RESEARCH ARTICLE

The neuropsychiatry of multiple sclerosis: Focus on disorders of mood, affect and behaviour

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Abstract

Neuropsychiatric symptoms are common in multiple sclerosis (MS). They include two broad categories of disturbances: abnormalities in cognition, and abnormalities of mood, affect and behaviour. The present review deals with the epidemiology, clinical features, etiology and treatment of disturbances included in the second category, i.e., major depression, fatigue and sleep disorders, bipolar disorder, euphoria, pathological laughing and crying, anxiety, psychosis and personality changes. Major depression is one of the most common neuropsychiatric disorders in MS with an approximate 50% lifetime prevalence rate. Early recognition and management of depression in MS is of major importance because it is a key predictor of morbidity, mortality, quality of life, possibly physical outcome and disease exacerbations, adherence to immunomodulatory treatments and suicide risk in MS patients, as well as of the caregiver’s distress and quality of life. The etiopathogenesis of neuropsychiatric disorders in MS has been incompletely investigated. It is postulated that a complex interplay of biological, disease-related, behavioural and psychosocial factors contribute to the pathophysiology of most of them. Management of neuropsychiatric symptoms in MS is often effective, although commonly based on evidence provided by case studies and uncontrolled trials. A comprehensive biopsychosocial neuropsychiatric approach is essential for the optimal care of patients with MS.

Keywords: Multiple sclerosis, neuropsychiatry, disorders, mood, affect, behaviour

Introduction

Multiple sclerosis (MS), the most frequent demyelinating disease of the central nervous system (CNS) in populations of European origin, is also the most common non-traumatic cause of neurological disability in young and middle-aged adults in the western world. MS can affect any part of the CNS with a predilection for white matter tracts in the cerebral hemispheres, optic nerves, brainstem, cerebellum, and spinal cord. Its cardinal clinical features include motor and sensory symptoms, such as impaired vision, weakness, cerebellar signs, bowel and bladder dysfunction and sensory deficits, as well as neuropsychiatric symptoms. The latter are in fact quite common (Diaz-Olavarrieta, Cummings, Velazquez, & Garcia de la Cadena, 1999) and include two broad categories of disturbances: abnormalities in cognition, and abnormalities of mood, affect and behaviour; partial overlap can exist between the two categories as expected. The present review focuses on the epidemiology, clinical features, etiology and treatment of disturbances included in the second category, such as major depression, fatigue and sleep disorders, bipolar
disorder, euphoria, pathological laughing and crying, anxiety, psychosis and personality changes.

Most studies have focused on a single or a few psychiatric symptoms in MS patients, such as depression and anxiety. Few studies have investigated the full range of neuropsychiatric syndromes assessed with specifically developed tools (Diaz-Olavarrieta et al., 1999; Figved et al., 2005). In such a study, mild neuropsychiatric symptoms as assessed with the Neuropsychiatric Inventory (Cummings et al., 1994) were found to be almost always present among MS patients (95%) even when their disease was at an early stage or of mild severity (Diaz-Olavarrieta et al., 1999). Symptoms of depression and/or dysphoria were the most frequent, occurring in nearly 80% of the patients; agitation, anxiety, and irritability were present in one third of patients. Apathy, euphoria, disinhibition, hallucinations, purposeless behaviours, and delusions occurred in a smaller number of patients. Rarely, neuropsychiatric symptoms, especially cognitive deficits, can be the presenting manifestation of the disease, correlating more strongly with otherwise silent brain lesions than neurological symptoms and signs (Feinstein, Kartsounis, Miller, Youl, & Ron, 1992b). Symptoms of apathy and depression have been also closely associated with higher levels of cognitive impairment in MS patients (Demaree, Gaudino, & DeLuca, 2003; Feinstein, 2006; Figved et al., 2008). Moreover, the severity of neuropsychiatric symptoms has been found to correlate with caregiver’s distress and quality of life, even after controlling for level of disability due to neurological symptoms (Figved, Myhr, Larsen, & Aarsland, 2007).

Major depression

Major depression (MD) is the most common neuropsychiatric disorder encountered in MS (Minden & Schiffer, 1990). Major depression lifetime prevalence rates in patients with MS are close to 50%, i.e. three times higher than in the general population, depending on the criteria used and the clinical settings of the studies (community, outpatients or tertiary clinics) (Minden & Schiffer, 1990; Patten, Beck, Williams, Barbui, & Metz, 2003; Schubert & Foliart, 1993). The phenomenology of depression in MS is essentially similar to that of primary MD, although some suggest that irritability may be more common than guilt and low self-esteem (Minden, Orav, & Reich, 1987). However, several symptoms shared by both MD and MS (such as fatigue, poor concentration, sleep and appetite disturbances) can impede the detection of MD in MS (Ferentinos, Kontaxakis, Havaki-Kontaxaki, Paplos, & Soldatos, 2007); in fact, MD continues to be under-diagnosed and under-treated in MS patients (McGuigan & Hutchinson, 2006). The validation of specific rating scales excluding the physical symptoms items, such as the 7-item Beck Fast Screen for Medically Ill Patients (Beck, Steer, & Brown, 2000; Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003), has helped clinicians screen MD symptoms in MS patients despite symptom overlap between the two disorders. Early recognition and management of MD in MS patients is of utmost importance because depression is a major contributor of morbidity and mortality and a key predictor of quality of life (D’Alisa et al., 2006), possibly physical outcome and disease exacerbations (Dalos, Rabins, Brooks, & O’Donnell, 1983; Figved et al., 2005), cognitive functioning (Arnett et al., 1999; Demaree et al., 2003; Feinstein, 2006), adherence to immunomodulatory treatments (Mohr et al., 1997) and suicide risk in these patients (Feinstein, 2002). Patients with MS have a significantly increased rate of suicide compared with the general population as well as patients with other neurological disorders (Sadovnick, Eisen, Ebers, & Paty, 1991). Risk factors for suicidal ideation and behaviour in MS include male gender, social isolation, substance misuse, current or previous diagnosis of MD and a younger age at onset (Feinstein, 2002; E. N. Stenager, Koch-Henriksen, & E. Stenager, 1996).

Both biological and psychosocial variables are thought to be implicated in the etiopathogenesis of MD in MS. Most data on the contribution of genetic factors to MS-related MD are negative (Joffe, Lippert, & Gray, 1987; Minden et al., 1987), although some more recent studies have presented opposite findings (Patten, Metz, & Reimer, 2000). Structural neuroimaging provides some evidence that a higher lesion load in the medial inferior prefrontal cortex and anterior temporal lobe in the dominant hemisphere, as well as dominant anterior temporal atrophy, are associated with depression, accounting for over 40% of the depression variance (Bakshi et al., 2000a; Feinstein et al., 2004; Pujol, Bello, Deus, Martí-Vilalta, & Capdevila, 1997). Functional neuroimaging may allow a more thorough investigation of the neuroanatomical correlates of MD in MS (Sabatini et al., 1996). Other investigators have suggested that immune abnormalities, in association with a dysfunctioning hypothalamic–pituitary–adrenal axis, may be the mechanism underlying MD in MS (Fassbender et al., 1998; Michelson et al., 1994; Pucak, Carroll, Kerr, & Kaplin, 2007). Early concerns about the potential depressogenic effect of disease-modifying treatments, particularly interferons beta-1a and beta-1b, have been mitigated by subsequent studies; however, caution is recommended for patients with a pre-morbid history of depression (Feinstein, 2000). A younger age at onset and shorter disease duration...
have been associated with increased risk of depression (Beiske et al., 2008), whereas data on the relationship between depression and physical disability, as measured by the Expanded Disability Status Scale (EDSS), are contradictory (Chwastiak et al., 2002; Figved et al., 2005; Janssens et al., 2006). The burden of adjusting to a chronic, progressive illness possibly plays a role in the development of depression as well. Psychosocial determinants of liability to depression include uncertainty about the future, helplessness, hopelessness, inadequate coping strategies (avoidant or emotion-centred coping as opposed to active, problem-centred coping), poor social relationships, loss of recreational activities, high levels of stress, and fatigue, which may all account for up to another 40% of the depression variance (Lynch, Kroencke, & Denney, 2001; Patten et al., 2000). Therefore, the etiology of MD in patients with MS is most likely multifactorial; a complex interplay of premorbid predisposing factors, biological disease-related effects and individual circumstances apparently contribute to the emergence of the depressive phenotype.

Treatments of MS-related MD lack rigorous evidence-based accreditation. There is only one randomized controlled trial of an antidepressant, namely desipramine, in MS patients (Schiffer & Wineman, 1990). Open-label trials and case-reports have given promising results for selective serotonin reuptake inhibitors (SSRIs) and monoaminooxidase inhibitors (Barak, Ur, & Achiron, 1999; Flax, Gray, & Herbert, 1991). Electroconvulsive therapy (ECT) may be helpful in the management of severe treatment-resistant depression (Krystal & Coffey, 1997) despite a 20% risk of exacerbation in MS symptoms following ECT (Mattingly, Baker, Zoromski, & Figiel, 1992). Individual or group psychotherapy, in particular cognitive–behavioural therapy (CBT), can be helpful for mild to moderate depression, and in more severe cases it can be a useful adjunct to antidepressants (Larcombe & Wilson, 1984; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). In fact, 16 weeks of CBT were shown to be equally effective as sertraline treatment in depressed MS patients (Mohr et al., 2001). The Goldman Consensus Group on depression in MS concluded that optimal treatment for patients with moderate to severe depression should be individualized and include a combination of an antidepressant and a form of psychotherapy, be it supportive, CBT or interpersonal (Schiffer et al., 2005).

**Fatigue and sleep disorders**

Fatigue may be the most frequent symptom in MS with a prevalence up to 75–85%; 50–60% of patients consider it as the most disabling symptom of the disease with adverse effects on their quality of life, mood, cognitive and social functioning (Bakshi et al., 2000b; Schreurs, de Ridder, & Bensing, 2002). However, little is known about predictors of MS-related fatigue. Reportedly it is not related to gender, age, educational status, neuropsychological performance or neuroanatomical findings (Bakshi et al., 1999) and it is weakly or moderately associated with disease duration, level of physical disability as measured with the EDSS, and the progressive forms of the disease (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Trojan et al., 2007).

Despite its importance, fatigue is inadequately understood and has been difficult to define (Rosenberg & Shafor, 2005). It has often been divided into motor fatigue and mental fatigue, the former referring to physical weakness developing following sustained muscle activity (Ford, Trigwell, & Johnson, 1998), and the latter to an overwhelming sense of tiredness or exhaustion out of proportion to the associated level of activity (Freal, Kraft, & Coryell, 1984). A useful working definition has been recently proposed, defining MS fatigue as ‘a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities’ (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998).

The etiopathogenesis of MS-related fatigue is unknown. Two forms of fatigue have been suggested: primary (disease-related) and secondary (related to comorbid conditions). Therefore, fatigue in MS is multidimensional and a point of overlap of various contributors, such as the disease itself, comorbid depression and sleep disorders (Ferentinos et al., 2009a). The following factors are thought to be implicated in the pathogenesis of the symptom: axonal demyelination and associated conduction delay in central pathways, monoamine neurotransmitter systems disturbance, localized dysfunction in various brain regions, immune dysfunction (disease-related and side-effect of immunomodulatory treatments), increased muscle energy demands due to spasticity, physical deconditioning, pain, autonomic instability, sleep disorders, psychological variables (depression, anxiety, helplessness, feeling of loss of control over symptoms) and personality traits (Attarian, Brown, Duntley, Carter, & Cross, 2004; Bakshi et al., 2000b; Lobentanz et al., 2004; Merkelbach, Dillmann, Kolmel, Holz, & Muller, 2001; Schreurs et al., 2002; Trojan et al., 2007).

Regarding the treatment of fatigue in MS, once depression has been ruled out, the most commonly used agents are amantadine and modafinil. Amantadine, an antiviral agent with dopaminergic properties and minimal side effects, has been shown to be moderately effective (Krupp et al., 1995). Modafinil, an agent developed for the treatment of
narclepsy, has also shown promise and is generally well tolerated (Rammohan et al., 2002). Exercise training programmes may be an alternative approach to MS-related fatigue (Mostert & Kesselring, 2002; Oken et al., 2004).

Sleep problems are more frequent in patients with MS (reported in over 50%) than in the general population, albeit clinically under-recognized by most physicians (Bamer, Johnson, Amtmann, & Kraft, 2008). The most common sleep disorders in this population are insomnia, nocturnal movement disorders, sleep-disordered breathing, narcolepsy, and REM sleep behaviour disorder. Sleep disturbances in MS patients can be primary (disease-related) or secondary to pain, spasticity, nocturia, depression and medication side-effects (Attarian et al., 2004; Lobentanz et al., 2004; Soldatos & Paparrigopoulos, 2005). Clinicians should be aware that poor sleep is an independent predictor of quality of life in MS patients (Merlino et al., 2009).

**Bipolar disorder**

Bipolar disorder (BD) is twice as common in MS as in the general population (Schiffer, Wineman, & Weitkamp, 1986). Research findings on the comorbidity of BD and MS are limited. Only part of the recorded association is accounted for by the well-known mania-inducing properties of steroids (Minden, Orav, & Schildkraut, 1988). Data on the contribution of genetic vulnerability to the emergence of BD in MS patients have been scarce and contradictory (Joffe et al., 1987; Schiffer et al., 1986). There are no studies investigating neuroanatomical correlates in MS patients with BD, although there is MRI evidence suggesting that patients with psychotic mania have predominantly bilateral plaques in the temporal horn areas (Feinstein, du Boulay, & Ron, 1992a). In the absence of published treatment trials, anecdotal reports suggest management with mood stabilisers (lithium, valproate, carbamazepine), antipsychotics and benzodiazepines. In the case of steroid-induced mania, lithium prophylaxis and reduction of steroid dose may allow clinicians to avoid steroid treatment discontinuation (Falk, Mahnke, & Poskanzer, 1979).

**Euphoria**

‘Euphoria sclerotica’ describes a fixed mental state of unusual cheerfulness and optimism about the future despite the presence of significant neurological disability. Euphoria should best be considered as a personality change and it is distinct from hypomania in spite of having some superficial similarities with it (Surridge, 1969). In an influential early paper, euphoria was reported in over two thirds of patients and was considered as pathognomonic of the disease (Cottrell & Wilson, 1926). This proved to be a gross overestimation, largely due to selection bias. Patients were also reported to present ‘eutonia sclerotica’, i.e. physical well-being with a lack of concern about physical disability. Studies until 1990 reported a median prevalence of 25% in MS (Rabins, 1990). Estimates have since declined to a mere 10 to 15%, with emotional lability and pseudobulbar affect emerging as distinct entities (Díaz-Olivarrieta et al., 1999; Fishman, Benedict, Bakshi, Priore, & Weinstock-Gutman, 2004). Euphoric MS patients have a high EDSS score, significant cognitive impairment, lack of insight, a progressive disease course, enlarged ventricles, significant cerebral atrophy and a high MRI lesion load, often with a more frontal distribution (Rabins, 1990).

**Pathological laughing and crying**

Pathological laughing and crying (PLC) is a condition characterized by frequent, sudden outbursts of uncontrollable crying and/or laughing that are disproportionate or incongruent to underlying feelings or external triggers (Wortzel, Oster, Anderson, & Arciniegas, 2008). Alternative terms often used to describe this syndrome are pseudobulbar affect, emotional incontinence, affective lability, organic or pathological emotionalism and involuntary emotional expression disorder (Cummings, 2007). The condition is distinct from emotional lability, although considerable overlap may exist. It is associated with various neurological disorders, such as stroke, Parkinson’s disease, traumatic brain injury, dementia, amytrophic lateral sclerosis, and MS. PLC is prevalent in about 10% of MS patients (A. Feinstein, O’Connor, Gray, & K. Feinstein, 1999b). Patients with the syndrome tend to have longer disease duration, more extensive disease, greater cognitive decline and higher disability scores (A. Feinstein, K. Feinstein, Gray, & O’Connor, 1997). PLC can be socially and occupationally disabling and is a source of distress for affected patients and their families. However, it is largely ill-recognized or misdiagnosed in clinical settings. An important first attempt in the recognition and accurate measurement of PLC has been accomplished with the introduction of specific rating scales, such as the interviewer-administered Pathological Laughter and Crying Scale validated for use with stroke victims (Robinson, Parikh, Lipsey, Starkstein, & Price, 1993) and the self report Center for Neurologic Study-Lability Scale validated for use with MS patients (Moore, Gresham, Bromberg, Kasarkis, & Smith, 1997).

The basic mechanisms implicated in affective lability are not well understood. Presumably, PLC results from interruption of cortical inhibition of
postulated laughing and crying centres in the upper brainstem or from lesions in the cerebro-ponto-cerebellar pathways involved in appropriate adjustment to social/cognitive context (Parvizi, Anderson, Martin, H. Damasio, & A.R. Damasio, 2001). Furthermore, the monoaminergic neurotransmitter systems are thought to have a role in the manifestation of PLC episodes (Wortzel et al., 2008). Treatment of the PLC syndrome has included, with varying success, behavioural interventions and pharmacological agents. SSRIs are recommended as first-line pharmacotherapy (Nahas, Arlinghaus, Kotrla, Clearman, & George, 1998). PLC usually responds to treatment much faster than depression (often in 1–3 days); this difference suggests that PLC and depression are distinct entities, although they frequently co-occur in neurological disease. When SSRIs are ineffective or poorly tolerated, tricyclic (Robinson et al., 1993; Schiffer, Herndon, & Rudick, 1985) and novel dual-action antidepressants, venlafaxine (Smith, Montalegre-Orjuela, Douglas, & Jenkins, 2003), duloxetine (Ferentinos et al., 2009b), mirtazapine (Kim et al., 2005), lamotrigine (Ramasubbu, 2003), levodopa (Udaka, Yamao, Nagata, Nakamura, & Kameyama, 1984), and dextromethorphan/quinidine (Panitch et al., 2006) have been reported as second-line PLC treatments.

Anxiety

Symptoms of anxiety among MS patients have not been well-studied and are often overlooked and under treated. The prevalence of anxiety disorders in MS populations varies from 14% to 41%, with a female preponderance (Beiske et al., 2008; Janssens et al., 2003; Korostil & Feinstein, 2007). An increase in frequency of reported anxiety symptoms is often recorded soon after announcement of the diagnosis to MS patients (Janssens et al., 2003). Anxiety often co-occurs with depression and is associated with increased suicidal ideation, more physical complaints, greater social dysfunction, and excessive alcohol consumption (A. Feinstein, O’Connor, Gray, & K. Feinstein, 1999a; Korostil & Feinstein, 2007). A recent study reported the following lifetime prevalence rates of anxiety disorders in MS patients: generalized anxiety disorder (18.6%), panic disorder (10%), obsessive-compulsive disorder (8.6%), and social anxiety disorder (7.8%) (Korostil & Feinstein, 2007). On the other hand, stress and anxiety (along with depression) have often been regarded as precipitants of MS relapses (Buljevac et al., 2003). Therefore, management of psychosocial burden could help avert or delay disease exacerbations.

Psychosis

Most reports of MS and psychosis are single case studies and until recently the co-occurrence of the two disorders was believed to be uncommon. An early comprehensive literature review identified 39 case reports, which alluded to a frequency estimated not to exceed chance expectation (Davison & Bagley, 1969). However, a recent study has challenged previous beliefs suggesting an elevated rate of psychosis (2–3%) in patients with MS compared to the general population (Patten, Svenson, & Metz, 2005). The phenomenology of MS-related psychosis and schizophrenia is essentially similar, but the former is characterized by more frequent complex delusional states, relatively intact affective responses, seldom seen negative symptoms, later onset, better prognosis with faster symptom resolution, better response to treatment, and fewer relapses (Davison & Bagley, 1969; Feinstein et al., 1992a).

The etiopathogenesis of psychosis in MS is unknown. The role of premorbid vulnerability (genetic, psychiatric history) has not been adequately investigated. Some researchers have suggested that psychosis is associated with certain demyelinating lesions; a higher lesion load in the medial temporal lobe regions bilaterally has been recorded in MS patients with psychosis (Feinstein et al., 1992a). Others have postulated that psychosis and MS share a common pathophysiological pathway, possibly exposure to a virus at a critical developmental stage (Sanders et al., 1996). The psychosis-inducing effects of medications, such as steroids and interferons, have also been proposed to contribute to the increased prevalence of psychosis in MS (Sechi, Piras, Demurtas, Tanca, & Rosati, 1987). There are no published treatment trials. On the basis of anecdotal evidence, small dose atypical antipsychotics are generally preferred, mainly because of the reduced risk of extrapyramidal side-effects.

Personality changes

Personality changes occur in MS but have received relatively little attention. An early investigation recorded irritability in 40.7% and apathy in 10% of MS patients (Surridge, 1969). In a subsequent study the figures were quite similar, i.e. irritability (35%), apathy (20%), and disinhibition (13%) (Diaz-Olavarrieta et al., 1999); in the most recent report, irritability/emotional lability (42%) and apathy (31%) came out as unique disease manifestations independent of disability and duration of disease (Figved et al., 2005). Purportedly, the type of personality change is determined by the location and extent of brain lesions and atrophy. Demyelinating lesions are postulated to cause these
Concluding remarks

Neuropsychiatric symptoms are present in the majority of patients with MS even in the early stages of the disease. Major depression is the most common neuropsychiatric disorder in MS and a key determinant of morbidity, mortality, patient quality of life and possibly disease progression; it has also been found to correlate with the caregiver’s distress and quality of life. Therefore, early recognition and effective management of depression and other neuropsychiatric symptoms are essential parts of optimal care for patients with MS. A comprehensive biopsychosocial neuropsychiatric, and not strictly neurological, approach is warranted in the diagnostic and treatment modalities provided to patients with MS.

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References


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