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SPECIAL ARTICLE

Psychiatric event in multiple sclerosis: could it be the tip of the iceberg?

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Multiple sclerosis (MS) is a chronic progressive inflammatory disease of the central nervous system. Psychiatric comorbidities are highly prevalent in patients with MS, and can have drastic impact on quality of life and interpersonal relationships. Despite this high prevalence, whether psychiatric manifestations may represent the first signs of MS is still debatable. This constitutes an important issue, since early diagnosis of ''psychiatric-onset MS'' would result in prompt management, which usually ameliorates long-term prognosis. Here, we discuss clinical and radiological hints that suggest a diagnosis of psychiatric-onset MS. Briefly, this entity should be considered in healthy patients presenting with late-onset psychiatric symptoms, with or without cognitive decline, and with negative family history of psychiatric diseases. A thorough neurological exam is crucial to detect any subtle neurological signs. Brain magnetic resonance imaging is recommended to rule out frontotemporal lesions that might explain the clinical picture. Poor response to standard psychiatric treatments provides additional evidence for the diagnosis of an organic disease (e.g., MS). Combining psychopharmaceuticals with intravenous corticosteroids would result in good outcomes, but patients should be monitored carefully for possible psychiatric exacerbation, a common side effect of steroids.

Keywords: Psychiatric relapse; multiple sclerosis; mood; depression; mania; psychosis

Introduction

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system (CNS) and represents the major cause of non-traumatic disability in young adults.[1] The precise etiology of MS remains unclear, and involves a constellation of mechanisms. The disease course usually includes relapses and progressive functional decline. It is very heterogeneous among individuals, and characterized by the accumulation of sensorimotor, cerebellar, cognitive, and psychiatric symptoms.[1]

Psychiatric comorbidities can affect up to 95% of MS patients during their lifetime[2] and are thought to be related to the pathological changes of the disease. The most frequent complaint is depression, followed by anxiety, with a prevalence of around 50% for the former and from 14 to 41% for the latter.[2] In addition, psychotic features are found to affect 2-3% of MS patients, and bipolar disorder appears to be twice as common in those with MS as in the general population.[2] All of these conditions can have a drastic impact on quality of life and interpersonal relationships, which can translate into altered social interactions, high rates of divorce, and unemployment.[3-5]

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Despite the prevalence of psychiatric manifestations, it is still debatable whether an acute psychiatric episode in a previously healthy individual may constitute the initial presentation of MS. Answering this question is very important, since early diagnosis would result in prompt initiation of treatment and is usually associated with a better prognosis. In spite of the real challenge presented by these difficult situations, some valuable clinical and radiological hints exist, which could help solve this dilemma and establish the diagnosis of psychiatric-onset MS. These hints constitute the main scope of our paper.

Prevalence of psychiatric-onset multiple sclerosis

In one of the earliest studies on this topic, Lyoo et al.[6] aimed to search for MS in a psychiatric population. They found that 0.83% of patients presenting for psychiatric evaluation had white-matter hyperintensities on T2-weighted magnetic resonance imaging (MRI), and that these lesions fulfilled the criteria for MS diagnosis proposed by Paty et al.[7]

Other authors have since studied the prevalence of psychiatric-onset MS. In a case report by Jongen,[8] psychiatric onset was suggested to occur in at least 1% of the MS population. This was later proved by Carrieri et al.,[9] who screened 148 MS patients for psychiatric onset and found the latter to constitute 1.3% of all cases. Two other groups of authors assessed larger MS cohorts and reported that around 2% of patients had a psychiatric episode as

the initial sign of the disease.[10,11] This was particularly notable in Skegg et al.,[12] who found 9% of their patients to have received psychiatric diagnoses prior to that of MS. A striking 52% of patients in the Sullivan et al.[13] cohort described the occurrence of depression prior to establishment of an MS diagnosis. However, this latter prevalence should be interpreted with caution given the retrospective nature of the study, which could have resulted in recall bias.

Berna et al. compared the characteristics of neurological and psychiatric relapses.[14] Although both episodes seemed to occur on average at a similar age, the diagnosis of MS was delayed by about 7 years in patients who first presented with psychiatric manifestations compared to those with neurological or mixed first episodes.[14] Taken together, these data highlight the need to disentangle the possibility that psychiatric episodes may herald MS.

Clinical hints suggesting diagnosis of an MS-related psychiatric event

Our insight into the occurrence of psychiatric events in MS originates mostly from case series and reports documenting depression, mania, hypomania, psychosis, obsessive compulsive disorder, personality disorders, and catatonia.[8,9,11,14-33]

A psychiatric event can be expressed as a pure psychiatric episode as the inaugural MS manifestation[9,14-18,21-24,29-31,33] in association with neurological symptoms[8,14] or occurring later, after a neurological relapse.[14,19,24,27,31]

Logically, the presence of neurological symptoms makes the last two presentations relatively easier to identify than the first one. Unfortunately, the first form might occur several times before a diagnosis of MS is considered.[14,20,31]

The resemblance of psychiatric symptoms in MS to those observed in pure psychiatric disorders[32] makes it even more difficult for psychiatrists to differentiate between the two. However, this scenario could be avoided if physicians rely on some red flags in the history and physical exam. Late-onset psychiatric symptoms,[20,26] negative personal or family history of psychiatric diseases,[21,26,27,29,31,33] positive family history of MS,[24,25] and presence of cognitive decline[15,26] should raise further attention to the etiology of symptoms and prompt physicians to consider organic causes.

First, according to the DSM-5, the mean age at onset of first psychiatric episode is approximately 18 years for bipolar 1 disorder, the mid-twenties for bipolar 2 disorder, the twenties for major depressive disorder, and the mid-thirties for psychotic illnesses.[34] Hence, the onset of psychiatric symptoms in late mid-life or late life speaks more in favor of an organic etiology, such as MS.[34] Second, a positive family history of MS should also raise the possibility of MS in the presenting patient. For instance, a report by Solomon[25] described a patient in manic episode whose father and brother were affected by MS. Another example is found in a paper by Modrego & Ferrández,[24] who described familial MS in a mother and daughter who initially experienced manic episodes. Third, psychiatric patients commonly have a positive family history of mental illness; thus, the absence of psychiatric illnesses among a patient's relatives should suggest an organic origin.[20,24,25,27,29,30] Fourth, although symptomatology is very similar in MS and psychiatric disorders, some reports have proposed distinguishing features. For instance, compared to schizophrenia, psychosis in MS is characterized by faster resolution, fewer relapses, and probably better psychiatric outcome.[35] Additionally, depression in MS usually manifests with anxiety, irritability, anger, and somatic disturbances, while apathy and withdrawal are rare in this context.[36]

Although the neurological exam might be unremarkable,[14,37] the presence of minor abnormalities constitutes a warning sign that can guide clinicians to the correct diagnosis.[8,15,21,24,26,31]

Further clues could be obtained from response to treatments. The classical management of any psychiatric symptom consists of the introduction of appropriate and commonly used medications, such as, antidepressants, anxiolytics, and antipsychotics. Limited or absent efficacy of these compounds should prompt the medical team to reappraise the diagnosis, search for an organic etiology, and try alternative therapies. In other words, the response of MS patients to psychiatric medications is poor compared to those with pure psychiatric disorders. This seems to resemble other situations in which white-matter hyperintensity lesions have been found and correlate negatively with response to treatment, such as geriatric depression.[38-44]

In this context, some authors have documented the beneficial role of immunomodulatory treatments, such as glatiramer acetate, interferons, and steroids, in the management of manic and depressive psychosis secondary to active MS.[21,24] Clinicians should be aware of the possibility of exacerbation of psychiatric symptoms following administration of high-dose methylprednisolone. However, it is worth noting that this side effect is transient and not constant[45] and thus should not limit or postpone steroid therapy.[31]

Symptomatic treatment options are also very important in MS management and have shown some efficacy in ameliorating various symptoms, including cognitive decline, spasticity, pain, and bladder dysfunction.[42] Moreover, since pharmacological treatment alone does not always lead to satisfactory results, rehabilitation and alternative interventions are required to optimize the therapeutic strategies.[46] Interestingly, cognitive-behavioral therapy has been reported to have favorable influence on depression in MS.[46,47] Combining psychotherapy and pharmacotherapy may yield a better clinical outcome.

Radiological hints toward the diagnosis of psychiatric-onset MS

In addition to clinical features, some imaging findings offer some help in determining the accurate etiology of a psychiatric episode. Some reports have revealed an association between psychiatric manifestations and abnormalities in specific brain regions. For instance, frontal lobe lesions were found to co-occur with episodes of mania, psychosis, and catatonia.[24,29,31,33] This is supported by the results of a comparative study in which depressed MS

patients exhibited significantly more frontal lobe pathologies than nondepressed ones.[48] In fact, frontal lobe lesions could result in inappropriate behavior, lack of empathy, abnormal affect, and executive/cognitive dysfunction, which could be the presenting psychiatric symptoms of MS.[26,49]

Temporal lobe pathologies, particularly on the left side, were found to be associated with the occurrence of psychosis in MS.[9,27] Notably, the role of temporal lobe lesions in psychiatric manifestations was further highlighted in studies comparing MS groups with or without psychiatric symptoms.[35,50] New cerebellar and brainstem lesions have been documented in one patient presenting with catatonia.[29] This is an interesting finding, since the cerebellum and brainstem are known to be highly involved in the control of movement.[51,52]

Apart from abnormalities occurring in specific brain areas, some authors have reported periventricular,[8,18,20-33] subcortical,[9] and diffuse white matter lesions.[26]

Taken together, these reports suggest that discovering specific or nonspecific brain abnormalities should encourage physicians to perform a full workup to rule out, or in, other differential diagnoses. Unfortunately, there are no well-established guidelines on neuroimaging in clinical psychiatry, an issue that is still a matter of debate.[53] Ordering MRI is still not mandatory in psychiatric wards to establish a diagnosis. Facing these limitations, some authors have proposed a set of clinical situations that merit neuroimaging, including atypical psychiatric presentations as noted above.[54,55]

Conclusion

Giving the high prevalence of psychiatric symptoms in MS patients and taking into consideration previous reports of ''psychiatric relapses,'' it might be wise to consider MS among the differential diagnosis of patients presenting to psychiatric clinics. This is particularly important when a ''psychiatric attack'' precedes or follows a single neurological relapse that does not otherwise fulfill the 2010 revised McDonald criteria for MS diagnosis.[56] Here, unveiling a psychiatric manifestation would help the physician establish the correct diagnosis. A multidisciplinary approach involving neurologists, psychiatrists, psychologists, and radiologists would be ideal to ensure the needed workup is performed and early MS treatment is instituted, aiming to improve long-term outcomes.

In this perspective, brain MRI is the imaging modality of choice to depict any structural pathology that might explain clinical findings. However, one should keep in mind that standard imaging techniques might not be able to rule out all pathologies, such as normally appearing white matter (NAWM) abnormalities and intracortical lesions, which can be visualized using magnetic resonance spectroscopy and 7 Tesla MRI, respectively. It is also worth remembering that inflammatory processes might manifest as psychiatric manifestations way before they appear on brain imaging.

Additional helpful tests in these cases include neurophysiological testing and cerebrospinal fluid analysis to search for prominent oligoclonal bands. Although intrathecal synthesis of oligoclonal bands can occur in various pathological settings (infectious or paraneoplastic CNS disorders, etc.), their presence could help reveal an undergoing demyelinating condition, such as MS.[57-59]

Disclosure

The authors report no conflicts of interest.

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