Fatigue and Depression in Patients with Multiple Sclerosis

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Received: July 25, 2023, Manuscript No. JMSO-23-92987; **Editor assigned**: July 29, 2023, PreQC No. JMSO-23-92987 (PQ); Reviewed: August 12, 2023, QC No. JMSO-23-92987; **Revised**: August 15, 2023, Manuscript No. JMSO-23-92987 (R); **Published**: August 25, 2023, DOI: 10.35248/2376-0389.23.10(8).515.

Abstract

Multiple sclerosis patients frequently receive diagnoses for fatigue and Melancholy (MS). The subjective lack of physical and or mental energy known as fatigue is present in 35%-97% of MS patients, who list it as one of the most severe symptoms affecting everyday activities and quality of life. 50 percent of MS patients have depression, according to diagnosis. Since

melancholy and fatigue frequently coexist, it might be challenging to tell the two apart. In MS, inflammatory, oxidative/nitrosative, and neurodegenerative processes that cause demyelination, axonal damage, and brain atrophy are the main causes of primary fatigue and primary depression. The concentration of inflammatory mediators like tumour necrosis factor, interleukins (IL-1a, IL-1b, and IL-6), interferon, and neopterin is found to be higher in the serum and cerebrospinal fluid of MS patients who also have comorbid fatigue and/or depression. In addition, prefrontal, frontal, parietotemporal, thalamic, and basal ganglia atrophy were seen in MS patients who also experienced fatigue and/or melancholy.

People with MS may experience secondary fatigue and secondary depression due to emotional factors, sleep issues, pain, the coexistence of other illnesses, and medication use. In some studies, the use of disease modifying therapies had a beneficial impact on fatigue, likely by reducing the inflammatory response, demonstrating how closely immunological factors relate to both fatigue and depression

Keywords: Depression • Immunological factors • Inflammatory response • Sleep issues

Introduction

People with multiple sclerosis are frequently identified with fatigue and depression (MS). 35% to 97% of MS patients experience fatigue. It is regarded as one of the most severe symptoms that affect the Quality of Life (QoL) and interferes with everyday activities [1]. A subjective lack of bodily and/or mental energy is referred to as fatigue. There are two types of MS related fatigue: Bodily and cognitive [2]. Physical exhaustion is the root cause of and the outcome of muscle weakness and is described as a decline in motor performance during sustained muscle exercise. A decline in performance during cognitive activity is known as cognitive fatigue, and it is caused by problems with focus, memory loss, and emotional instability. In the early stages of MS, cognitive fatigue develops independently from physical disability and may even exist before the illness is diagnosed [3].

One of the main causes of a lower QoL in all MS patients is cognitive exhaustion. About 50% of MS patients have depression and depression in MS patients [9]. Numerous studies have revealed that individuals with MS identified. It can be challenging to distinguish between these conditions because depression can present itself as exhaustion and its symptoms can be mistaken for fatigue. There is a significant link between fatigue and depression, according to recent research. More than half of MS patients also have one or more of these disorders [4].

Anhedonia, which is characterized by decreased motivation, a lack of positive affect, and a decreased capacity for enjoyment, is the most prominent and typical sign of cognitive fatigue and depression. When neurotransmitters like dopamine and serotonin are insufficient, it can cause anhedonia by impairing the mesocorticolimbic circuits that connect the midbrain to the basal ganglia, limbic system, and prefrontal cortex. It causes the brain's incentive and valence system to be disrupted. Neuroimaging studies in MS patients with fatigue and/or depression have verified the structural and functional changes of mesocorticolimbic pathways [5].

Literature Review

Depression and fatigue in multiple Sclerosis: Their causes and progression

Fatigue and melancholy may be brought on by the neuroinflammatory process that underlies the pathogenesis of MS and disrupts neural function. Proinflammatory cytokines, such as Tumor Necrosis Factor (TNF), interleukins (IL-1a, IL-1b, IL-2, and IL-6), IFN released by mitogen stimulated peripheral blood lymphocytes, and neopterin produced by macrophages upon IFN stimulation, play a crucial role in the pathomechanisms of fatigue and depression in MS [6]. Tryptophan catabolism is induced as a result of proinflammatory molecules. Serotonin and kynurenine are metabolic products of tryptophan. Fatigue and sadness may result from the low levels of these monoamines. There have been reports of higher serum and CSF concentrations of pro-inflammatory cytokines like Interleukins (IL-1a, IL-1b, IL-2, IL-6), TNF and IFN in MS patients who also have comorbid fatigue and/or melancholy.

The levels of fatigue and depression are directly correlated with the elevated concentrations of those pro-inflammatory mediators. By interfering with dopamine and serotonin neurotransmission in the mesocorticolimbic pathways that connect the midbrain with the basal ganglia, limbic system, and prefrontal cortex, proinflammatory cytokines in MS patients cause sickness behavior, which results in abnormal reward processing and anhedonia. Pro-inflammatory cytokines interfere with the production of dopamine and serotonin by decreasing the synaptic supply of precursor amino acids, interfering with their release, and causing an increase in monoamine reuptake [7].

By activating Indoleamine 2,3 Dioxygenase (IDO), the cytokines speed up the alternative kynurenine route, which increases the metabolism of the serotonin precursor tryptophan. Additionally, the cytokines reduce the

availability of co-factor Tetrahydrobiopterin (BH4) restricting the turnover of the precursor amino acids phenylalanine and tyrosine and hindering the production of dopamine. Reduced presynaptic release and increased activity of proinflammatory cytokines functioning as reuptake transporters lower the synaptic availability of serotonin and dopamine [8]

Structural abnormalities in MS related fatigue and depression

Gray matter atrophy in the prefrontal brain, the basal ganglia, the striatum, and the limbic system is linked to fatigue who experience fatigue and melancholy have decreased monoaminergic neurotransmission in frontostriatal and frontolimbic pathways. In a positron emission tomography, an investigation demonstrated the reduced glucose metabolism in the prefrontal cortex and basal ganglia. Additionally, the functional connectivity between the ventral striatum, the amygdala, and the prefrontal cortex was found to be reduced in the functional magnetic resonance imaging research by Finke, et al. and Jaeger, et al. [10].

Discussion

Secondary reasons for MS related fatigue and/or depression

When a person is identified with a chronic illness like multiple sclerosis, their lifestyle changes can result in fatigue and/or depression. Sleep issues, pain, and the presence of other illnesses can all contribute to fatigue and depression. Compared to the general population, individuals with MS experience more sleep disorders, which can be brought on by nocturia, taking medications, emotional disturbances, muscle spasticity, and Restless Legs Syndrome (RLS). RLS affects the quality of sleep in 30 percent to 50 percent of MS patients [11]. The Expanded Disability Status Score (EDSS) measures the progression of a disability and the incidence of RLS. RLS may result from injury to the dopaminergic diencephalospinal and reticulospinal pathways that project to the spinal cord during the course of MS. Medullary lesions that impact the respiratory centers can cause central sleep apnea in MS patients. Fatigue and melancholy risk are proportionately increased by the degree of disability as determined by the EDSS.

Conclusion

Depression and lethargy are extremely common in MS patients. Multiple factors, including inflammatory and neurodegenerative processes, oxidative/nitrosative stress, which causes axonal damage and demyelination, as well as brain atrophy of the prefrontal, frontal, parietotemporal regions, thalamus, and basal ganglia, contribute to fatigue and depression in MS patients. Evidence of elevated serum and CSF concentrations of inflammatory mediators like TNF, Interleukins (IL1a, IL1b, IL6), IFN, and neopterin provided support for the inflammatory etiology of fatigue and melancholy in MS. People with MS may experience secondary fatigue and secondary depression due to emotional factors, sleep issues, pain, the coexistence of other illnesses, and the use of certain medications. The use of any medication to address fatigue caused by MS is not sufficiently supported by research. Drugs that increase monoamine neurotransmission are commonly used to treat depression and fatigue in MS patients, in addition to non-pharmacologic treatments like CBT, relaxation therapy, occupational therapy, and physical rehabilitation.

Recently, improvements have been made in the evaluation of CBT or OT, but there hasn't been much advancement in the evaluation of patient education, which teaches self-management skills, aids in coping with disease-related fatigue, and improves QoL. Due to the numerous potential outcome dimensions, measurement tools, and time points, interventions like self-management education are challenging to evaluate.

Therefore, additional studies on the pathogenesis of fatigue and melancholy in MS patients are required. These studies should focus on neuroimmune interactions, inflammatory biomarkers, the HPA axis, and neurotransmitters. Additionally, there is a critical need for the creation of new assessment tools for the diagnosis of fatigue and its distinction from depression, the evaluation of the efficacy of pharmacological and non-pharmacological treatments, and the impact of DMTs on the onset and progression of MS related fatigue and depression

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Cite this article: Pharasi D. "Fatigue and Depression in Patients with Multiple Sclerosis". J Mult Scler, 2023, 10(8), 515