them as well as having input into how positive change can be made. Referral for counselling is recommended.

Lifestyle interventions in people with MS

Diet should be reviewed in patients with continual weight loss or evidence of malnutrition. It is possible that there are additional benefits to improving nutrition in people with MS, and some guidelines suggests that a diet rich in sunflower, corn, soya and safflower oils may slow disease progression, however, the evidence for this is not strong.[7] The "Swank Diet" is gaining popularity in Australasia, largely due to the fact that it is being promoted by a clinician who himself has MS. The diet is low in saturated fat and high in vegetables, but there is currently no controlled evidence of benefit.

People with MS may be concerned about their vitamin D intake. The increased incidence of MS with increasing distance from the equator is the main reason behind such thinking. People who wish to increase their intake of vitamin D can be advised to spend more time in direct sunlight. During winter, eating more oily fish, e.g. salmon or cod liver oil, will also increase vitamin D intake. If there is ongoing concern about vitamin D deficiency, cholecalciferol 1.25 mg, once a month, is an appropriate supplement.[13]

For further information see: "Vitamin D supplementation: Navigating the debate", BPJ 36 (June 2011).

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