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MENTAL DISORDERS AMONG PATIENTS WITH MULTIPLE SCLEROSIS - A MINI REVIEW

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease and a commonest cause of non-traumatic disability in young adults. It affects up to 2.8 million people globally. In addition to the symptoms directly related to the disease, patients with multiple sclerosis often experience various mental disorders. The aim of this narrative review is to summarize the most common mental health conditions associated with multiple sclerosis and to highlight their clinical relevance by analyzing articles found in the Google Scholar database. As the data show, mental illnesses such as depression, anxiety, bipolar disorders and psychotic disorders affect MS patients more often than the general population and negatively impact their daily life, reducing its quality. The development of these conditions appears to be multifactorial, involving neuroinflammatory and immunological mechanisms, structural brain changes, psychosocial stressors related to chronic illness, and potential adverse effects of disease-modifying therapies. Therefore, it is crucial to raise awareness of these disorders to diagnose the condition promptly and administer appropriate treatment as quickly as possible.

KEYWORDS

Anxiety, Depression, Mental Disorders, Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is a neurodegenerative condition affecting the central nervous system in which autoimmune processes lead to inflammatory demyelination with axonal transection [1]. MS commonly impacts young adults in their 20s or 30s years of age and is considered a commonest cause of non-traumatic disability in this age group [1,2]. Multiple sclerosis remains a global issue and its prevalence has increased referring to the available data [3, 4]. It is highly encountered in North America, Western Europe and Australasia and the incidence is up to more than 100 cases per 100,000 population. In countries that are centred around the equator the situation is quite different. The prevalence there is less than 30 cases per 100,000 population [4]. It is worth noting that the global estimated number of people living with MS rose to 2.8 million in 2020. The estimate is 30% higher than it was in 2013 [5]. As data indicates the number of people living with multiple sclerosis has increased, but as observed the course of the condition has become milder [3].

Multiple sclerosis can have different courses: the more common relapsing form, characterized by neurological disorders that may resolve completely, partially or not at all, and the rarer progressive form, which involves a gradual deterioration of neurological functions from onset. In the case of relapsing-remitting multiple sclerosis, gradual deterioration may occur, leading to the secondary progressive form of the disease. The symptoms of MS vary in patients depending on the location and severity of the lesions [4]. One type of symptoms that patients with MS may experience is mood and mental dysfunctionality such as depression, anxiety, bipolar disorder, psychosis and suicidal ideation. Although they may be invisible to other people, they have a significant impact on patients' quality of life [6].

Studies show that patients with multiple sclerosis experience a noticeably higher prevalence of mental disorders compared to the general population. In fact it is estimated that up to 75% of individuals with MS are affected by various mental health conditions [7]. There are factors considered to contribute to the development of mood and anxiety disorders in these patients - MS is a chronic, incurable disease that causes changes in the central nervous system, disrupts functioning in society and can lead to an inability to work [8]. What more it has been observed that the symptoms of mental disorders may be aggravated by medications used in multiple sclerosis such as corticosteroids and interferon beta [9]. Therefore, as psychiatric disorders affect a significant number of patients with MS, the aim of this review is to present them in order to raise awareness.

Methodology

A literature analysis was performed using the PubMed and Google Scholar database. This review draws on secondary data derived from previously published systematic reviews, meta-analyses, and network meta-analyses. The literature search employed keywords related to multiple sclerosis, used either independently or in conjunction with terms referring to mental disorders, depression, anxiety, bipolar disorders, and psychotic disorders. Only articles published in English were considered. A broad range of publication types was included in the analysis. This narrative review integrates current scientific evidence with recommendations and position statements issued by major international health authorities, including the World Health Organization.

Depression

One of the most common emotional changes that people with MS diagnosis experience is depression [6]. It is a disease that can be characterized by symptoms occuring in its course such as sadness, emptiness, anhedonia, irritability, fatigue, apetite changes, sleep disturbances, agitation, feeling of guilt or worthlessness, impaired concentration or even persistent thought about death or suicide that last at least 2 weeks and make a significant reduction of the patient’s capacity to function [6, 10]. This is a symptom-based definition. The precise criteria that are required for a diagnosis of depression and other psychiatric disorders are included in International Classification of Diseases 11th Revision (ICD-11).

According to literature the prevalence of depression among patients with MS vary between studies. As data says depression may affect approximately from 27,01% up to 50% of patients with MS making the proportion 2-5 times higher than in the population of people not suffering from MS [6,11,12]. Importantly depression more often affects patients with the progressive form of multiple sclerosis than those with the relapsing-remitting form [12].

The exact etiology of depression in multiple sclerosis remains unclear although psychosocial and biological factors are known to underlie this condition. The progressive course of the disease and relapses contribute to the occurrence of depressive disorders [8,13]. Some authors suggest that depressive disorders are reported in patients with multiple sclerosis regardless of the level of disability [14]. However there are reviews that reported a relationship between disability and depression symptoms [15]. There are some hypotheses

suggesting that activation of the immune system contributes to the onset of depression. For example elevated levels of pro-inflammatory cytokines are observed in both peripheral blood and cerebrospinal fluid (CSF) of patients with depressive disorder. Additionally, a higher incidence of depression is reported during or shortly after disease exacerbations in relapsing-remitting multiple sclerosis. Nevertheless distinguishing between a depressed mood in multiple sclerosis as a response to a potentially disabling illness and depressed mood in multiple sclerosis linked to the inflammation and autoimmunity is difficult [13]. Other encouragement for a biological factor includes the presence of lesions in the left arcuate fasciculus, temporal lobes, right temporal areas, periventricular zone and frontal lobes. Whatsmore it has been noticed that the severity in individuals with cerebral lesions is higher compared to those with spinal cord involvement [16].

The occurrence of depression in patients suffering from multiple sclerosis can cause significant and severe consequences. According to the presence of major depression, its severity, functioning in society and alcohol misuse, an increased risk of suicide or premature mortality occur [17,18]. The suicide risk in the MS population is twice as high as in the general population as the standardized mortality ratio (SMR) indicates [19]. Other consequences of co-occurrence of depression and MS include reduced quality of life, impaired ability to perform daily activities independently, challenges in employment and decreased medication adherence [17].

Anxiety

Among mental disorders affecting patients with multiple sclerosis are various anxiety disorders [8, 20, 21]. Patients suffering from anxiety experience overwhelming sense of unease and worry that is not manageable and disrupts everyday functioning. Due to unpredictable outcome of future relapses and possible seriousness of the symptoms of MS anxiety may be intense and prolonged [22, 23]. What is worth noting patients with MS most often suffer from Generalized Anxiety Disorder followed by Panic Disorder and then Obsessive-Compulsive Disorder [11].

Anxiety along with depression is most common psychiatric manifestation among patients with MS. It affects from 22.1% even up to 63% of these patients but it is worth noting that the prevalence vary between studies [21, 24-26]. Data shows that anxiety disorder occurs in average of 22% of patients with MS [27]. In comparison anxiety may affect 0,8% to 6,4% of population in worldwide estimates [22].

It is known that underlying causes of the anxiety are biological and psychosocial factors. Among the biological factors unusual neuronal pathways involving the amygdala, basal ganglia, and cerebral cortex, along with a variety of neurotransmitter systems are noticed [16, 28]. But in the literature anxiety is increasingly viewed as a reaction to the underlying disease [20]. Concerning psychosocial factors, female, patients with a shorter disease progression, lower levels of disability, an earlier age of onset and a history of depression

are more likely to experience anxiety [16]. What is worth noting it has been noticed that for some patients the diagnosis of MS is the major factor of triggering their anxiety [29].

Occurrence of anxiety also leads to changes in life of the patients with MS. Commonly to depression anxiety seriously affects the quality of life of the patients and the consequences of both disorders are similar. Depression, decreased quality of life, suicidal thoughts and poor adherence are observed in patients with MS suffering from anxiety [16, 27].

Bipolar disorders

Another psychiatric disturbances affecting patients with diagnosis of MS are bipolar disorders (BD) represented by a diverse range of chronic conditions. They include two main types of the bipolar disorders such as bipolar I disorder that can be characterized by a syndromal, manic episode and bipolar II disorder characterized by syndromal, hypomanic episode and a major depressive episode [30].

Multiple sclerosis do not coexist with bipolar disorders as frequently as depression or anxiety but their coexistence is well documented [31]. However according to an analysis of the research of Chwasiak and Ehde it is observed that patients with multiple sclerosis may encounter the signs of bipolar disorder up to two times more often than the general population [8,14]. Based on review and meta-analysis of Boney Joseph in patients with MS the lifetime prevalance of BD is high and reaches to 8,4% [32]. But it is worth noting that in the study by Marrie et al., bipolar disorder co-occurred with MS in only 3.15% of the patients tested — still nearly twice as high as the prevalence of BD in the control group, which was 1.69% [8, 33].

Unfortunately as studies show coexistence of bipolar disease and multiple sclerosis have not yet been fully understood [27, 31]. The main risk factor for comorbidity of multiple sclerosis and bipolar disease is considered to be family history of the last one disease and as some studies say, there might be a genetic transfer

of both diseases. Actually some studies from previous years indicate that genetic links between multiple sclerosis and bipolar disorder have been identified in the human leukocyte antigen (HLA) DR2 gene and mitochondrial transcriptomes [34-36]. It has also been noted that medication used in the treatment of multiple sclerosis may serve as a contributing factor to the development of bipolar mood symptoms. For instance, it has been documented that steroid treatment may contribute to the onset of a manic episode, whereas tizanidine, baclofen, and dantrolene have been implicated in the induction of hypomania. Turning to the biological changes in the brain, the available literature presents divergent views, and the pathophysiology of bipolar disorder remains unclarified [27]. Whereas a study by Lorefice et al. noted that the volumes of the whole brain, white matter, and cortical gray matter did not differ between patients with both multiple sclerosis and bipolar disorder and those with MS alone. However the same study found that patients with both multiple sclerosis and bipolar disorder had smaller volumes of the putamen, nucleus accumbens, and globus pallidus [37].

The comorbidity of bipolar disorder and multiple sclerosis leads to a significantly decreased quality of life. It has been observed that this adversely affects health perception, fatigue, physical functioning limitations, social participation and physical distress [38].

Psychotic disorders

Psychiatric disorders affecting patients with multiple sclerosis also include psychotic disorders. To define psychotic disorders, or psychoses, they can be described as medical conditions characterized by delusions, hallucinations, disturbances in consciousness, significant emotional disturbances, and changes in behavior, accompanied by disorders of thinking and complex activities [39]. Schizophrenia is one of the disorders included in this category.

It is worth noting that the available literature on the occurrence of psychotic disorders in patients with MS is limited and primarily based on case studies and case series [40]. In any case, according to the available studies, psychotic disorders occur 2 to 3 times more often in patients with MS than in the general population. The incidence of psychotic disorders in these patients varies between studies. According to data, approximately 4.3% of MS patients suffer from psychotic disorders, while another source estimates the incidence from 0.41% up to to 7.46%, and specifically when it comes to schizophrenia, the prevalence among these patients ranges from 0% to 7.4% [41, 42].

According to the cause of psychotic symptoms in patients with MS, a link between a greater number of lesions in the medial temporal lobe and the presence of psychotic disorders has been noticed [41, 43]. In addition 73% of MS patients with psychosis had lesions in the periventricular white matter [44]. Whatsmore some studies suggest that there may be an etiological link between psychotic disorders and MS, as genetic markers of immune activation play a role in both of them [41, 42]. Also genomic studies have revealed significant overlaps in the genetic markers associated with both schizophrenia and MS. Nonetheless, it is also important to highlight previous studies that identified 21 independent loci linked to both schizophrenia and MS, focusing on the shared HLA alleles between the two conditions [27]. Another although not fully understood cause of psychosis in MS patients is the use of medications for this neurodegenerative disease. Glucocorticosteroids are primarily implicated, although psychotic symptoms have also been observed with interferon beta [41].

Psychotic symptoms, as well as other previously mentioned psychiatric disorders, further worsen the patient's condition in neurological diseases, affecting their functioning and increasing the overall burden of the disease. Also it has been observed that when the psychotic symptoms appear early, they can complicate the accurate diagnosis, delay the identification of the underlying brain condition, and lead to improper treatment and a poorer prognosis [42].

Suicidal ideation

According to this review, a significant number of MS patients suffer from various psychiatric conditions, and one of the symptoms may be suicidal ideation. A meta-analysis published in 2020, which included 8 studies, estimated that 13% of patients with MS experience suicidal thoughts [45]. Whatsmore as studies on suicide in people with MS shows, the risk of suicide is significantly higher in this group compared to the general population, and a significant association between MS and suicide has been demonstrated by the meta-analysis of 16 studies (with a pooled standardised rate ratio (SRR) of 1.72 (95% Cl 1.48-1.99)) [46, 47]. Therefore, to prevent deaths caused by suicide, knowledge and awareness of this issue are essential [46].

Conclusions

Patients with MS are much more likely to experience mental health issues such as depression, anxiety disorders, bipolar disorder, and psychotic disorders compared to the general population. The diagnosis, disease symptoms, its impact on daily life, and physical changes in the body can all contribute to the development of these conditions. Although these mental health issues may not be immediately visible, they significantly affect patients' lives, leading to a reduced quality of life, difficulties in social integration, and sometimes dependence on others. Therefore, it is crucial to recognize the importance of being aware of these mental health disorders in patients with multiple sclerosis to ensure early detection and prompt treatment as quickly as possible.

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