

Neuropsychiatric symptoms in multiple sclerosis

Andrew Sommerlad MBBS, BSc, MRCPsych, **Gary Price** MBChB, MRCPsych, MSc, PhD, **Anand Trip** BSc, MBChB, MRCP, PhD

Multiple sclerosis is associated with a high prevalence of psychiatric comorbidity, including affective, psychotic and cognitive disorders. In this review, Dr Sommerlad and colleagues discuss the epidemiology, aetiology and management of neuropsychiatric symptoms in multiple sclerosis, using case vignettes to demonstrate the wide range of clinical presentations.

Introduction

Multiple sclerosis (MS) is the commonest cause of neurological disability in young and middle-aged adults¹. The characteristic pathological features are demyelinating plaques, astrocytic gliosis and immune-mediated inflammation anywhere within the central nervous system, with the periventricular region, brainstem, juxtacortical region, optic nerves and spinal cord being particularly common targets. The neurological manifestations are diverse although usually reflect the function of the affected anatomical site, and the course of the illness is variable and initially difficult to predict with accuracy.

In 80-90% of cases, the illness is *relapsing-remitting* in nature with two thirds of these developing a *secondary progressive* form of the condition a variable number of years after onset and a third having a relapsing-remitting course which does not result in long-term serious disability; the remaining 10-20% of patients have a *primary progressive* course with gradually worsening symptoms². The prognosis can be poor in the long-term but progression is frequently slow; recent evidence suggests a median of 28 years before a stick is required for walking³.

The UK annual incidence of MS is 10/100,000 with a prevalence of 200/100,000⁴. There is estimated to be over 100,000 people suffering from the condition in the UK. The median age of onset is 31 years and it is approximately twice as common in women⁵. There is multifactorial aetiology with genetic and environmental factors shown to be important. There is 31% monozygotic concordance compared to 5% in dizygotic twins⁶ while the environmental influence is demonstrated by marked variations in prevalence in genetically homogenous populations⁷. Prevalence increases with increasing distance from the equator and those who emigrate in childhood have prevalence rates consistent with their adopted country.⁸

MS commonly presents with weakness, tingling or numbness in the limbs; diplopia, visual loss or impaired visual acuity; vertigo; dysarthria and ataxia; fatigue or bladder and bowel disturbance⁵. The array of presenting symptoms in MS can lead to diagnostic uncertainty and neuropsychiatric conditions such as somatisation disorder are sometimes suspected. A study demonstrated that 16% of patients with MS had been referred to a psychiatrist between the onset of neurological symptoms and diagnosis of MS. In spite of neurological symptoms being present in the majority of cases, these remained largely overlooked and diagnoses of conversion disorder and hysterical personality disorder were applied⁹. While neurological features are the most recognised manifestations of the

condition, psychopathology, including affective, psychotic and cognitive disorders, is also common in MS. The identification of these symptoms is often more difficult and diagnosis can be delayed. Psychiatric symptoms can occur at onset or later in the MS disease process and initial psychiatric symptoms tend to improve later than neurological symptoms and frequently never resolve¹⁰.

In this review article, we will describe a range of neuropsychiatric disorders which can develop in MS, illustrated by case vignettes from our clinical practice, and consider the most appropriate management.

Mood disorders

Depression

Case vignette 1 – Major depressive disorder

Andrea is a 45 year old woman with a 5 year history of relapsing-remitting MS with limb sensory deficit being the predominant feature. She presented with three month history of low mood, reduced motivation and feelings of hopelessness associated with suicidal thoughts. Cognitive assessment was normal and treatment with sertraline 100mg daily and cognitive behavioural therapy was initiated with good therapeutic effect at four month follow-up.

Depressive symptoms are common in patients with significant disability but distinction should be made between sufferers with these symptoms and those with the syndrome of major depression, which is characterised by pervasive mood change, diurnal mood variation, altered sleep and appetite and distorted beliefs including feelings of guilt and worthlessness and suicidal ideation. The lifetime prevalence of major depression in MS, replicated in a number of studies, is around 50% with a point prevalence of 14%¹¹, which is higher than matched populations with non-neurological disability and around three times higher than the general population.

Due to the potential overlap between somatic symptoms of depression and features of MS, clinicians should use a screening tool which gives weight to depressive thoughts to identify patients at risk of depression that warrant more detailed clinical interview. The Beck Depression Inventory¹² and Hospital Anxiety and Depression Scale¹³ are suitable and have been validated for patients with MS.

The identification of depression in people with MS is important as it is linked with lower quality of life, more functional impairment, poor cognitive function and reduced adherence to medication regimes¹⁴ as well as higher rates of suicide than the general population. Suicidal ideation is common in MS with a quarter of patients considering suicide at some point during their illness. Young males within five years of diagnosis are at highest risk of completed suicide while presence and severity of depression, social isolation and alcohol abuse are other notable risk factors¹³.

Biological and psychosocial factors are implicated in the aetiology of depression in MS. Evidence suggests that the individual's adjustment to adversity and their coping strategies is more closely related to physical deterioration than the severity of depression; loss of recreational opportunities and poor quality relationships are also important¹⁵. Studies have not demonstrated significant correlation between depression and plaque load¹⁶ but the location of lesions is significant. A higher lesion load in the anterior temporal lobe and inferior medial prefrontal cortex of the dominant

hemisphere as well as dominant anterior temporal lobe atrophy are associated with depression¹⁷. Genetic factors have not been shown to be relevant, while some have proposed that dysfunction in the hypothalamic-pituitary-adrenal axis underlies the increased risk of depression in MS.

There has been some concern in the past that the use of disease-modifying drugs (DMDs), particularly interferon- β , resulted in increased risk of depression and suicide. However, recent evidence has suggested that this is not the case and the value of interferon in maintaining remission in MS means that it should remain a treatment option in all individuals, including those with a past history of depression, but used with caution in those with severe depression. It is appropriate to screen high-risk individuals for depression following the initiation of treatment with DMDs and, if depression develops, the agent need not be stopped automatically, but depression should be treated using standard options¹⁸.

Several treatment options seem to be effective in treating depression in MS but the strength of evidence for any particular treatment is poor. Although open label trials and case-reports suggest efficacy of many different antidepressants in the treatment of depression in MS, there have been only two previous blinded randomised-controlled trials (RCT), of desipramine¹⁹ and paroxetine²⁰, which have shown only a non-statistically-significant trend towards improvement in the drug groups compared to placebo. Electroconvulsive therapy (ECT) shows efficacy in severe depression but can result in exacerbation of symptoms of MS²¹. Results from trials of individual or group psychological treatments have shown more promise and cognitive-behavioural therapy (CBT) can be helpful in mild-moderate depression and as effective as treatment with the antidepressant sertraline²². A well-conducted RCT of telephone-administered CBT compared to a control group of supportive therapy by telephone demonstrated a significant reduction in cases of depression and depressive symptoms after therapy but the difference between the groups were no longer significant at one year follow-up²³.

Treatment of depression in MS remains difficult and is poorly guided by evidence but the Golman Consensus Group recommends individualised treatment of moderate-severe depression with a combination of an antidepressant and a form of psychotherapy, either supportive, CBT or interpersonal therapy¹⁴.

Bipolar affective disorder

Co-occurrence of bipolar affective disorder (bipolar disorder) and MS is uncommon but prevalence of bipolar disorder in people with MS is at least double the expected rate²⁴ and a number of potential explanations have been proposed although none fully explain the association. Some can be attributed to the mania-inducing properties of steroids but a shared genetic diathesis has also been proposed²⁵. White matter hyperintensities are often reported in patients with bipolar disorder but these are not always seen and their aetiology is unclear. However, a study of patients with psychosis in MS demonstrated a predominance of plaques bilaterally in the temporal horn areas – this was common to both affective and schizophrenia-like presentations²⁶.

Management of bipolar disorder in MS is not guided by robust evidence but lithium and sodium valproate have previously been used with success. The diuretic effect of lithium in patients prone to bladder pathology and the potential for additional neurological impairment from lithium toxicity, however, necessitates caution in this patient group. The administration of exogenous steroids remains a mainstay of treatment in MS but care should be taken in those with a personal or family history of depression. The proven efficacy of lithium as prophylaxis against steroid-induced mania²⁷ suggests that careful monitoring of mental state on a reduced steroid dose, along with the addition of lithium, is likely to prove effective if a manic episode occurs during treatment.

Disorders of affect

Pseudobulbar affect

Pseudobulbar affect (PBA), synonymous with the condition of *pathological laughing and crying*, is characterised by uncontrollable laughing and/or crying without the associated subjective feelings of happiness or sadness and usually without any discernable stressor. PBA is socially and occupationally disabling and distressing for patients and their families. It is seen in around 10% of MS patients and is associated with long disease duration, a progressive course, cognitive impairment and greater physical disability²⁸. PBA is also seen in other neurological conditions, including Parkinson's Disease, Motor Neurone Disease and stroke. Cognitive assessment usually demonstrates poor performance on tasks involving prefrontal function. Structural brain changes predict pseudobulbar affect²⁹; bilateral medial inferior frontal and bilateral parietal hyperintense lesions and brainstem hypointense lesions are seen.

Use of the Centre for Neurologic Study Emotional Lability Scale, a seven-item self report tool, is recommended for screening¹². While treatment with small doses of amitriptyline, fluoxetine or levodopa has previously shown some benefit, new guidelines from the American Academy of Neurology propose the use of a combination of dextromethorphan and quinidine, which were shown in two RCTs to reduce emotional lability and significantly improve quality of life¹².

Euphoria

Case vignette 2 – Euphoria

Jane, a 22 year old woman with secondary progressive MS characterised by optic neuritis and limb weakness, presented to neurology outpatient clinic with her mother who was concerned about her inappropriate public behaviour; she would react with extreme excitement to unremarkable situations. She was inappropriate and incongruously optimistic during assessment while neuropsychological assessment showed mild frontal and subcortical deficit. Symptomatic treatment with sodium valproate yielded little benefit.

In possibly the earliest large study of neuropsychiatric problems in MS in 1926, Cottrell and Kinnier Wilson reported the presence of euphoria in 63 of 100 consecutive cases of disseminated sclerosis at Queen Square³⁰, although recent studies have suggested prevalence in MS sufferers to be around 10%³¹. Euphoria should not be confused with hypomania or mania seen in bipolar affective disorder. It is a fixed mental state change (rather than fluctuating as seen in mania) distinguished by unconcern over physical disability and incongruous optimism and is associated with more severe MS, greater physical disability, cognitive dysfunction, lack of insight and a severe, often frontal, brain

lesion load. It is seen in around 10% of MS sufferers and is likely to be related to impairment of the self-regulatory orbito-frontal network.

Psychotic disorders

Case vignette 3 – Psychotic episode

Simon is a 26 year old man who presented to the emergency department following two possible seizures and encephalopathy. He became emotionally labile and developed persecutory delusional ideas that he was the target of a conspiratorial plot. The addition of risperidone 2mg BD was effective in controlling these symptoms. MRI brain showed multiple white matter lesions in the corpus callosum and temporal horns which enhanced with gadolinium and CSF analysis revealed oligoclonal bands. The initial diagnosis was possible acute disseminated encephalomyelitis but treatment with interferon-beta was initiated after a year when he developed a sensory spinal cord syndrome characteristic of MS.

Although psychosis in people with MS is a rare occurrence, studies suggest that the prevalence rate surpasses that expected by chance³². The reason for this is unclear; it may be due to direct effect of demyelinating lesions as patients with MS and psychosis are more likely to have plaques affecting the temporal horns bilaterally²⁶ although a viral precursor to both conditions has also been proposed.

Affective and schizophrenia-like presentations are seen equally when MS patients become psychotic but the predominant presentation is one of positive psychotic symptoms (usually persecutory delusions) with relative lack of negative symptoms (apathy, restricted affect and thought²⁶). In addition, compared to schizophrenia, MS-related psychosis tends to present later (mean age around 36 years) and there is quicker resolution of symptoms, fewer psychotic relapses and a better long-term outcome with 60% of patients having only one psychotic episode over six year follow-up²⁶.

The evidence to favour a particular antipsychotic is scarce but atypical agents are preferred due to lower risk of adverse neurological effects; olanzapine, quetiapine and risperidone. As irritability and agitation is common in people with MS and psychosis, hospital admission is sometimes required and benzodiazepines are appropriate if added sedation is required.

Cognitive Disorders

Case vignette 4 – Cognitive impairment

Derek, a 20 year old man with a five year history of relapsing-remitting MS, was admitted to neuropsychiatry ward due to a two month history of disorganised behaviour at home. During assessment, his behaviour was bizarre at times and he displayed fixed, concrete thinking and impaired attention. He scored 30/30 on MMSE but was slow to answer some aspects of this screen. Formal neuropsychological testing demonstrated significant impairment in executive functioning and information processing speed with reduced naming and facial recognition.

Cognitive deficit in MS was described by Charcot in 1877 who noted that MS causes ‘marked enfeeblement of the memory, conceptions are formed slowly and intellectual and emotional faculties are blunted in their totality’³³. Slowed cognitive processing is present early in the disease and can be seen in people with clinically isolated syndromes – a single episode of demyelination in one area of the central nervous system, eg optic neuritis or brainstem or spinal cord syndrome – who had asymptomatic lesions elsewhere in the brain on Magnetic Resonance Imaging (MRI)³⁴. In people with established MS, around 40% have cognitive abnormalities³⁵. Risk factors for impaired cognitive function in MS are age greater than 40 years, low premorbid intelligence or educational

attainment and depression and cognitive impairment tends to develop alongside worsening physical disability, disease duration and the onset of a progressive disease course³⁵. Patients with a relapsing-remitting disease course generally perform better than those with progressive illness in whom the predominant deficit is executive function, rather than memory which is affected in relapsing remitting disease³⁶.

Cognitive dysfunction adversely affects daily functioning, employment and quality of life and is frequently missed in routine assessment; when a neurologist suspects cognitive impairment, they are correct in over 90% of cases but when they do not suspect cognitive impairment, they are wrong in half of cases³⁷. Thorough neuropsychological assessment is time-consuming and costly so approaches have been proposed to assess those in greatest need. The Mini-Mental State Examination is not useful in screening MS patients for cognitive impairment but screening using the Multiple Sclerosis Neuropsychological Screening Questionnaire³⁷, a 15-item self- or informant-rated measure of cognitive and neuropsychiatric problems which has been validated for use in MS, may be a helpful strategy. More thorough assessment using a battery of neuropsychological tests which assess the cognitive domains most affected in MS patients (processing speed, learning and memory, executive function, visuospatial processing and word retrieval) is recommended for people in whom cognitive dysfunction is suspected; the Minimal Assessment of Cognitive Function in MS battery is a valid approach to neuropsychological assessment in MS patients³⁸.

MS has been suspected of causing a subcortical pattern of cognitive deficit (ie forgetfulness, emotional or personality changes, slowed thought processes and impaired executive function) as it affects classic subcortical white matter tracts such as periventricular white matter tracts and the corpus callosum and this has been borne out by research; information processing speed, verbal memory, cognitive flexibility and executive function are all impaired³⁹.

The presentation of cognitive deficit in MS is variable. Cognitive function tends not to vary with other markers of relapse and remission and the syndrome of a rapidly progressive dementia is rare but there is usually a progressive course with more cognitive domains affected, and correlation with markers of physical disability and social dysfunction⁴⁰. Some patients can present with predominant severe cognitive impairment without significant impairment in other neurological domains and in these patients, brain atrophy is commonly seen on neuroimaging and DMDs are frequently ineffective⁴¹.

Cognitive impairment can be predicted on traditional MRI imaging by brain atrophy but not by the degree or location of demyelinating lesions⁴² although more advanced MRI techniques are showing more promise in this regard. The combination of structural and functional MRI imaging has demonstrated altered cerebral activation in MS patients performing as well as controls on tasks requiring attention while MS patients who performed worse on a planning ability task did not have abnormal brain activation, suggesting that compensatory mechanisms related to neuronal plasticity can mitigate the pathological changes but can become overwhelmed, leading to the manifestation of cognitive symptoms³⁵. There is also increasing evidence that grey matter pathology, reflected by atrophy, is implicated in cognitive dysfunction as MS progresses⁴³.

DMDs are the first-line of treatment for MS and secondary outcome data from some large RCTs have demonstrated that early treatment with interferon beta results in better processing speed and working memory⁴⁴ but no RCTs have assessed this as a primary outcome so the methodology does not allow sound conclusions to be drawn. Initial enthusiasm for the use of acetyl-cholinesterase inhibitors or memantine, which are used in dementia, has dispersed as they have been shown to be ineffective⁴⁵. Symptomatic treatment with the stimulants L-amphetamine and methylphenidate have been proposed by some authors but this is controversial⁴⁶.

Of non-pharmacological treatments, cognitive rehabilitation is likely to be the most effective and has two components; restoration of function and compensation for loss of function. Relying on neuronal plasticity, restorative approaches aim to identify specific cognitive deficits and introduce remedial therapies to increase performance in a given area, such as graded practice for improving memory. Compensatory strategies aim to maximise the use of the retained cognitive abilities in order to improve social and occupational function, such as using notebooks or calendars to record important information or appointments and developing time management skills³⁵.

Conclusions

An understanding of neuropsychiatric disorders in MS is important for all professionals involved in the care of people with MS. These disorders occur early in the disease, affect about half of patients at some point and have a significant impact on social/occupational function and quality of life. Furthermore, they negatively affect patients' ability to adhere to the recommended treatment regimens for other neurological symptoms in MS. Timely detection is essential as therapies can often be successful and improve quality of life, although the paucity of empirical treatment data demonstrates the need for targeted research on the management of these disorders.

Declaration of interests

None related to the subject of this article.

Author roles

Dr Sommerlad is a clinical training fellow in Old Age Psychiatry at University College London and Camden & Islington NHS Foundation Trust. Dr Price is a Consultant Neuropsychiatrist & Honorary Senior Lecturer and Dr Trip is a Consultant Neurologist & Honorary Senior Lecturer at the National Hospital for Neurology and Neurosurgery, Queen Square, UCLH NHS Foundation Trust, London.

Figures

Table 1

Useful Assessment Schedules	
Depression	Beck Depression Inventory, Hospital Anxiety and Depression Scale
Pseudobulbar Affect	Centre for Neurologic Study Emotional Lability Scale
Cognitive function Screening	Multiple Sclerosis Neuropsychological Screening Questionnaire
Neuropsychological assessment	Minimal Assessment of Cognitive Function in MS

Table 2

Treatment options in multiple sclerosis	
Depression	Sertraline, CBT
Mania	Lithium, Sodium valproate
Pseudobulbar palsy	Dextromethorphan and Quinidine

Psychosis	Olanzapine, Quetiapine, Risperidone
Cognitive impairment	Disease modifying drugs. Cognitive rehabilitation

Table 3

Key Points
Neuropsychiatric disorders are common in MS, especially depression and cognitive impairment which affect around 50% of individuals at some point.
They can occur at any time in the disease process but are rarely the first presenting symptom.
Untreated neuropsychiatric symptoms result in worse social and occupational function and reduced quality of life.
Neuropsychiatric are under-recognised but appropriate screening and diagnostic tools are available.
There should be close liaison between psychiatry and neurology teams to achieve holistic management of these disorders.

-
- ¹ Leary S, Giovannoni G, Howard R, *et al.* Multiple Sclerosis and Demyelinating Diseases. In: Clarke C, Howard R, Rossor M, Shorvon S, eds. *Neurology: A Queen Square Textbook*. Oxford: Wiley-Blackwell, 2009; 411-48
- ² Sibley W. Diagnosis and course in multiple sclerosis. In: Rao S, ed. *Neurobehavioural aspects of multiple sclerosis*. New York: Oxford University Press, 1990; 5-14
- ³ Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. *Neurology* 2006; 66: 172-77
- ⁴ Mackenzie I, Morant S, Bloomfield G, *et al.* Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry* 2014; 85: 76-84
- ⁵ McDonald W, Ron M. Multiple sclerosis: the disease and its manifestations. *Phil Trans R Soc Lond* 1999; 354: 1615-22
- ⁶ Sadnovik A, Armstrong H, Rice G, *et al.* A population-based study of twins in multiple sclerosis: update. *Ann Neurol* 1993; 33: 281-85
- ⁷ Miller D, Morrissey S, McLeod J, *et al.* Multiple sclerosis in Australia and New Zealand: are the determinants genetic or environmental? *J Neurol Neurosurg Psychiatry* 1990; 53: 903-05
- ⁸ Dean G. Annual incidence, prevalence and mortality of multiple sclerosis in white South-African-born and in white immigrants to South Africa. *BMJ* 1967; 2: 724-30
- ⁹ Skegg K, Cormin P, Skegg D. How often is multiple sclerosis mistaken for a psychiatric disorder? *Psychol Med* 1988; 18: 733-36
- ¹⁰ Lo Fermo S, Barone R, Patti F, *et al.* Outcome of psychiatric symptoms presenting at onset of multiple sclerosis: a retrospective study. *Mult Scler* 2010; 16: 742-48
- ¹¹ Sadovnik A, Remick R, Allen J, *et al.* Depression and multiple sclerosis. *Neurology* 1996; 46: 628-32
- ¹² Minden S, Feinstein A, Kalb R. Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014. e-pub ahead of print. Doi: 10.1212/WNL.000000000000013
- ¹³ Feinstein A. Multiple sclerosis and depression. *Mult scler* 2011; 17: 1276-81
- ¹⁴ Golman Consensus Group. The Goldman Consensus Group statement on depression in multiple sclerosis. *Mult Scler* 2005; 11: 328-37
- ¹⁵ Lynch S, Kroencke D, Denney D. The relationship between disability and depression in multiple sclerosis: the role of uncertainty, coping and hope. *Mult Scler* 2001; 7: 411-16
- ¹⁶ Ron M, Logsdail S. Psychiatric morbidity in multiple sclerosis: a clinical and MRI study. *Psychol Med* 1989; 19: 887-95
- ¹⁷ Vattakatchery J, Rickards H, Cavanna A. Pathogenic mechanisms of depression in multiple sclerosis. *J Neuropsychiatry Clin Neurosci* 2011; 23: 261-76
- ¹⁸ Goeb J-L, Even C, Nicolas G, *et al.* Psychiatric side effects of interferon- β in multiple sclerosis. *Eur Psychiatry* 2006; 21: 186-93
- ¹⁹ Schiffer R, Wineman N. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *Am J Psychiatry* 1990; 147: 1493-97
- ²⁰ Ehde D, Kraft G, Chwistak L, *et al.* Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. *Gen Hosp Psychiatry* 2008; 30: 40-48
- ²¹ Krystal A, Coffey C. Neuropsychiatric considerations in the use of electroconvulsive therapy. *J Neuropsychiatry Clin Neurosci* 1997; 9: 283-92
- ²² Mohr D, Boudewyn A, Goodkin D, *et al.* Comparative outcomes for individual cognitive-behavioural therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *J Consult Clin Psychol* 2001; 69: 942-49
- ²³ Cosio D, Jin L, Siddique J, *et al.* The effect of telephone-administered cognitive-behavioural therapy on quality of life among patients with multiple sclerosis. *Ann Behav Med* 2011; 41: 227-34
- ²⁴ Schiffer R, Wineman N, Weitcamp L, *et al.* Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatr* 1986; 143: 94-95
- ²⁵ Kosmidis M, Bozikas V, Giannouli V, *et al.* Familial comorbidity of bipolar disorder and multiple sclerosis: Genetic susceptibility, coexistence or causal relationship? *Behav Neurol* 2012; 25: 341-49
- ²⁶ Feinstein A, Du Bourlay G, Ron M. Psychotic illness in multiple sclerosis. A clinical and magnetic resonance imaging study. *BJ Psych* 1992; 161: 680-85
- ²⁷ Falk W, Mahnke M, Poskanzer D. Lithium prophylaxis of corticotropin-induced psychosis. *J Amer Med Assoc* 1979; 24: 1011-12
- ²⁸ Wortzel H, Oster T, Anderson C, *et al.* Pathological laughing and crying: epidemiology, pathophysiology and treatment. *CNS Drugs* 2008; 22: 531-45
- ²⁹ Ghaffar O, Chamelian L, Feinstein A. Neuroanatomy of pseudobulbar affect: a quantitative MRI study in multiple sclerosis. *J Neurol* 2008; 253: 406-12
- ³⁰ Cottrell S, Kinnier Wilson S. The affective symptomatology of disseminated sclerosis. *J Neurol Psychopathol* 1926; 7: 1-30
- ³¹ Chiaravalloti N, Deluca J. Assessing the behavioral consequences of multiple sclerosis: an application of the Frontal Systems Behavior Scale (FrSBe). *Cogn Behav Neurol* 2003; 16: 54-67

-
- ³² Patten S, Svenson L, Metz L. Psychotic disorders in MS: population-based evidence of an association. *Neurology* 2005; 65: 1123-25
- ³³ Charcot J-M. Lectures on the diseases of the Nervous System delivered at La Salpêtrière. London: New Sydenham Society, 1877; 194-95
- ³⁴ Callanan M, Logsdail S, Ron M, *et al.* Cognitive impairment in patients with clinically isolated lesions of the type seen in multiple sclerosis: a psychometric and MRI study. *Brain* 1989; 112: 361-74
- ³⁵ Messinis L, Kosmidis M, Lyros E, *et al.* Assessment and rehabilitation of cognitive impairment in multiple sclerosis. *Int Rev Psychiatr* 2010; 22: 22-34
- ³⁶ Zakzanis K. Distinct neurocognitive profiles in multiple sclerosis subtypes. *Arch Clin Neuropsych* 2000; 15: 115-36
- ³⁷ Benedict R. Integrating cognitive function screening and assessment into the routine care of multiple sclerosis patients. *CNS Spectr* 2005; 10: 384-91
- ³⁸ Benedict R, Cookfair D, Gavett R, *et al.* Validity of the Minimal Assessment of Cognitive Function in Multiple Sclerosis. *J Int Neuropsych Soc* 2006; 12: 549-58
- ³⁹ Calabrese P. Neuropsychology of multiple sclerosis: An overview. *J Neurol* 2006; 253: 10-15
- ⁴⁰ Feinstein A. The natural history of cognitive change in MS. In: Feinstein A, ed. *The clinical neuropsychiatry of multiple sclerosis* 2nd edition. Cambridge: Cambridge University Press, 2007; 145-54
- ⁴¹ Staff N, Lucchinetti C, Keegan B. Multiple sclerosis with predominant, severe cognitive impairment. *Arch Neurol* 2009; 66: 1139-43
- ⁴² Benedict R, Weinstock-Guttman B, Fishman I, *et al.* Prediction of neuropsychological impairment in multiple sclerosis. Comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol* 2004; 61: 226-30
- ⁴³ Penny S, Summers M, Swanton J, *et al.* Changing associations between cognitive impairment and imaging in multiple sclerosis as the disease progresses. *J Neuropsychiatry Clin Neurosci* 2013; 25: 134-40
- ⁴⁴ Kappos L, Freedman M, Polman C, *et al.* Effect of early versus delayed interferon beta 1-b treatment on disability after a first clinical event suggestive of multiple sclerosis: A three year follow-up analysis of the BENEFIT study. *Lancet* 2007; 370: 389-97
- ⁴⁵ Krupp LB, Christodoulou C, Melville P. Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis. *Neurology* 2011; 76: 1500-7
- ⁴⁶ Patti F. Treatment of cognitive impairment in patients with multiple sclerosis. *Expert Opin Investig Drugs* 2012; 21: 1679-99