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ABSTRACT

Nowadays, the success of multiple sclerosis therapy does not only mean the absence of relapses or the existence of a stationary clinical status under disease-modifying therapy, but the maintenance of a high quality of life index. Thus, in recent years, the attention of neurologists has focused on the relationship between depression and MS, depression being the most important factor influencing the MS patient's quality of life. In this regard, the article aims to present a selection of the most important scientific data published during the last 5 years on this topic. Structured in two parts, the initial issue discussed is the etiopathogenesis of depression in MS, with focus on the presentation of theories on the causes of depressive symptoms in demyelinating disease, as well as the intricate relationship between the two clinical entities. Subsequently, the article focuses on capturing the latest developments in currently available pharmacological and non-pharmacological therapeutic means and future prospects for treatment.

Keywords: multiple sclerosis, depression, etiopathogeny, treatment

Abbreviations

CNS – central nervous system

MS – multiple sclerosis

RRMS – relapse-remitting multiple sclerosis

ROS – reactive oxygen species

RNS – reactive nitroative species

IFNB-1b – beta 1b interferon

BDI – Beck Depression Inventory

GDS – Geriatric Depression Scale

BPRS – Brief Psychiatric Rating Scale

TCA – tricyclic antidepressants

SSRI – selective serotonin reuptake inhibitors

SNRI – serotonin-norepinephrine reuptake inhibitors

INTRODUCTION

Multiple sclerosis, a chronic autoimmune inflammatory disease, characterized by the presence of demyelinations in the central nervous system (CNS), is a public health problem in the young and middle-aged adult population, affecting over 2 million people worldwide [1]. While in the past, the attention of neurologists was focused on the study and treatment of motor, sensitive or autonomous symptoms (see EDSS scale criteria), in recent years, the neurological patient's quality of life has become increasingly important. This aspect is essential especially in the case of young, profes-

sionally active people affected by multiple sclerosis, for whom the appearance of the disease has both personal and social consequences. One of the most important factors affecting the of MS patient's quality of life is depression, which is found in a variable but significant percentage (20-40%) of cases [2]. Recent data show that the prevalence of depression characterized by a major depressive episode during lifetime is higher in MS compared to the general population [3], but also compared to patients suffering from other chronic diseases such as diabetes, chronic heart failure, celiac or autoimmune diseases [4].

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According to both older studies [5] and new research that confirm an increased prevalence of depressive symptoms in demyelinating diseases [6], it is natural for the neurologist to want a better understanding of the phenomenon, from risk and etiological factors, to the influence of psychiatric pathology on the natural evolution of the organic disease and on the chronic disease-modifying treatment. This explains the numerous studies in this direction, simultaneously with the existence of studies on potential adjuvant treatment to standard MS therapy, used in order to better control depressive symptoms.

ETIOPATHOGENESIS

The etiology of depression in MS, although intensively researched in recent years, remains unknown [7]. On the one hand, depression can be considered as a symptom associated to the disease, on the other hand, as an autonomous pathology, overlapping MS. There are many theories that try to provide an anatomical-physiological basis for the appearance and evolution of depressive symptoms in MS, thus attesting the complex and intricate relationship between demyelinating disease and major depressive episode.

A first finding is the closer relationship between depression and MS compared to other chronic diseases, the immune cascade resulting from the activation of the innate immune system being proposed as a potential common causal factor for the two pathologies. Based on this premise, depressive symptoms should be correlated with the degree of lesion load, white matter abnormalities and cerebral atrophy; however, according to Colasanti et al., this association between lesions with a certain location and specific depressive symptoms has not been confirmed [8]. The authors thus hypothesized that the high prevalence of depressive symptoms in patients with MS is a direct consequence of chronic activation of the immune system in certain brain regions of functional importance, such as the hippocampus. On the one hand, even though hippocampal atrophy is an important predictive marker for depression, Colasanti et al. decided to go one step further and quantify the immune activation response of the hippocampal microglia through [18F]-PBR111 PET, to correlate subsequently this phenomenon with the functional connectivity of

the hippocampus with other structures, evaluated using functional resting MRI (fMRI). The authors found that the activation of microglia in the hippocampus affects the functioning of this structure, by altering its connectivity with other regions of the brain that contribute to maintaining general affective homeostasis. The results would justify the improvement of depressive symptoms in some patients with MS who benefit from effective control of cerebral neuroinflammation [8].

Similar results are found in the study led by Riccelli et al., which showed a negative correlation between the severity of depression (high score on depression scales) and the activity of the subgenual cingulate cortex, respectively the functional connections between hippocampus, amygdala and prefrontal cortex [9]. In addition, the fact that there was no significant link between depression and the degree of global neurological disability shows the association of depressive symptoms with dysfunctions within the neural networks consisting the connections of the prefrontal lobe with the hippocampus and amygdala.

Atrophic changes in the frontal cortical regions appear to be the structural basis for depressive symptoms in MS. A study led by van Geest et al. objectified the presence of more severe atrophy of the frontal regions and more significant white matter lesions in the frontal lobe (decreased fractional anisotropy on 1.5T MRI) in MS patients and associated depression compared to those without depression [10]. These changes are an additional argument for fronto-limbic disconnection, mentioned in other recent research [8,9].

In addition to damages of the frontal lobe, recent research also shows the involvement of the temporal lobe and basal ganglia as structural cause for MS depression. Stuke et al. observed in a prospective analysis that there is a correlation between the onset and evolution of depressive symptoms and significant gray matter losses in the right middle cingulate lobe, right globus pallidus and right middle frontal gyrus [11]. The study confirms the theoretical concept of cortico-striato-palido-thalamic loop which is altered in depression. In this sense, the atrophy of the gray matter in the basal ganglia (including globus pallidus and thalamus) can lead to disorders of hedonic motivation, while atrophy of the prefrontal cortex additionally contributes to an unfavorable evolution of depressive symptoms by influencing adaption strategies.

Despite the increasingly evidence that structural alteration of the hippocampus is the morphopathological basis of depression in MS, a study led by Rocca et al. aims to bring a positive component to this observation. According to the authors, the specific feature of the hippocampus is, along with susceptibility to damage, the potential for neurogenesis manifested by increased synaptic neuroplasticity [12]. Methods to amplify this hippocampal neuroplasticity through exercise (especially aerobic exercise) and cognitive rehabilitation in the process of physiological aging, mild cognitive impairment, Alzheimer's disease and, to a lesser extent in MS, have also been studied, however with inconclusive results due to the variability of the methods used and the small number of patients in the sample. Still, there are beneficial effects of interventions on memory function, with increased hippocampal volume and functionality [13].

Also regarding the inflammation-depression relationship, the results of Lee & Giuliani attest the fact that depression is characterized by inflammation at the periphery of the CNS, especially at the blood-brain barrier level, which has increased permeability [14]. It is thus allowed the entry of inflammatory molecules and immune cells into the CNS, resulting in increased inflammatory signaling, and finally with structural and functional changes, more important in certain regions, such as the hippocampus.

Another interesting theory refers to the incompletely studied biochemical abnormalities found in both MS and major depression, which, according to the results of Morris et al., would explain the interrelationship between the two diseases [6]. The theory of chronic oxidative and nitrosative stress suggests that these pathologies are a result of damaging changes in proteins, lipids and DNA, followed by loss of immunogenic tolerance. At the same time, prolonged oxidative stress leads to impaired functionality of mitochondria, as explained by Balmus et al. [15]. Among cellular organs, mitochondria are the most active in the production of ROS / RNS, while in psychiatric pathologies (eg bipolar disorder), there is a high rate of occurrence of mitochondrial DNA mutations. This path of research remains open, in the desire to find a way to correct mitochondrial metabolism that could improve (even suppress) the symptoms subsequently.

Last but not least, psychosocial factors such as the psychological impact of disability and illness, social impact (with early retirement) or low socio-economic status (eg rural people or those living alone) must be considered. Psychosocial factors have been shown to explain a significant percentage of patients' self-reported depression [16].

According to Corallo et al., depressive symptoms could be a psychological reaction to the diagnosis of MS, or an indirect consequence of losing social or occupational function or status. Even though external (psychosocial) factors, due to the numerous interpenetrations of pathophysiology between MS and depression are recognized, the authors consider depressive symptoms as part of the clinical picture of the disease, and not independent pathology [17].

On the other hand, careful examination of the clinical phenotype of depression does not reveal differences between MS patients and other depressed patients, which would argue for the independent pathology status of depression in demyelinating disease, although bioimmunochemical pathways are similar [18].

The appearance and evolution of depression in MS remains certainly a subject only partially known, requiring more in-depth research of pathophysiology to determine the etiological factors and molecular pathways of the pathology.

TREATMENT OF DEPRESSION IN MS

The importance of treating depression in MS results primarily from epidemiological data that attest the increased frequency of psychiatric pathology encountered in patients with MS [4]. In addition, two studies show that depression depends on the stage of the disease, with an increase in the incidence and prevalence of depression, along with an increase rate of prescriptions for antidepressants, even 2 years before the diagnosis of MS, which confirms the theories of similar pathogens causing depression and demyelinating disease [19,20].

Besides numerical data, the influence of depression on other parameters of the individual's life, as well as the relationship with other organic or psychiatric symptoms must be mentioned. Depression is the most important factor in determining the

QoL of MS patients, regardless their disability [21]. In addition, depressed patients associate a higher rate of hospitalizations and lower adherence to disease-modifying therapy [22].

Although it has been known for many years that depression is the most common psychiatric symptom encountered in patients with MS [23], there is currently no established consensus regarding the optimal method of treatment of this pathology, in the case of association with MS. From a practical point of view, we can divide therapeutic resources into pharmacological resources and non-pharmacological adjuvant options.

Regarding drug therapy, it should be mentioned from the beginning that there is no standard protocol. Optimal management is thus evasive, left to the choice of the clinician, because, despite the existence of more and more studies, the controlled and systematized evidence to form clinical practice guides is substantially missing. Pharmacotherapy must be patient - tailored, as the safety and tolerability of antidepressants has individual variability. Ideally, medication is a choice advised by both the neurologist and the psychiatrist.

Currently, this antidepressant treatment should follow the same directions as for the general popu-

lation, but with some modifications and precautions. SSRIs, such as sertraline, escitalopram, citalopram, and fluoxetine, are considered first-line pharmacological treatment because they are as effective as other antidepressants and have a good risk-benefit ratio, unlike paroxetine known for frequent interruptions due to side effects. Other effective agents, like serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine, TCA and mirtazapine, should be considered second-line treatments due to an increased risk of potential side effects, such as the associated anticholinergic properties when using TCA [24].

Initial antidepressant doses for MS patients should generally be lower than for non-MS patients [25]. The psychological treatments with the highest degree of recommendation are cognitive behavioral therapy and interpersonal therapy. In moderate to severe depression, a combination of psychological and pharmacological therapy is recommended [26].

Particular attention should be paid to the side effects of antidepressant medication. Among the most relevant examples, we mention the fact that SSRIs can increase spasticity and reduce libido

TABLE 1. *The most used antidepressants in neurological practice*

Medication	Pharmacological Class	Important clinical features	Reference
Fluoxetine	SSRI	Used as a first line in the treatment of depression in MS	Bruno et al., 2020 [28]
Paroxetine	SSRI	Slight anticholinergic effect It aggravates urinary retention, male fertility and cognition Causes vision problems (blurred vision), weight gain to be avoided in MS	Nevels et al., 2016 [29]
Amitriptyline Nortriptyline	Tricyclic antidepressants (TCA)	Used as a second line of treatment due to its associated anticholinergic properties	King & Ashraf, 2018 [24]
Duloxetine	SNRI	It causes an increase in the concentration of norepinephrine reduces anxiety relieves fatigue and painful somatic perception	Muscattello et al., 2019 [30]
Bupropion	norepinephrine-dopamine disinhibitor (NDDI)	reduces painful somatic perception and anhedonia does not cause obesity or sexual dysfunction	Khan et al., 2016 [31]
Pregabalin Gabapentin	α (2) δ GABA receptor subunit antagonist	It causes decreased levels of anxiety and somatic pain does not act on depression	Solaro et al., 2018 [32]
Lithium	-	The low dose of lithium is well tolerated in people with MS. subjects who took lithium did not report worsening fatigue or physical well-being. mood and mental health, subjects scored more favorably while taking lithium.	Rinker et al., 2020 [33]
Mirtazapine	adrenergic and serotonin receptor antagonist	Hormonal effect with reduced cortisol levels Significant improvement in the symptoms of major depressive disorder in the first 1-2 weeks of treatment lower rates of depressive relapses	Schwasinger-Schmidt & Macaluso, 2019 [34]

(already affected in some MS patients). Table 1 summarizes the most widely used antidepressants in current practice [27].

Another important antidepressant therapy arm is the non-pharmacological one that has come to the attention of several researchers in recent years. Psychological therapies are an adjuvant method with good results, as observed by Fiest et al., the severity of depression in MS has improved with psychological therapy, including through cognitive behavioral therapy [35].

Other relatively new psychological techniques in health research, but increasingly seen as a key to effective management in chronic diseases, are self-management interventions [36]. These techniques aim to facilitate a person's ability to make lifestyle changes and to manage the symptoms, treatment, physical and psychosocial consequences that occur in the case of MS associated or not with depression [36].

It is worth mentioning two studies that aimed to demonstrate the beneficial effects of adjuvant supplements. Rolf et al. studied the relationship between vitamin D administration and depression in MS by researching immunological biomarkers. Following administration of 14,000 IU vitamin D/day, for 48 weeks in patients with RRMS, no reductions in pro and anti-inflammatory cytokines were observed [37]. Another compound, omega 3, administered 3 g/day for 3 months, although safe and well tolerated by subjects, did not demonstrate an improvement in major treatment-resistant depressive disorder in people with MS [38].

In the case of severe depression and treatment-resistant depression, a final option is electroconvulsive therapy (ECT) which, in MS patients, can be administered with the usual precautions, without additional risks [39].

Finally, the patient should benefit from psychotherapy, social assistance, occupational counseling and physical therapy regardless of the prescribed antidepressant medication.

THE LINK BETWEEN SPECIFIC MS TREATMENT AND DEPRESSION

Worth mentioning in this review are the relationships between specific MS treatment (especially chronic treatment with disease-modifying drugs) and psychiatric symptoms, given that in the

past there have been references to a potential correlation between beta interferon treatment and the onset or worsening of depression [40]. Numerous studies and meta-analyses have followed on this topic, among them, it is worth referring to a multi-center, prospective, randomized controlled study with a large number of patients (over 2,200 patients from 21 countries), led by Schippling et al., which denied the existence of an increased risk of depression with standard or double-dose treatment for both IFNB-1b and glatiramer acetate [41]. The results of glatiramer acetate therapy on psychiatric comorbidities were also studied by Fricska-Nagy et al., in a multicenter study (19 centers in Hungary), which aimed to determine the correlations between quality of life, level of disability, fatigue depression and chronic treatment of MS. The prevalence of depression was lower (13.4%) than that described in previous studies, and glatiramer acetate did not show any psychiatric adverse effects [42].

Regarding the rest of the chronic disease modifier treatment options in MS (Natalizumab, Fingolimod, Teriflunomide, Alemtuzumab), Gasim et al. summarized the associations between these second-line medications and the full spectrum of psychiatric disorders that occur in MS, with the most commonly reported pathologies being depression and anxiety. No increased risk of psychiatric symptoms was identified during chronic treatment, whether we refer to randomized clinical trials, observational or case studies. In addition, in patients diagnosed with psychiatric symptoms prior to initiating second-line treatment, there was an improvement in depression and anxiety, especially with Fingolimod and Natalizumab. On the one hand, one explanation would be the pathophysiology pathway with many points of interpenetration in case of MS and depression, another explanation being the fact that, under better control of the disease, the patient regains (at least partially) autonomy and decreases the stress of uncertainty, subsequently relieving anxiety or depressive episodes [43].

We must not forget the treatment of acute MS relapses, more precisely the administration of high doses i.v. methylprednisolone and its relationship to psychiatric symptoms. In this regard, Lotan et al. conducted a study on patients with inflammatory neurological diseases who received as relapse

treatment up to 1,000 mg/day methylprednisolone for 5 days. To objectify depressive symptoms, subjects were assessed using the BDI, GDS, BPRS scales before initiating acute phase treatment, at the end of treatment, and at reevaluation after one month. Decreased scores on the BDI and GDS questionnaires were observed throughout the study, indicating a general beneficial effect of therapy on depression [44].

In addition, although unrelated to MS, but with possible implications for relapse treatment, glucocorticoids have been shown to be effective in reducing the risk of post-traumatic stress disorder, the pathophysiological mechanism being still incompletely elucidated [45].

It can be stated that high-dose corticosteroid treatment in neurological patients without significant pretreatment psychiatric disorders is relatively

safe, both in the acute phase and at a distance, without leading to the occurrence of depressive phenomena.

CONCLUSIONS

Depression, a topic intensely researched in psychiatry, is gradually becoming an area of interest for the neurologist as there are various therapeutic opportunities with satisfactory results, especially in young, socio-professionally active MS patients, to whom the additional presence of psychiatric symptoms has a significant negative influence on the prognosis. It remains a priority to fully understand the etiopathogenesis, being mandatory also a systematization of antidepressant treatment, with the establishment in the coming years of a specific treatment guide for MS patients.

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