

The neuropsychiatry of multiple sclerosis

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Abstract Multiple sclerosis is the most common disabling neurological illness affecting young and middle-aged adults. Although attention has tended to focus mainly on its neurological manifestations, reports of the presence of neuropsychiatric symptoms date back to the writings of Charcot in 1877. This article details the neuropsychiatric sequelae of multiple sclerosis and the evidence base for available treatments.

Multiple sclerosis usually starts between the ages of 20 and 40 and is characterised by multiple demyelinating lesions with a predilection for the optic nerves, cerebellum, brain-stem and spinal cord. The disorder presents with diverse neurological signs, which reflect the presence and distribution of plaques. Multiple sclerosis is predominantly a white matter disease. The course of the illness is variable and difficult to predict: 5–10% of those affected show a steady progression of disability, with no remissions (primary progressive multiple sclerosis); 20–30% follow a relapsing–remitting course but never become seriously disabled; and about 60% enter a phase of progressive deterioration following a number of relapses and remissions (secondary progressive) (Feinstein, 1999).

There is evidence of an autoimmune-mediated inflammatory response targeted against myelin in the central nervous system. With demyelination, nerve conduction becomes impaired, transmission of nerve impulses is delayed and symptoms ensue. Diagnosis is based on the clinical history and examination (Box 1). It requires a patient to have had at least two episodes of neurological disturbance implicating different white matter sites. Investigations such as neuroimaging, evoked potentials and cerebrospinal fluid electrophoresis can be helpful adjuncts in the diagnosis (Feinstein, 1999).

In the UK, the lifetime risk is 1:8000; therefore about 60000 people are affected by the disease at any one time. The true prevalence may be higher than this as some cases are discovered only on post-mortem examination. Curiously, multiple sclerosis is seen with greater frequency as the distance from the equator increases. It is twice as common in women as in men (Feinstein, 1999).

The aetiology is unknown, but both genetic and environmental influences are considered important.

Box 1 Differential diagnosis of multiple sclerosis (Rolak, 1996)

- Somatisation disorder
- Postviral demyelination
- Vasculitis
- Stroke
- Retroviral infection
- Metachromatic leucodystrophy
- Tumours

There is a 25% monozygotic concordance. Evidence of environmental factors are supported by the following observations: migration studies show that those who emigrate during childhood assume the risk of the adopted country; disease epidemics have been reported in isolated communities; and marked variations in prevalence are found in genetically homogeneous populations (Feinstein, 1999).

The disease can result in a number of psychiatric disorders, the incidence and treatment of which I will discuss in this article.

Depression

Depression is the most common mental disorder in multiple sclerosis and it represents a considerable source of morbidity and mortality. Hence, its detection and treatment is of utmost importance.

Pooling figures from published reports shows that clinically significant depression in association with multiple sclerosis has a lifetime prevalence of about 25–50% (Minden & Schiffer, 1990), about three times higher than the rate in the general population. Chwastiak *et al* (2002) studied the rates of depression in people with multiple sclerosis living in the

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community and found that 42% had significant and 29% had severe depression. Individuals with advanced multiple sclerosis were much more likely to experience clinically significant depressive symptoms than those with minimal disease. Shorter duration of multiple sclerosis was also associated with a greater likelihood of significant depressive symptoms, but the pattern of illness progression was not. Psychological and social factors are also known to play a role in depression. For example, patients who possess active coping strategies and are able to deal with problems, rather than avoiding them, and those with a good level of support tend to have lower levels of depression.

Last year the Goldman Consensus Group (2005) issued a statement on depression in people with multiple sclerosis. They noted that it has been linked with poorer cognitive functioning, more time off work and a lower quality of life than multiple sclerosis without depression. They also cited evidence suggesting that people with depression are less likely to adhere to their medication regimens. The report advises that people with multiple sclerosis should be regularly screened for depression and those found to be depressed should be treated quickly.

Diagnosis

The typical somatic symptoms of depression tend not to be good discriminators for the disorder in people with multiple sclerosis. The symptoms listed in Box 2 may be more helpful diagnostic indicators.

Measuring depression using rating scales may be complicated by the fact that many of the somatic symptoms of depression also occur in chronic multiple sclerosis. There has been some debate as to whether the common assessment scales for depression should exclude certain somatic symptoms when they are used in multiple sclerosis. In an attempt to provide some guidance on this dilemma, Moran & Mohr (2005) evaluated the utility of the individual items of the Beck Depression Inventory and the Hamilton Rating

Box 2 Symptoms of depression in multiple sclerosis

- Pervasive mood change
- Diurnal mood variation
- Suicidal ideation
- Functional change not related to or out of proportion to physical disability
- Pessimistic or negative patterns of thinking

Scale for Depression. They assessed the validity of these instruments by measuring how individual items of these scales changed when 42 people with multiple sclerosis were treated for their depression. They found that scores for all of the items in the Beck Depression Inventory and 12 of the 17 items in the Hamilton Rating Scale for Depression decreased significantly with treatment, suggesting that these items are correctly tapping depression in multiple sclerosis.

Drug-induced low mood is an important differential diagnosis of depressive disorder in multiple sclerosis. Steroids, baclofen, dantrolene and tizanidine are all drugs that can cause depression in their own right. There has been some controversy over whether interferon treatment is a risk factor for depression in multiple sclerosis. Feinstein *et al* (2002) carried out an interesting study of the subject. They recruited 42 people with multiple sclerosis before they had started treatment with interferon. The Structured Clinical Interview for DSM-IV (SCID) was administered at 3, 6 and 12 months. The results showed that the percentage with depression fell as length of interferon treatment increased. However, participants who developed depression were treated as soon as it was identified.

There is no clear association between brain abnormalities identified by magnetic resonance imaging (MRI) and depression. The failure of MRI studies to find such an association may relate to methodological limitations inherent in the studies.

There is a suggestion that immune abnormalities, in association with dysfunction of the hypothalamic-pituitary-adrenal axis, may be the mechanism underlying the high lifetime risk for depression (Michelson *et al*, 1994; Wei & Lightman, 1997; Fassbender & Schmidt, 1998).

Treatment

There has been only one double-blind placebo-controlled trial of antidepressant medication for depression in multiple sclerosis. Schiffer & Wineman (1990) studied 28 people with major depression and multiple sclerosis. In a 5-week trial, 14 participants were randomly assigned to desipramine and individual psychotherapy and 14 to placebo and individual psychotherapy. Half of the 14 in the desipramine group were unable to attain the desired serum level of the drug because of side-effects. However, the participants on desipramine showed a statistically significant improvement in mood compared with those in the placebo group according to scores on the Hamilton Rating Scale for Depression.

Anecdotal evidence suggests that selective serotonin reuptake inhibitors (SSRIs) could be

the treatment of choice for depression in multiple sclerosis, owing to their less troubling side-effects. In an open trial (Scott *et al*, 1995), 11 people with multiple sclerosis and depression were treated with 100mg sertraline per day. All 10 who remained on the drug for 3 months improved and none reported side-effects. There is no evidence that any one SSRI is better for the treatment of depression in multiple sclerosis, but fluoxetine may be helpful for some of the neurological symptoms as well as fatigue. In patients who do not respond to antidepressants, lithium augmentation may prove effective.

Clinical experience suggests that it is best to start at a low dose of an antidepressant and to increase it slowly. If side-effects are experienced it might be preferable to reduce the dose rather than stop the drug completely.

Individual or group psychotherapy can be particularly helpful for less severe depression, and in more severe cases it can be a useful adjunct to antidepressants. Larcombe & Wilson (1984) found that cognitive-behavioural therapy (CBT) for depression was more effective than no treatment. Participants were carefully screened to ensure they met the criteria for definite or probable depression and those with cognitive impairment were excluded. The sample size was small in this study, with 9 patients receiving CBT and 10 put on a waiting list with no intervention. The CBT took place in groups for 90 min a week for 6 weeks. At the end of the trial the participants receiving CBT showed a significant improvement in mood.

Electroconvulsive therapy (ECT) may be used to treat severe drug-refractory depression and there are a few case reports of its use (Krystal & Coffey, 1997). However, there appears to be a 20% risk of triggering a relapse of multiple sclerosis, and the presence of active brain lesions on MRI before treatment is a potential risk factor for neurological relapse following ECT (Mattingley *et al*, 1992).

Fatigue and depression

The possible link between fatigue and depression in multiple sclerosis has puzzled clinicians. Earlier studies found little evidence of any relationship between the two. One of the first studies to report a statistically significant link between fatigue and depression (Schwartz *et al*, 1996) was investigating the psychosocial correlates of fatigue in 139 people with multiple sclerosis. However, the correlation was low. A stronger association was demonstrated by Ford *et al* (1998) in a study of fatigue and depression in 78 consecutive patients attending a multiple sclerosis clinic. This study gave separate scores for mental, physical and total fatigue and

Box 3 Risk factors for suicide in multiple sclerosis

- Male gender
- Young age at onset of illness
- Current or previous history of depression
- Social isolation
- Substance misuse

found that depression was more strongly related to mental, rather than physical, fatigue. Further research has confirmed the link between depression and fatigue and has identified moderating factors such as activity levels and helplessness. A study by Janardhan & Bakshi (2002) showed that depression and fatigue were independent predictors of quality of life. When both were present, treating the depression seemed to reduce fatigue. It is still not known whether fatigue occurs as a direct result of brain lesions or as a psychological reaction.

Suicide and self-harm

Suicidal ideation is very common in multiple sclerosis (Box 3). Feinstein (2002) studied 140 consecutive patients attending a multiple sclerosis clinic in Canada and found a lifetime prevalence of suicidal intent of 28.6%; 6.4% of the sample had actually attempted suicide. In addition, people with multiple sclerosis have a significantly increased rate of suicide compared with the general population and patients with other neurological disorders (Sadovnick *et al*, 1991; Stenager *et al*, 1992). As yet, there is no study proving a link between suicide and depression in multiple sclerosis, although such an association is likely to exist.

Kahana *et al* (1971) reported that 3% of 295 people with multiple sclerosis died by suicide over a 6-year period, but it is unclear how many were depressed or how representative the sample was. This figure contrasts with a lifetime prevalence of 1% for suicide attempts in the general population, only 1 in 10 of which is successful. In a study of 3126 people with multiple sclerosis followed up over 16 years, suicide accounted for 15% of all ascertained deaths (Sadovnick *et al*, 1991).

Mania and euphoria

Mania might occur as part of the physical disorder or secondary to drug treatments. Manic episodes in multiple sclerosis occur more frequently than expected by chance. Schiffer *et al* (1986) attempted to

trace all people in Monroe County, New York, who had both multiple sclerosis and bipolar disorder. Individuals were excluded if a manic episode had occurred in the context of steroid therapy. Twice the expected numbers of people were found to have both conditions. The possibility of a shared genetic cause could explain the association but further replication of results is required to confirm this.

Both multiple sclerosis and mania are associated with white matter changes on MRI, although the pathogenesis is likely to be different (Young *et al*, 1997). There is MRI evidence suggesting that patients showing mania with psychotic symptoms have plaques that are distributed predominantly in the bilateral temporal horn areas (Feinstein *et al* 1992).

Mania can also be drug induced: steroids, baclofen, dantrolene, tizanidine and illicit drugs are all culprits. Mild to moderate degrees of mania may occur in up to a third of patients given steroids. People with multiple sclerosis who become hypomanic on steroid therapy are more likely to have a family or premorbid history of affective disorder and/or alcoholism. This should not be a contraindication to treatment with steroids, although it should signal caution.

Lithium carbonate is an effective treatment for manic episodes, but there are no controlled trials of its use to treat manic symptoms in multiple sclerosis. Sodium valproate is also effective and can be used in those unable to tolerate lithium, although again there are no trials of its use in people with manic symptoms and multiple sclerosis.

Euphoria bears some similarity to hypomania in terms of elevated affect but lacks the associated overactivity. In an influential paper published in 1926, Cottrell & Wilson reported euphoria in over two-thirds of their sample of people with 'disseminated sclerosis', as multiple sclerosis was then named. Few studies since have reported such high rates, and summarising the studies to date a median rate of 25% is reported (Rabins, 1990).

Pathological laughing and crying

Although pathological laughing and crying may overlap with emotional lability, they are not synonymous. Pathological laughing and crying is defined as uncontrollable laughing and/or crying but without the associated affect. The symptoms of the full syndrome are shown in Box 4.

Cottrell & Wilson's 1926 study was one of the first to look at pathological laughing and crying in multiple sclerosis. They found that 95% of their sample had pathological affect. However, they did not define pathological laughing and crying and

Box 4 Pathological laughing and crying syndrome

The behaviour occurs:

- 1 in response to non-specific stimuli
- 2 in the absence of an association between affective change and observed expression
- 3 in the absence of voluntary control of facial expression
- 4 in the absence of a corresponding change in mood exceeding the laughing or crying

recruited participants from a tertiary referral centre, which would have biased the results.

Some 40 years later, Surridge (1969) compared psychiatric abnormalities in 108 people with multiple sclerosis and 39 controls with muscular dystrophy. Muscular dystrophy was chosen as it is a disabling disease but it spares the brain, so the effects of disability could be controlled for. The results showed that there were exaggerated emotional responses with no associated feelings of distress in 10% of participants with multiple sclerosis and none of the controls.

Feinstein *et al* (1997) performed a case-control study of pathological laughing and crying in multiple sclerosis. A sample of 152 out-patients with multiple sclerosis was screened for pathological laughing and crying, and 10% (15) were found to have the syndrome. Cases (11 of the 15) and controls (13 of the remaining 137) were matched for age, gender, duration of multiple sclerosis, level of disability, disease course and premorbid IQ. Among the cases, uncontrollable crying was more common than laughing. The demographics and disease course showed that there was no difference between genders, but longstanding disease and progressive, severe disability were linked with pathological laughing and crying syndrome. Patients with the syndrome were also more likely to be intellectually impaired and to have extensive brain lesions.

Treatment

Schiffer *et al* (1985) showed that 66% of people with multiple sclerosis who had the laughing and crying syndrome responded to 75 mg of amitriptyline per day, and tolerated it well. It was felt that this improvement might relate to enhancement of dopamine transmission. This theory is further supported by demonstration of an improvement in symptoms with treatment with both amantadine and levodopa (Udaka *et al*, 1984). More recent evidence suggests that fluoxetine may also be of

benefit and have fewer side-effects, although these trials had small samples (Seliger *et al*, 1992; Sloan *et al*, 1992).

Emotional lability

Emotional lability is defined as an excessive, generally brief, emotional response to a minor stimulus. From a survey of clinic attendees it was estimated that 20% of people with multiple sclerosis have emotional lability (Feinstein, 1999). Anecdotal evidence suggests that treatment is with carbamazepine, SSRIs or amitriptyline.

Psychosis

Co-occurrence of psychosis and multiple sclerosis is uncommon. Most reports of psychoses and multiple sclerosis are single case studies. Davison & Bagley's (1969) literature review identified 39 case reports, a number that does not exceed chance expectation. Examining large in-patient psychiatric populations for multiple sclerosis has validated this finding. There are, however, no community-based epidemiological studies.

Feinstein *et al* (1992) compared 10 patients with multiple sclerosis and psychosis with 10 control patients without psychosis who were matched for age, gender, duration of illness and disability. Participants were compared with respect to the site and extent of lesions on MRI. This demonstrated that people with multiple sclerosis and psychosis are more likely to have plaques involving the temporal horns bilaterally.

The authors suggested that psychosis in multiple sclerosis is distinct from schizophrenia as it has a later age at onset, quicker resolution, fewer relapses, better response to treatment and a better prognosis.

Given the current media descriptions of relief of the symptoms of multiple sclerosis by the use of cannabis, we may see a rise in the number of cases of drug-induced psychosis.

Treatment

There are no studies of treatment of the psychosis associated with multiple sclerosis. Low doses of atypical antipsychotics such as risperidone (Furmaga *et al*, 1995) or clozapine (Chacko *et al*, 1995) should be the treatment of choice, as they have fewer side-effects than the older antipsychotics. Clinical experience suggests that benzodiazepines may also be used for sedation.

Cognitive impairment

In 1877 Charcot observed that people with multiple sclerosis might show

'marked enfeeblement of the memory, conceptions are formed slowly and intellectual and emotional faculties are blunted in their totality' (pp. 194–195).

Since the demyelinating action of multiple sclerosis predominantly affects the white matter, cognitive dysfunction associated with the disease might be termed a subcortical dementia. Cognitive impairment can, of course, vary within and between patients, depending on the location of lesions (Box 5).

Two studies have looked at the prevalence of cognitive impairment in multiple sclerosis using representative samples and controlling for disease and demographic variables. Rao *et al* (1991) recruited 100 community-based people with multiple sclerosis and 100 healthy controls matched for age, gender and number of years of education. Both groups completed 31 neuropsychological tests, and cognitive function was rated as impaired if the individual's score on each test fell below the fifth percentile. The people with multiple sclerosis failed significantly more tests. This study was replicated by McIntosh-Michaelis *et al* (1991) with 147 community-based people with multiple sclerosis. The control group in this study comprised 34 people with rheumatoid arthritis. Again a battery of neuropsychological tests was completed, and 46% of the multiple sclerosis group and 12% of the rheumatoid arthritis group were found to be impaired. These studies also showed that cognitive dysfunction is not closely associated with physical disability, disease duration or disease course.

Decline in IQ does occur in multiple sclerosis, as shown by Canter (1951), who administered the Army General Classification Test to 23 men who developed multiple sclerosis after enrolment in the army. This decline is mainly related to measures on the performance sub-scale.

Memory function has been well studied and reveals that short-term memory deficits are present but are less marked than long-term memory deficits. Verbal and non-verbal memories are adversely

Box 5 Symptoms of a subcortical dementia

- Forgetfulness
- Slowness of thought processes
- Emotional or personality changes
- Impaired ability to manipulate information

affected and the mechanism involves failure at both the acquisition and retrieval stages. Deficits are more apparent on tests of recall than recognition (Feinstein, 1999: chapter 6).

Although people with multiple sclerosis display a high lifetime prevalence of depression, cognitive impairment cannot be accounted for by the presence of depression alone (Brassington & Marsh, 1998). Moreover, psychotropic medication does not seem to affect the performance of patients in memory testing (Rao *et al*, 1991).

The Mini-Mental State Examination has been shown to be unhelpful in screening for cognitive impairment in multiple sclerosis (Franklin *et al*, 1988).

There is empirical evidence that cognitive impairment exerts a negative effect on the patient's quality of life in many domains and is linked to the patient's level of day-to-day functioning.

Treatment

Donepezil has been shown to improve memory in multiple sclerosis in a randomised clinical trial (Krupp *et al*, 2004). This single-centre double-blind placebo-controlled trial evaluated 69 people with multiple sclerosis and cognitive impairment, who were randomly assigned to receive a 24-week course of either donepezil (10 mg daily) or placebo. Patients underwent neuropsychological assessment at baseline and after 24 weeks. Donepezil-treated participants showed significant improvement in memory performance on the Selective Reminding Test (SRT) compared with placebo. The benefit of donepezil remained significant after controlling for age, Expanded Disability Status Scale score, baseline SRT score, reading ability, multiple sclerosis subtype and gender. The donepezil-treated participants did not show significant improvements on other cognitive tests, but were more than twice as likely to report memory improvement as those in the placebo group. The clinician also reported cognitive improvement in almost twice as many in the donepezil than in the placebo group. A larger multicentre investigation of donepezil in multiple sclerosis is warranted to assess more definitively the efficacy of this intervention.

Conclusions

Both the disease process and treatment of multiple sclerosis can affect the mental state of patients, producing a variety of symptoms. Despite the fact that Charcot wrote over a century ago about the effect multiple sclerosis can have on the mental

state of people with the disease this aspect of the illness has only more recently begun to attract the interest of researchers. Psychiatric symptoms can greatly compound the mortality and morbidity of multiple sclerosis and can be costly in terms of complementary / alternative remedies and practitioners (Patten *et al*, 2002). Treatment is often effective but does not alter the overall outcome of the illness.

Declaration of interest

None.

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MCQs

1 Multiple sclerosis:

- a is more common in men than women
- b occurs more commonly nearer the equator
- c is not of well-known aetiology
- d presents with diverse physical signs
- e has a variable course.

2 Depression in multiple sclerosis:

- a has a lifetime prevalence of up to 50%
- b can be caused by the drugs used to treat the multiple sclerosis
- c can be treated with SSRIs
- d can be treated with cognitive-behavioural therapy
- e can be treated with ECT, but only with caution.

3 Mania in multiple sclerosis:

- a is more common than in the general population
- b can be induced by prescribed treatments for multiple sclerosis
- c is treated with mood stabilisers
- d is the same as euphoria
- e can occur as part of the primary physical disorder.

4 Psychosis in multiple sclerosis:

- a is more common than in the general population
- b is similar in nature to schizophrenia
- c has been the subject of many well-conducted treatment trials
- d should be treated with atypical antipsychotics as treatment of choice
- e should be treated with typical antipsychotics as the treatment of choice.

5 Cognitive impairment in multiple sclerosis:

- a is no more common than in the general population
- b can be explained by the increased prevalence of depression in multiple sclerosis
- c is best screened for using the Mini-Mental State Examination
- d can be treated with donepezil
- e has the same features as a subcortical dementia.

MCQ answers

1	2	3	4	5
a F	a T	a T	a F	a F
b F	b T	b T	b F	b F
c F	c T	c T	c F	c F
d T	d T	d F	d T	d T
e T	e T	e T	e F	e T