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The Psychiatric Manifestations of Multiple Sclerosis and their Treatment

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Abstract

Multiple sclerosis (MS) is a potentially disabling disease of the central nervous system (CNS). It could be manifested by physical and psychological symptoms. The historical background, etiology, diagnosis and treatment of MS with disease-modifying therapies are briefly summarized. The psychiatric manifestations of MS and their treatment are reviewed and include major depression, bipolar disorder, psychosis, anxiety, insomnia, personality changes, cognitive impairment, pseudobulbar affect and substance use disorders.

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Introduction

Multiple sclerosis (MS) is the most common autoimmune demyelinating and neurodegenerative disease of the central nervous system, and the leading cause of nontraumatic neurological disability in young adults[1]. Demyelinating diseases of the nervous system occur because of damage of the myelin sheath of neurons. This damage impairs the conduction of signals in the affected nerves. In turn, the reduction in conduction ability causes deficiency in sensation, movement, cognition or other CNS functions depending on the location of the involved nerves. Clinically MS is expressed in several forms with new symptoms either occurring in isolated attacks usually termed the relapsing form or the building up of symptoms over time referred to as the progressive forms [2]. Patients with MS could experience complete remission of symptoms in between attacks; however permanent neurological complications often persist as the disease advances [3]. Specific symptoms can include vision difficulty, with diplopia, blurred vision, weakness, gait disturbance, vertigo, fatigue, urinary retention and incontinence and speech and swallowing difficulties Bowel control and sexual dysfunction could also occur [4]. The psychiatric manifestations of MS could include major depression, bipolar disorder, psychosis, anxiety, insomnia, personality changes, cognitive impairment, pseudobulbar affect and substance use disorders [5].

Historical Background

The history of MS could be traced back to 1846, when Augustus d'Este, a grandson of King George III, first documented the case of the disease and kept a diary of its symptoms, which subsequently were thoroughly indexed over the issuing years [6]. The term multiple sclerosis was first described in 1868 by the French neurologist Jean-Martin Charcot to refer to the numerous glial scars, plaques or lesions that develop on the brain white matter and spinal cord [7]. In 1935, Dr. Thomas Rivers created an animal model that showed the nerve tissue was at the heart of the cause of MS rather than the original model that was used to study the illness as a virus described as experimental allergic encephalomyelitis (EAE) [8].

Etiology

The precise etiology of MS is still unclear. It has been proposed that MS is an autoimmune disorder of the central nervous system resulting from interactions between environmental stimuli, infections in genetically susceptible individuals [9]. MS is considered a single disorder with clinical variants that may consist of several related conditions with distinct immunologic, pathologic and genetic features [10].

Diagnosis

MS is a clinical diagnosis that relies on a detailed history and a comprehensive physical examination. Magnetic resonance imaging (MRI) is considered the test of choice to support the clinical diagnosis of MS [11]. In addition to MRI which has become the established tool in diagnosing and monitoring MS progression; cerebrospinal fluid studies and determination of CSF-specific oligoclonal bands, visual evoked potentials, optical coherence tomography, antinuclear antibody (ANA) titer and erythrocyte sedimentation rate (ESR) can be useful in the evaluation of suspected MS when the clinical presentation and the MRI findings

are insufficient to support its diagnosis [12]. Measuring vitamin B12 level, homocysteine, folate, thyroid-stimulating hormone levels (TSH), serologic testing for syphilis and a complete blood cell count (CBC) could be ordered to rule out vitamin deficiency, thyroid dysfunction, and infections [13]. In certain geographic setting known for Lyme disease, evaluating Lyme disease titers could also be ordered [14].

Treatment

Effective management of MS requires a multifaceted approach to control acute attacks, manage progressive worsening, and remediate bothersome or disabling symptoms associated with this illness. Remarkable advances in treatment of all forms of MS and especially for relapsing disease have favorably changed the long-term outlook for many patients. There also has been a conceptual shift in understanding the immune pathology of MS away from a purely T-cell-mediated model to recognition that B cells also play a key role in its progression [14]. Effective and relatively well tolerated medications are currently recommended to be used as first-line treatment for many patients with early onset MS to prevent its progression and the development of permanent disability [15]. Several disease-modifying therapies (DMTs) have transformed MS to being treatable disease. These compounds target the inflammatory response in MS. They minimize the frequency of symptoms relapse and decrease the recurrence of new lesion formation slowing the accumulation of disability as detected by MRI of the CNS [16]. Interferon-β and glatiramer acetate modulate the inflammatory response via different mechanisms and were the first generation of agents to treat MS. Newer agents have since become available and have significantly changed MS prognosis. These include fingolimod, dimethyl fumarate and teriflunomide, which are oral agents. Other second-line and third-line Food and Drug Administration (FDA) approved medications include natalizumab and alemtuzumab. Natalizumab is considered one of the most potent treatments for relapse prevention. However, the high risk of progressive multifocal leukoencephalopathy (PML), which is caused by the John Cunningham (JC) virus infection in the brain, tempers the more widespread use of this agent; nevertheless, JC virus antibody tests have helped to stratify the risk of PML[16]. A summary of the FDA Approved Disease-Modifying Therapies for Multiple Sclerosis MS is outlined in table 1 [17].

Table 1: FDA-Approved Disease-Modifying Therapy for Multiple Sclerosis

Treatment	FDA approval	Treatment dose and route of administration
Interferon beta-1b	RRMS	Starting dose: 0.0625 mg SC every other day
		Titration: increase over a 6-week period to 0.25 mg every other day
		Recommended dose: 0.25 mg SC every other day
Interferon beta-1a	RRMS	30 µg IM once weekly
Interferon beta-1a	RRMS	Starting dose: 8.8 µg SC TIW
		Titration: After 2 weeks of initial dose increase to 22 µg SC TIW for 2 weeks, then titrate if needed
		Recommended dose: 22 or 44 ug SC TIW
Glatiramer acetate	RRMS	20 mg SC daily or 40 mg SC TIW
Fingolimod	RRMS	0.5 mg PO once daily
Mitoxantrone	RRMS	12 mg/m 2 IV infusion every 3 months
	PRMS	
	SPMS	
Natalizumab	RRMS	300 mg IV infusion every 4 weeks
Teriflunomide	RRMS	7 mg or 14 mg PO once daily
Dimethyl fumarate	RRMS	120 mg PO twice a day for 7 days
		After 7 days: 240 mg PO twice a day
Peginterferon beta-1a	RRMS	125 µg SC every 2 weeks
Alemtuzumab	RRMS	First course: 12 mg/d infusion on 5 consecutive days
		Second course: 12 mg/d infusion on 3 consecutive days given 1 year after first treatment course

PRMS = progressive-relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TIW = 3-times weekly.

MS is considered among the major contributors to healthcare costs and it is critical that healthcare providers be aware of the availability and benefits of DMTs. It is imperative that prompt and adequate treatment to be implemented once the MS diagnosis is established. Changes in therapy should be considered when there is evidence of disease recurrence, during period of increased disability or in response to safety or tolerability of the prescribed DMTs.

The Psychiatric Manifestations of MS and their Treatment

A significant incidence and prevalence of psychological disorders in multiple sclerosis (MS) has been reported. However, the pathogenesis of their underlying mechanisms and the extent to which they are reactive to the MS pathological process itself has not been clearly delineated [5, 18]. Psychiatric signs and symptoms associated with MS, either present initially prior to a definitive diagnosis of MS or more commonly with the disease progression [19]. The psychiatric manifestation of MS could include major depression, bipolar disorder, psychosis, anxiety, insomnia, personality changes, cognitive impairment, pseudobulbar affect and substance use disorders [5].

Major Depressive Disorder

Depression is considered the predominant psychological disturbance with lifetime prevalence around 50% and annual prevalence of 20% [18]. Depression is common in the early disease course and during relapses. Depression seems not to be clearly related to specific MS brain lesions but is frequently associated with other symptoms such as fatigue or cognitive impairment. Depression in MS is more frequent than in an age-matched population or in other chronic diseases and could be associated with an increased risk of suicide [20]. MS treatments and especially interferon have also been associated with a 30-70% risk of treatment-emergent depression [21]. There is no firm evidence confirming that interferon induces depression which could also so due to the interaction between MS and interferon or related to preexisting depressive disorder [22]. The screening for depression and monitoring of mood should be a feature of the medical management of all patients with MS, regardless of whether they are receiving interferon. MS patients with depression respond well to treatment, either with psychotherapy or antidepressants or both. Treating depression would also improve adherence with the DMTs.

Bipolar Disorder

There is a high lifetime prevalence of bipolar disorder (BD) in patients with MS [23]. This increased rate is not just attributed to the effects of the medications used to treat MS [24, 25]. Medications induced manic symptoms appear generally to be dose dependent and occur early in treatment and are usually responsive to treatment [25]. Non-medication induced manic symptoms may precede other MS neurological signs but more commonly become evident approximately 1 year after the diagnosis is confirmed [26]. Manic symptoms would be manifested by increased energy, pressured or rapid speech, overfamiliarity, psychomotor agitation, disinhibition, decreased need for sleep and impulsivity [27]. Genetic predisposition could contribute to the development of BD, based on reports of familial clustering of both MS and BD [28]. It is recommended that all patients with MS to be screened for BD and to be treated with the same pharmacotherapeutic agents used in those individuals without MS while exerting caution in monitoring a possible increase in adverse effects. Lithium, in addition to its mood-stabilizing effects, has an associated disease-modifying effect in MS [29]. Additionally, lithium could reduce the risk of suicide [30]. The side effects of polyuria need to be distinctly separated from MS bladder dysfunction. Antipsychotic medications can also be used for mood stabilization with careful monitoring of their potential adverse effects on balance, coordination, fatigue and possible weight gain [31].

Psychosis

The rate of psychosis in MS has been reported at 2%–4%, with over 90% of individuals having symptoms of MS prior to the onset of psychosis [32, 33]. The exact etiology of psychosis in MS is not known. However, several possibilities have been suggested. The first suggestion attributes psychosis and MS to the infectious and immunological causes of both conditions [34]. The second possibility could be related to MS fronto-temporal regions demyelination [35]. The third possibility could be induction of psychosis by the medications used for the treatment of MS particularly corticosteroids and beta interferon [35, 36]. The medicinal use of cannabis by individual with MS could also exacerbate psychosis [37]. Antipsychotics are used to treat psychosis in patients with MS while initiating rigorous monitoring of their adverse effects [31]. Some antipsychotics could exert disease-modifying characteristics with secondary effects in the treatment of MS [38]. Some data have shown remission of psychotic symptoms with disease-modifying agents used for MS treatment [39].

Anxiety Disorders

Several risk factors for anxiety disorders have been identified in MS, including being newly diagnosed, increased MS disease activity, experiencing pain, fatigue or sleep disturbance [40]. Anxiety symptoms can present with clinical characteristics similar to those found during a relapse of MS and can often be related to the underlying disease process itself [41]. The co-occurrence of depression and anxiety symptoms has been associated with increased rates of suicidal ideation in MS [42]. It is clinically important to screen for anxiety in MS patients, its early identification would subsequently lead to its prompt treatment and would also improve the course of cooccurring depression resulting in improving the course and prognosis of MS. Antidepressants, the non-benzodiazepine buspirone, beta-blockers, pregabalin, gabapentin could also be used for the treatment of anxiety in patient with MS [43]. Cognitive behavioral therapy (CBT) and stress management could also be considered alone or in combination with pharmacological intervention [44]. It has also been reported that in some patients, the treatment of anxiety could prevent the development of new MS brain lesions [44]. Eye movement desensitization reprocessing (EMDR) could also be used to minimize anticipatory anxiety about the unpredictable physical and cognitive declines related to the future progression of MS [45].

Insomnia

The prevalence of sleep disorders in individuals with multiple sclerosis (MS) is 3-5 times higher compared to the general population [46]. Insomnia also led to significant fatigue which is the most common and disabling symptom of MS [47]. The co-occurrence of fatigue and insomnia in patients with MS also can overlap with and exacerbate other psychological and physical symptoms [47]. Cognitive behavioral therapy for insomnia (CBT-I) has been shown as an effective treatment for chronic insomnia in several medical conditions including MS [48]. Fatigue is a significant symptom of MS, affecting approximately 80% of patients with MS [49]. Fatigue may mask the existence of a sleep disorder in patients with MS. Assessment to determine the source of fatigue is important in devising multidisciplinary treatment plans that are tailored to address fatigue as a squeal of sleep difficulty or as a component of MS. Implementing treatment intervention to address fatigue and sleep difficulties would lead to improved quality of life in patients with MS [50].

Personality Changes

Changes occur in the personality of some patients with MS and could be expressed in the form of anger, irritability, apathy and disinhibition [51]. These personality changes need to be assessed independently of the co-occurrence of anxiety, mood, or psychotic disorders in patients with MS [52]. A detailed psychiatric and neurologic evaluation is important for the assessment of personality changes in MS patients [53]. The comprehensive management of a variety of personality changes in MS includes supportive psychotherapy, cognitive behavioral therapy and pharmacological intervention if needed for relief of symptoms severity [54]. Personality changes could also precipitate a high degree of caregiver distress [55]. Group psychotherapy, combined individual and group psychotherapy, couples and family therapy may need to be initiated as a component of an integrated treatment plan to address personality changes in MS [54].

Cognitive Impairment

The prevalence of cognitive impairment in MS varies across the lifespan and might be difficult to distinguish from other causes especially in older patients with MS [56]. MRI studies show that widespread changes to brain networks contribute to cognitive dysfunction and grey matter atrophy is an early sign of potential future cognitive decline and that cognitive processing speed and episodic memory are the most frequently affected cognitive domains in MS [56]. Cognitive processing speed and memory could respond to cognitive training interventions [56]. The available DMTs may reduce the development of new lesions and therefore prevent or minimize the progression of cognitive decline [57]. The search for effective therapeutic strategies involving the use of both pharmacologic and rehabilitative approaches combined with early DMTs are highly advisable to prevent or delay the development of severe cognitive impairment in patients with MS [58].

Pseudobulbar Affect

Pseudobulbar Affect (PBA) is a clinical description of an emotional disinhibition syndrome characterized by sudden and involuntary episodes of crying or laughing which are not in proportion to applied stimuli and could occur without any precipitating stimulus. The prevalence of PBA in MS is low, but its symptoms may co-occur or overlap with depression and could be associated with cognitive impairment in patients with MS [59]. When it is under recognized and undertreated PBA could lead to considerable distress for patients and their caregivers [60]. The initiation of treatment with antidepressants and dopaminergic agents is advisable for patients with MS who developed PBA [61]. The FDA-approved medication for the treatment of PBA which combines dextromethorphan hydro bromide and quinidine sulfate may be beneficial in treating potentially disabling PBA in patients with MS [62].

Substance Use Disorders

Patients with MS can be vulnerable to the use of alcohol and other illicit drugs [63]. The use of substances contributes to increased rates of depression and could worsen and exacerbate MS associated motor and cognitive impairments. Comprehensive MS treatment plans should incorporate screening and treatment of substance use disorders as an integral component of the overall management of MS [64].

Summary

The psychiatric manifestations of MS may include major depression, bipolar disorder, psychosis, anxiety, insomnia, personality changes, cognitive impairment, pseudobulbar affect, and substance use disorders [5]. However, their relationship with MS is complex and the extent to which they might be reactive to countless psychosocial factors or symptoms resultant of the pathological process itself remains unclear. In general, these disorders contribute to aggravate MS physical symptoms and lead to increased disability, suffering and significant disruption of family, work, and social life, which represents a huge increase in the overall burden of the disease. Health care professionals providing care for patients with MS need to be astute in screening for the psychiatric manifestations of MS and promptly initiate treatment to reverse or decrease the intensity of these psychiatric manifestations. The management of the psychiatric manifestations of MS patients should be based on the standard psychiatric treatment guidelines that are used for the treatment of these conditions in individuals who do not have MS. A comprehensive MS treatment approach that incorporates the overall medical management of MS with its psychiatric manifestation would ultimately lead to the reduction of disability and improve the prognosis and the wellbeing of patients, their family, their significant others and would ultimately minimize the disease burden of MS.

Conflict of Interest Statement

The materials described in this manuscript are those of the author and do not reflect the views of the Department of Veterans Affairs or the VA Central California Health Care System or the Department of Psychiatry of UCSF-Fresno medical Education Program.

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