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Neuroimmune, clinical and treatment challenges in multiple sclerosis-related psychoses

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Abstract

In recent years, epidemiological and genetic studies have shown an association between autoimmune diseases and psychosis. The question arises whether patients with schizophrenia are more likely to develop multiple sclerosis (MS) later in life. It is well known that the immune system plays an important role in the etiopathogenesis of both disorders. Immune disturbances may be similar or very different in terms of different types of immune responses, disturbed myelination, and/or immunogenetic predispositions. A psychotic symptom may be a consequence of the MS diagnosis itself or a separate entity. In this review article, we discussed the timing of onset of psychotic symptoms and MS and whether the use of corticosteroids as therapy for acute relapses in MS is unfairly neglected in patients with psychiatric comorbidities. In addition, we discussed that the anti-inflammatory potential of antipsychotics could be useful and should be considered, especially in the treatment of psychosis that coexists with MS. Autoimmune disorders could precipitate psychotic symptoms, and in this context, autoimmune psychosis must be considered as a persistent symptomatology that requires continuous and specific treatment.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) that is characterized by neuroinflammation, demyelination, axonal loss and neurodegeneration[1]. It is one of the most common neurologic disorders and the most common cause of acquired neurological disability in young adults, that has an effect on 2.5 million people worldwide[2]. MS patients are two to three times more likely than the general population to suffer from mood and mental disorders[3,4].

Neurological and psychiatric diseases often overlap and co-occur[5,6]. Psychiatric symptoms may occur at any time during a neurological autoimmune disease, but they may also be an initial clinical manifestation and precede the onset of typical neurological symptoms[7]. The initial or early presence of these symptoms may complicate the establishment of a correct diagnosis, hinder the early recognition of the underlying brain disorder, and lead to inadequate treatment and a poorer prognosis[8,9]. Furthermore, the presence of various psychotic symptoms in neurological diseases additionally compromises these conditions and has an impact on individual functioning and overall disease burden[10]. The prevalence of psychosis/psychotic disorders is approximately 4.3%[11].

Mental disorders in neurological diseases may have different underlying causes[12]. In MS patients, the onset of psychiatric symptoms may be a consequence of the MS diagnosis itself[13]. Brain lesions, physical disabilities, symptoms of MS and pharmacological treatments may cause psychopathological manifestations[14].

There is limited scientific evidence that could be useful for clinical decision-making in the resolution of psychotic symptoms in patients with MS. Recent data by Sabe and Sentissi have confirmed our clinical observations[15]. There is a lack of data considering MS and psychosis, especially schizophrenia (SCH), simultaneously. We might think that this is due to a lack of interest in the field, but it is also possible that these disorders do not exist at their full capacity simultaneously. In this mini-review, we aim to resolve some clinical dilemmas. First, we discuss the timing of the onset of psychotic symptoms and MS. Second, whether the use of corticosteroids is unfairly neglected and whether a more aggressive treatment approach is warranted. And third, whether antipsychotics may be

of benefit as adjunctive therapy is discussed. Immune disturbances may be similar or very different in terms of different types of immune responses, disturbed myelination, and/ or immunogenetic predispositions.

This mini-review was conducted through a systematic electronic search of the PubMed, Cochrane, and Web of Science databases to identify cases of MS with psychotic symptoms. The terms used were "multiple sclerosis"; "psychosis"; "schizophrenia"; "neurodegeneration"; "neuroinflammation"; "corticosteroids"; and "antipsychotics." We searched for studies published in English, with no restriction on year of publication. Experimental studies, randomized or nonrandomized clinical trials, cohort studies, and case-control studies were included. We have assessed the abstracts of potentially relevant titles and reviewed the full text of potentially eligible studies. In this mini-review, we attempted to select and focus on only up-to-date and clinically relevant data.

NEUROIMMUNOLOGICAL ASPECTS OF MS AND PSYCHOSIS

Genetic predisposition, individual and environmental factors, and specific immune responses had a significant impact on disease onset and clinical presentation. This suggests that the same etiological factors and pathophysiological pathways may influence the association between MS and psychosis. It raises the question of whether patients with SCH might also suffer from MS later in life. The genetic basis of MS is supported by the fact that the risk of disease is higher in MS family members than in the general population, that certain racial and ethnic groups have a lower illness tendency, and that the concordance rate is higher in monozygotic twins[16]. Previous genetic studies have shown that the predisposition to develop MS depends on several independent polymorphic genes and their interaction. No single gene variant is necessary or sufficient to cause MS, but each one increases the overall risk of the disease in an additive manner[17]. Genome-wide association studies (GWAS), which examine gene polymorphisms in the whole genome, suggest that over 200 gene loci that have different immune functions are responsible for the development of MS[18,19]. The risk genes control the differentiation and state of these cells through their function in specific cellular

processes in immune cells. In addition, recent evidence indicates that many immune cell populations are highly heritable, raising the possibility that MS risk genes define differences of immune cell populations that could also be involved in the pathogenesis of illness[18].

It is well known that the immune system plays an important role in the etiopathogenesis of MS and SCH[20,21]. Some authors assign them to the same group of neuroinflammatory and neurodegenerative properties, but with marked differences in the immune response. From the clinician's point of view, this fact could mean that these disorders are mutually exclusive. We have already considered confronting results of the prevalent immune responses in MS and SCH as prototypes of disorders of type 1 vs. type 2 immune responses, respectively[22,23]. In recent years, growing epidemiological evidence has suggested a bidirectional association between autoimmune diseases and increased risks with SCH[24]. A family history of autoimmune disease has been shown to be related to an increased risk of psychotic disorders and vice versa[25]. In addition, having a first-degree relative with SCH increases the risk of autoimmune diseases by 6%[26]. Previous studies have found that patients with MS are at an increased risk of developing SCH[27]. SCH and other psychotic disorders have been associated with genetic markers of immune activation, suggesting a possible etiological link between MS and psychosis[28]. GWAS emphasized the significant overlapping of genes, noted the involvement of similar HLA alleles, and identified 21 independent loci associated with SCH and also associated with MS. In these diseases it seems that the major histocompatibility complex is responsible for the genetic overlap[29,30]. A possible additional role of genetics in this association could be an inherited susceptibility to common risk factors for infections or a predisposition to abnormal immune responses that further increases the risk of autoimmune reactions[31]. Despite the contrasting nature of these diseases, some common features have been identified. Risk factors for both MS and SCH include an interaction between genetic and environmental factors[32,33]. Infection is one of the most important triggers for the development of both diseases[34,35]. In the last decade, considerable attention has been paid to the gut microbiome as a possible

etiological factor in the pathophysiology of MS and SCH[36]. It has been suggested that the composition of the intestinal flora plays an important role in CNS and immune system development[37]. Dysbiosis of the microbiome has been shown to affect the Th1/Th2 balance and the ratio of regulatory T cells to Th17 cells, which affects the immune response to pathogens[38,39]. Dysbiosis has been found to affect T cell-mediated inflammation in MS and SCH patients[40,41].

In SCH, it has been previously hypothesized that inflammation in the microvasculature persists as chronic, low-grade inflammation and does not disseminate in whole brain parenchyma as in acute encephalitis[21]. This organic substrate could be related to the soft neurological signs, observed in patients with SCH[42]. Similar to SCH, the clinical manifestations in MS may be the result of acute or chronic neuroinflammation. In the acute stage, the peripheral immune system is involved, and T cells, B cells, and macrophages enter into CNS and cause acute inflammation in the brain[21]. In addition, these mechanisms have no influence on the chronic phase. Recently, a concept of "compartmentalization" of the inflammatory process in the brain has been postulated, in which a local immune response in the CNS occurs separately from the peripheral immune system[43]. This hypothesis is supported by the fact that disseminated activation of microglial cells is the primary characteristic of the chronic phase of the illness[44]. There is ample evidence of biomarkers indicating a link between immunological processes, psychotic disorders and MS. Elevated levels of different inflammatory markers have been found in the blood and cerebrospinal fluid (CSF) of patients with psychosis and MS, with particularly high levels in patients with first-episode psychosis or acute relapse[45,46]. Dysregulation of regulatory T cells and Th17 cells may be essential for immunological homeostasis and play a role in the development of both diseases[47,48]. In recent years, much attention has been paid to B cells and their role in the autoimmune pathology of MS and psychosis[49,50]. Oligoclonal bands (OCBs) in CSF have been detected in approximately 90% of patients with MS[51]. In up 12.5% of patients with SCH were found OCBs[45]. It is important to keep in mind that there are other possible triggering and contributing factors besides the specifics of the immune response in MS and psychosis.

Within the new concept of nomothetic network psychiatry and causal models, perhaps the identification of these transdiagnostic classes could even be presented as new nosological categories[52].

CLINICAL ASPECTS OF MS AND PSYCHOSIS

In clinical practice, it is important to distinguish whether psychosis precedes the onset of MS, coincides with MS, or is observed in the later stages of this somatic disease. We remind that these psychotic symptoms could be integral to SCH, a schizoaffective disorder, affective disorders, or even delirium. Also, we must point out that psychosis should be considered as a much broader concept than SCH. This information is important for the choice of future MS treatment.

Symptoms and signs of MS include ataxia, loss of coordination, hyperreflexia, spasticity, loss of visual acuity, sphincter incontinence, fatigue, anxiety, depression, and cognitive deficits[53]. Most patients have a relapsing-remitting form of the disease which is characterized by progression of symptoms in relapse and possible further deterioration over time[53].

Neuropsychiatric symptoms were previously reported as a rare manifestation of MS. Recently, the most commonly observed behavioural disturbances preceding the onset of MS have been summarised. Symptoms described include lack of insight, delusions, auditory and visual hallucinations, mood disturbances, behaviour disorder, and confusion[15]. Psychotic symptoms reported in MS patients also include irritability/agitation, sleep disturbances, grandiosity, blunted affect, and rare symptoms such as catatonia and transient catalepsy[4,14].

In a recent systematic review of case reports and case series, the authors pointed out that psychotic symptoms preceded or accompanied the MS diagnosis in half of the cases, with a mean time to MS diagnosis of 0.8 ± 1.4 years, whereas 15.1% of MS diagnoses were discovered after isolated psychiatric symptoms. They observed a significant delay considering MS treatment initiation between initial psychotic symptoms and MS diagnosis (2.73±3 years), and in patients with the first episode of psychos and MS

diagnosis (0.8 ± 1.2 years)[15]. Another important observation in their analysis was that typical MS white matter lesions were found in a small group of patients with psychiatric disorders[54]. Finally, they pointed out that resistance or poor response to antipsychotics was associated with excellent improvement of both psychiatric and neurological symptoms with corticosteroids in most cases[15]. Autoimmune psychosis must be considered as a persistent symptomatology that requires continuous treatment[55].

Pathological changes in white and grey matter structures may play an important role in the pathogenesis of MS-related psychosis. Neuroimaging studies revealed that MS patients with psychotic symptoms have a higher total lesion score, especially in periventricular areas[56]. Psychotic symptoms in MS are correlated with a higher number or volume of lesions in the temporal or frontal lobes, cerebellum, and corpus callosum[57,58]. In addition, the presence of soft neurological signs in patients with sudden or acute psychotic symptoms without a prior personal or family history of psychosis is an indication for neurological exploration[15,59].

KNOWN FACTS AND TREATMENT CHALLENGES IN MS-RELATED PSYCHOSIS

Immunomodulatory medications for the treatment of MS could be useful to achieve remission of the disease, but in some cases may have a direct effect on the development of psychotic symptoms, although the mechanisms are poorly understood. This effect also occurs after initiation of corticosteroids or could be related with interferon beta (IFN-β) treatment. The study of 11 cases confirmed severe depression with suicidality in patients with MS, who were taking IFN-β and had no psychiatric history[60]. These patients also had phobic, aggressive, behavioural, psychotic, and manic symptoms, indicating the presence of a complex mood-behaviour disorder associated with IFN-β use. Complete remission of psychiatric complications was observed after discontinuation of IFN-β. Glatiramer acetate was generally not associated with deterioration of mood[61]. Gasim *et al*[62], 2018, conducted a systematic review to investigate whether the use of disease-modifying therapies is associated with adverse psychiatric effects in MS patients. This study included natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and

alemtuzumab and showed that their use do not increase risk of adverse psychiatric effects in MS, and some of them, such as fingolimod, even reduced the incidence of depressive symptoms. In addition, Krivinko *et al*[63], 2022, recently demonstrated that fingolimod treatment attenuated psychosis-associated behavioural deficits in rodents.

The standard MS treatment for acute exacerbations is pulse therapy with systemic glucocorticoids. Intravenous methylprednisolone at a dose of 1000 mg/d for 3 or 5 days or oral prednisone with or without tapering dose is usually used[64]. Administration of high-dose corticosteroids (HDC) may be repeated, depending on the MS course and disease activity[65]. Pulsed regimens of corticosteroid administration in the short term in MS have been reported to be well tolerated and safe, with only minor transient and dose-dependent side effects such as palpitations, hot flashes, dyspepsia, insomnia, and virulent taste[65].

An important clinical question is whether the use of corticosteroids, which are regularly used to treat MS relapses, can induce psychiatric symptoms. Several reports suggest that psychiatric side effects may occur with HDC use, including hypomania/mania, depression, psychosis, and suicidal ideation[66–71]. Mood changes, particularly (hypo)mania and depressive symptoms could be potentiated by HDC treatment [72]. In patients with MS, depression and mood disorders have been associated with pulse steroid therapy, suggesting that the risk may be related to the patient's psychiatric history[73].

Steroid-induced psychosis is a well-documented phenomenon[74]. In clinical practice, there are different approaches to corticosteroid treatment for MS-related psychosis. The literature on the treatment of corticosteroid-induced psychosis is very scarce and limited to MS reports and small-sample size studies. In our country, the prevailing opinion is that patients with psychosis should not be treated with corticosteroids because they may exacerbate psychosis. Moreover, nearly 30% of patients in the acute phase of their psychotic symptoms were successfully treated with corticosteroid therapies. [75]. The question arises whether it is more beneficial for the patient to keep the psychosis under control or to treat the acute relapse, act on the inflammation, and prevent further disease

progression and neurological disability. The Maudsley guideline indicates that the benefits of corticosteroid therapy may outweigh its adverse effects[76]. To date, however, few studies have explored the impact of corticosteroid therapy on psychosis in people affected by MS, and the specific risk factors predictive of psychiatric changes remain unclear[72,77]. Chronic consumption of corticosteroids and increase in their dose and duration of treatment are associated with these adverse effects [78]. As frequently mentioned, a general therapeutic strategy for corticosteroid-induced psychiatric symptoms should begin with dose reduction or discontinuation of the drug whenever possible[69,79].

Corticosteroid-induced hypomania, mania, and mixed mania showed to be successfully treated with a typical antipsychotic or mood stabilizer, most commonly haloperidol, haloperidol plus lithium, quetiapine, risperidone, olanzapine, olanzapine with valproate, carbamazepine, lithium, lamotrigine plus clonazepam, or clonazepam alone when lithium was ineffective[68]. In some cases, a combination of an antipsychotic and a benzodiazepine was needed[68]. In the case of medication-induced psychosis, adjustment of the MS drug should be considered and treatment with an antipsychotic should be initiated. There are few practical guidelines for the choice of antipsychotic drug and dosage, but there is evidence of good results with the use of clozapine, risperidone, ziprasidone, low-dose chlorpromazine, or the prophylactic use of lithium along with corticosteroid therapy[80]. In patients with steroid-induced psychosis, use of the antipsychotic quetiapine resulted in decreased irritability, reduced psychological distress, and improved sleep[81]. Atypical antipsychotics remain the treatment of choice in these patients because they have a more favourable tolerability profile, as they are less likely to affect the extrapyramidal system and reduce the risk of developing pseudoparkinsonism and catalepsy[82,83]. Researchers also presumed that patients with MS had an unexpected sensitivity to antipsychotic drugs[84]. MS is closely related to various movement disorders[85]. However, clinicians should be aware that movement disorders can also represent adverse drug reactions caused by chronic antipsychotic therapy[86], especially in cases of polypharmacy.

The anti-inflammatory potential of antipsychotics could be useful and should be considered especially in the treatment of psychosis that coexists with MS. Patients with SCH have been found to have decreased intracortical myelination, whereas certain antipsychotic agents may restore this defect. Patergnani *et al*[87], 2021, showed that human and experimental MS induce a mitochondrial deficit leading to activation of autophagy and mycophagy. These phenomena play a causal role in MS as their inhibition by antipsychotic drugs such as haloperidol and clozapine may prevent demyelination, induce remyelination, and reverse MS behavioural deficits[87]. In addition, Stamoula *et al*[88], 2022, argued that the atypical antipsychotics clozapine, risperidone, quetiapine, and olanzapine dramatically reduce the severity of experimental autoimmune encephalomyelitis and delay its onset by downregulating the production of pro-inflammatory cytokines and chemokines and attenuating T-cell infiltration, myeloid cell activation, and upregulation of T regulatory cells.

CONCLUSION

Psychotic symptoms could represent an acutisation of MS, considering the specific localization of the lesions. In this context, it can be assumed that causal therapy of MS also leads to resolution of psychosis. It is also important to exclude somatic comorbidities to make the diagnosis of SCH. Autoimmune disorders could precipitate psychotic symptoms, and in this context, special attention should be paid to patients with the first psychotic episode and soft neurological signs, sudden cognitive decline, and unsatisfactory response to antipsychotic treatment. Only when all of the previously mentioned facts have been ruled out can one conclude that psychosis is a separate entity (Figure 1). Physicians treating patients with MS and psychosis should assume, first and foremost, that the psychotic syndromes are related to MS and not triggered by medication. Based on the literature data, it is extremely important for clinicians to perform accurate screening of psychiatric status in patients with MS before initiating HDC treatment and to note that HDC should be used with caution in patients with an acute MS exacerbation. The properties and indications of available immunomodulatory

drugs need to be better understood, and the therapeutic approach should be adjusted with careful consideration of the individual's unique constellation of symptoms. The mechanism of action and pharmacokinetics of the antipsychotic drug, the safety and efficacy profile from clinical trials, and knowledge of potential side effects should also be incorporated into the therapeutic strategy.

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