Chapter 6
Psychiatric Comorbidity

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Abstract Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system. Psychiatric comorbidities, in particular depression and anxiety, are frequent in MS patients.

These disorders are underdiagnosed and undertreated although they have been associated with decreased adherence to treatment, functional status, and quality of life. Behavioral disorders are more common than severe psychiatric disorders and are probably secondary to cognitive impairment. Addictions may be underestimated. Although the high frequency of psychiatric co-morbidity might be due to psychosocial factors, the role of demyelinization and inflammation is possible. Psychiatric comorbidities in MS deserve clinical attention because they are associated with an increase risk of suicide.

Keywords Multiple sclerosis • Suicide • Depression • Bipolar disorders • Anxiety disorders • Psychosis • Schizophrenia • Personality disorders • Euphoria • Pseudobulbar affect • Somatoforms disorders • Substance abuse

Introduction

Patients with multiple sclerosis are more likely to have psychiatric symptoms or disorders than people without MS (Table 6.1).

In a study of co-morbidity at the diagnosis of multiple sclerosis, Fromont et al. found that 42.5 % of women and 35.6 % of men had a psychiatric disorder associated with the diagnosis of multiple sclerosis versus 29.9 % of women and 33.9 % of men who did not have multiple sclerosis [21]. These disorders are underdiagnosed and undertreated, and they have been associated with decreased adherence to treatment [22], functional status, and quality of life [23]. Additionally, the occurrence of a psychiatric disorder prior to the onset of MS delayed the diagnosis of MS

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Table 6.1 Increased prevalence of psychiatric disorders among persons with MS compared to the general population [1–20]

Disorder	Prevalence in MS	Prevalence in general population
Major depressive disorder, 12 months	15.7 % (33) [1]	7.4 % (33) [1]
Major depressive disorder, lifetime	22.8 % (100) [2]	16.2 % (101) [3]
Anxiety disorder, lifetime	36 % (14, 90) [4, 5]	25 % (102) [6]
Generalized anxiety disorder	18.6 % (14, 90) [4, 5]	3 % (103) [7]
Bipolar disorder lifetime	0.3 % (65) [8]	0.2 % (63) [9]
Schizophrenia	0.5 % (66) [10]	0.3–0.66 % (80) [11]
Brief psychotic disorders	3 % (84) [12]	0 % (84) [12]
Somatoform disorders	2 % (90) [5]	0 % (90) [5]
Paranoid disorders	25 % (85) [13]	3 % (85) [13]
Borderline disorders	25 % (85) [13]	0 % (85) [13]
Alcohol abuse, lifetime	13.6 % (92) [14]	7.4 % (99) [15]
Euphoria	15 % (72) [16]	0 % (72) [16]
Pseudobulbar affect	10 % (75) [17]	–
Substance misuse, past month	18.7 % (93) [18]	11.1 %

by 3.2 years [21]. This review aims to summarize the existing literature on the epidemiology, impact, and treatment of psychiatric disorders among persons with MS.

Suicide

The risk of suicide has been reported to be increased among patients with MS. In Sweden [24], the standardized mortality ratio (SMR) was significantly elevated: SMR = 2.3 among MS patients compared with the general population. Suicide risk was particularly high in the first year after initial admission with an MS diagnosis and among younger male MS patients. The crude suicide rate among MS patients during the study period was 71 per 100,000 person-years. In a large community-based study in Denmark, the suicide risk among people with multiple sclerosis was more than twice that of the general population (SMR = 2.12). The increased risk was similarly high during the first year after diagnosis (SMR = 3.15) [25]. In London, Ontario, the proportion of suicides among MS deaths was 7.5 times that of the age-matched general population [26]. The prevalence rate of suicide in MS ranges from 2.5 to 28.6 % [26–28]. This wide range of estimation is probably due to cultural variation and methodological considerations. In men (but not in women), risk factors for suicide were psychiatric co-morbidity, major depression, past suicide attempt, moderate disability, or recent accentuation of disability [25].

The frequency of suicidal intent in MS patients was 28.6 % in a study of 140 patients. The main risk factors were social isolation, familial psychiatric co-morbidity, social stress, past history of major depression, anxiety, and alcohol abuse [29].

Anxiety

As defined in the DSM-IV, symptoms can include prominent generalized anxiety symptoms, panic attacks, obsessions, or compulsions [30]. Anxiety is widely distributed in multiple sclerosis patients: A recent study using responses gained by the web portal of the UK MS register included 4,178 respondents. Over half of the respondents (54.1 %) scored > 8 for anxiety on the Hospital Anxiety and Depression Scale (HADS). Women were more frequently anxious than men: 56.4 % compared to 48.0 %. Anxiety was most frequent among people with relapsing remitting MS (RRMS) (56.5 %). Among the patients enrolled, 27.6 % had mild anxiety, 37.4 % moderate anxiety, and 10.6 % severe anxiety. Only 24.4 % did not have anxiety (score HADS < 8) [31]. The prevalence rates observed and the mean anxiety scores were higher than those found for the general UK population [32]. These figures were higher than in most of the previously published studies. The literature about anxiety and MS is reviewed in Chap. 4.

Depression

The essential feature of a major depressive episode (MDD), as described in the DSM-IV, is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. The individual must also experience at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts [30].

Bipolar Affective Disorders

Bipolar affective disorders refer to a group of affective disorders characterized by depressive and manic or hypomanic episodes. The DSM-IV contains four main types of bipolar disorders. Bipolar disorders type I (BD I) is defined by the occurrence of episodes of depression and at least one full-blown manic episode, bipolar type II (BD II) by several episodes of depression and at least one hypomanic episodes, cyclothymic disorders by many periods of hypomanic and depressive symptoms (not fulfilling criteria for depressive episodes), and bipolar disorders not otherwise specified [30].

Bipolar disorders are underdiagnosed in the general population because it is difficult to differentiate these disorders from unipolar depression (defined by recurrent episodes of depression) when hypomanic or manic episodes are not identified [33].

Bipolar disorders type I affects 0.2–4 % of the general population, bipolar II disorders 0.3–4.8 %, 0.5–6.3 % for cyclothymic disorders, and 5 % for bipolar spectrum [9].

Mania is characterized by euphoria or irritable mood, decreased need for sleep, talkativeness, racing thoughts, increased sexual activity and aggressive activity, increased motor activity or agitation, and poor judgment. It makes the severity of the disease as it interferes with patients' capability to work and familial functioning. Postpartum period is associated with an increased risk of exacerbations, and the prognosis of manic episodes in this period is associated with a severe prognosis. Atypic depression and mixed depression (defined by the combination of depression and non-euphoric subsyndromal manic or hypomanic symptoms) are more frequent than in unipolar depression [9].

Alcohol abuse and drug abuse are frequently associated with bipolar disorders and complicate the care of these patients.

A family history of bipolar disorders is found in 50 % of the patients. Studies of twins showed that the concordance for bipolar illness is between 40 % and 80 % in monozygotic twins and only 10–20 % in dizygotic twins suggesting a genetic component.

Acute mania is usually treated with antipsychotic drugs [34]. Classical and atypical neuroleptics are effective treatment. Lithium valproate and carbamazepine have established efficacy in the treatment of acute mania, but they work slowly. Bipolar depression responds to tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors. Lithium is effective in the treatment of acute bipolar depression and the prevention of recurrences of mania hypomania and depression. Other mood-stabilizing agents are used like valproic acid, carbamazepine, and lamotrigine or neuroleptics, but their use is limited by the risk of tardive dyskinesias. Cognitive-behavioral therapy is effective in nonpsychotic depressive disorders [34].

Most of the epidemiological studies showed an increased prevalence rate of bipolar disorders in MS patients [8]. The NARCOMS registry is a self-report registry for patients with MS in the USA. Among 8,828 responders (55.7 % response rate), the prevalence rate was 2.4 % for bipolar disorder in MS [35].

Using administrative data in Canada in 4,192 persons with MS and 20,940 matched persons, Marrie et al. found that the age-standardized prevalence of bipolar disorder in 2005 was 5.83 % (95 % CI: 5.01–6.65 %) in the MS population and 3.45 % (95 % CI: 3.17–3.73 %) in the general population (PR 1.70; 95 % CI: 1.55–1.87) [10]. In another study with a general population control group, hospitalized MS patients had bipolar affective disorder twice as often as hospitalized controls (1.97 % vs. 0.92 %) [36]. However, they found a slight to moderate agreement between the administrative case definitions and medical records, which illustrates the difficulty to accurately diagnose bipolar affective disorders.

A recent case-control study including 201 consecutive MS patients and 804 sex- and age-matched persons without MS used structured interview tools to perform psychiatric diagnoses according to DSM-IV. Compared to controls, MS patients had a higher lifetime prevalence of DSM-IV major depressive disorders (MDD; $P<0.0001$), BD I ($P=0.05$), BD II ($P<0.0001$), and cyclothymia ($P=0.0001$) [37].

The relationship between bipolar disorders and MS is not well understood but is regarded as being multifactorial. It is attributed to medications, demyelinating brain

lesions, genetics, psychological reactions, and adjustment difficulties. Several treatments used in MS could induce hypomanic or manic episodes as corticosteroids, baclofen, dantrolene, tizanidine, and illicit drugs [38]. Although cases of depressive episodes have been reported with interferon beta, sometimes accompanied by psychotic or manic behavior, there is no clear evidence that the administration of interferon to patients with MS increases the risk of depressive disorders [39].

Concerning the treatment, there are no controlled trials of mood stabilizers use in treating affective bipolar disorders in MS in particular.

Euphoria

Euphoria is defined as a stable elation of humor, an unsuitable cheerfulness, or a lack of concern to the consequences of the disease. It is secondary to personality disorders and it is not considered as a mood disorder. Euphoria is distinguished from mania. It is associated with childishness, disinhibition, impulsivity, emotional lability, anger outbursts, and lack of empathy. In modern studies the estimated prevalence rate of euphoria in MS patients is around 15 %. Two studies using the neuropsychiatric inventory (NPI), which covers ten domains including delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor activity, have evaluated the prevalence of euphoria in MS. In a study including 44 MS patients and 25 controls without MS, Diaz-Olavarietta et al. identified euphoria in 13 % of patients as compared to 0 % in the control group [40]. In 75 patients enrolled in a MS clinic, Fishman et al. found a prevalence rate of 7 % or 9 % as compared to 0 % in the control group and was associated with secondary progressive course, low agreeableness on personality testing, poor insight, and impaired cognition [16]. Euphoria is associated with the severity of the total T2 lesions load and the atrophy of gray and white matter [41].

Pseudobulbar Affect

Pseudobulbar affect (PBA) is defined as episodes of involuntary crying, laughing, or both that are inconsistent with the patient's underlying mood. The clinical condition has been known by different names, but the most widely used terms are "pseudobulbar affect," "emotional lability," "emotional incontinence," and "pathological laughter and crying" or "pathological laughing and crying (PLC)" [42]. Uncontrollable crying seems to be more common than laughing. This emotional incontinence causes significant social embarrassment. Although it is not a mood disorder, it can be associated with depression. In a cohort of 152 consecutive MS patients, Feinstein et al. found a point prevalence of 10 % [17]. Patients were severely disabled with a mean EDSS score of 6.5 and had progressive course. Emotional expression in PBA is secondary to a disconnection from cortical

voluntary control or cortico-pontine-cerebellar control responsible for appropriate emotional adjustments to social situations. It is thought that loss of voluntary control results in involuntary activation of laughing/crying centers. An MRI study has correlated the occurrence of PBA with lesions in the brainstem, the inferior parietal (bilateral) and medial inferior frontal (bilateral), and the right medial superior frontal region [43].

Agents that are effective for the treatment of mood disorders are also effective for the treatment of PLC. Most commonly, MS patients are treated with tricyclic antidepressants or selective serotonin reuptake inhibitors. Levodopa and amantadine have been proposed. More recently dextromethorphan/quinidine has been shown to be efficacious in a randomized control trial in MS and has been approved in the USA [11, 44–46].

Psychotic Disorders

In the DSM-IV, psychotic disorders are defined by the presence of prominent hallucinations or delusions and other positive symptoms of schizophrenia like disorganized speech, disorganized speech or behavior. Psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorders, shared psychotic disorders, and psychotic disorders due to general medical condition or substance-induced psychotic disorders.

Schizophrenia is applied to a syndrome characterized by long-duration, bizarre delusions, negative symptoms, and few affective symptoms (non-affective psychosis) [30]. In the general population, the lifetime prevalence and incidence are 0.30–0.66 % and 10.2–22.0 per 100 000 person-years [11, 47]. The risk of schizophrenia and related categories increases with an urbanized environment during childhood and with the exposure to dronabinol, the main psychotropic component of cannabis [11].

Occasionally, acute bizarre behavioral symptoms leading to a diagnosis of psychosis could inaugurate the course of the disease or be associated with a relapse. Of the four patients described by Blanc et al., who developed psychotic symptoms that led to the diagnosis of multiple sclerosis, two developed persecutory delusions, one presented a manic episode and the fourth melancholia with catatonia [48].

In a population-based study in Canada, Patten et al., using administrative data, found that the prevalence of psychotic disorders was 1.3 % and that of organic psychotic disorders was 0.5 % in MS patient ($N = 10{,}367$). The prevalence of psychotic disorders was highest in the 15–24-year age group [49]. Although the prevalence of psychotic disorders increased with age in MS patients and controls, people with MS consistently had a higher prevalence of psychotic disorders than people without MS. A later study in the same population did not find an increase of the age-standardized prevalence of schizophrenia in MS as compared to the general population (0.93 % vs. 0.93 %) [10].

In a case-control study including 37 consecutive MS patients and 37 matched controls, a psychiatrist administered a structured clinical interview. Among the MS patients, 1 (2.7 %) had brief psychotic disorder vs. none in the control group [12].

Personality Disorders and Behavioral Symptoms

As defined in the DSM-IV, personality traits are enduring patterns of perceiving, relating to, and thinking about the environment and oneself that are exhibited in a wide range of social and personal contexts. Only when personality traits are inflexible and maladaptive and cause significant functional impairment or subjective distress do they constitute personality disorders [30]. Several patterns are described: paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependant, and obsessive-compulsive disorders. The diagnosis of personality disorders requires an evaluation of the individual's long-term patterns of functioning.

One case-control study specifically examined the frequency of personality disorders in multiple sclerosis in 20 MS patients and 35 healthy controls. Paranoid disorders and borderline disorders were observed more frequently in MS patients than in healthy control, respectively, 25 % vs. 3 % and 25 % vs. 0 %. There was no difference for the frequency of narcissistic, histrionic, avoidant passive aggressive, and dependant personality between MS patients and healthy control [13].

In their review and meta-analysis of 23 controlled studies, Rosti-Otajarvi and Hamalainen found that MS patients were more likely to manifest behavioral symptoms such as aggression (23 %), apathy (22 %), euphoria (12 %), and lack of insight (11 %) as well as impairments such as adjustment disorder (17 %) than healthy controls and other patients with SLE, chronic fatigue syndrome, and muscular dystrophy [20].

These disorders might be due to a psychological reaction to a chronic disease, but the association with neuropsychological deficits suggests that it could be secondary to the cerebral lesions. In a study in 34 MS patients and 14 healthy controls, Benedikt et al. found that MS patients with cognitive impairment were more neurotic and less empathic, agreeable, and conscientious as compared with normal control subjects [50].

Unusual episodes of hypersexuality have been described in MS. A patient with recurrent periods of heightened sexual desire has been reported. These episodes were thought to be due to strategically located plaques in the frontal lobes [51].

Somatoform Disorders

It is well known that patients, without any evidence of neurological disease, presenting features or symptoms that suggest the diagnosis of MS can be misdiagnosis. Allanson et al. reported 25 patients with severe functional assessment, without

pathology to explain their neurological disability. The most common putative diagnosis was multiple sclerosis. Height of the patients had a final diagnosis of somatoform disorders and 13 of motor conversion disorder [52]. A more difficult situation could occur when hysterical symptoms add to MS symptoms during the course of the disease as the four cases reported by Caplan and Nadelson in 1980 [53].

Also well-recognized few studies have evaluated the frequency of this association. In one case-control study in 50 MS patients and 50 healthy control patients, Galeazzi et al. have found somatization disorder in 2 % of patients as compared to 0 % of the HC [5].

Substance Abuse

Alcohol and illicit drug abuse represent a growing challenge for the health of general populations. In their study on the global burden of disease attributable to mental and substance use disorders, Whiteford et al. found that illicit drug use disorders accounted for 10.9 % and alcohol disorders for 4.2 % of disability-adjusted life years [54]. In multiple sclerosis, substance abuse may be associated with mental disorders, may worsen neurological deficits, interact with MS treatment, and be associated with poor adherence. Several studies have found an increase in the prevalence of alcohol abuse in MS patients. In a study assessing drinking patterns in 140 MS patients, Quesnel and Feinstein found that 13.6 % have alcohol abuse. Patients with alcohol abuse were more likely to have suicidal ideation or other substances abuse [14].

In a large community-based study including 739 MS patients, Bombardier et al. found that 19 % of patients had alcohol or illicit drugs misuse. Alcohol abuse or dependence was detected in 14 % of the patients and illicit drugs in 7.4 % [18].

Cannabis and cannabinoids are used by MS patients to alleviate MS-related symptoms like pain, spasticity, tremor, and bladder dysfunction. Recently the nabiximols (Sativex) that contain two principal cannabinoids—delta-9-tetrahydrocannbinol (THC) and cannabidiol (CBD)—was approved for spasticity in MS [55]. The rate of cannabis misuse is high in MS patients, and in a survey in 220 patients, 36 % reported ever having used cannabis for any purpose. Use of cannabis was reported for symptom treatment by 14 % to relieve stress, sleep, mood, stiffness/spasm, and pain [56]. Although the majority of MS patients claimed that they use cannabis for medical purpose [57], patients and clinicians should be aware of the negative side effects of this use. Among patients treated with cannabinoids, the following side effects have been reported: nausea, increased weakness, behavioral or mood changes (or both), suicidal ideation or hallucinations (or both), dizziness or vasovagal symptoms (or both), fatigue, and feelings of intoxication. Psychosis, dysphoria, and anxiety are associated with high concentrations of THC.

Cognitive impairment in MS patients is also a matter of concern. Patients with MS who used cannabis performed significantly more poorly than nonusers on measures of cognitive working memory, information processing speed, executive

functions, and visuospatial perception [58, 59]. They are twice as likely to be classified as globally cognitively impaired as those who did not use cannabis [59].

Alcohol and substance disorders complicate assessment and treatment of MS and psychiatric problems. Clinicians should routinely screen for alcohol and illicit drug abuse. Treatment can include motivational interviewing, interventions to facilitate more healthy behaviors, detoxification to address withdrawal symptoms, cognitive-behavioral therapies to avoid relapses, and the use of drugs to diminish cravings or discourage relapses [15].

Conclusion

Psychiatric comorbidities are common in multiple sclerosis. The risk of suicide is particularly serious in the first years of the disease. Anxiety is frequent in the disease and is the most powerful predictor of depression. Major depressive disorder is underdiagnosed and undertreated. Behavioral disorders are more common than severe psychiatric disorders and are probably secondary to cognitive impairment. Addictions may be undervalued.

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