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REVIEW ARTICLE

A complex relation between depression and multiple sclerosis: a descriptive review

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Abstract

Background Multiple sclerosis (MS) is a demyelinating neurodegenerative disease that affects central nervous system (CNS). MS patients are more likely to develop depressive symptoms than patients with other chronic diseases.

Objective In this review, we have analysed if there is a correlation between brain lesions (BL), structural damage (SD) and depressive symptoms (DS).

Methods We Searched on PubMed and Web of Science databases and screening references of included studied and some review article for additional citations. From initial 745 studies, only 9 met the inclusion criteria. All studies conducted research on 389 patients with MS associated with DS and 120 HC (healthy controls).

Results The selected researches highlighted the involvement of limbic system, the role of hippocampus and the impact of brain lesions on the emotional status of MS patients.

Discussion In the genesis of depression are implicated many mechanisms including genetic, biochemical, immunological and psychosocial factors, even if a prominent role in the onset of DS seem to be associated with structural and functional brain alterations.

Keywords Anatomical–functional abnormalities · Depressive symptoms · Hippocampus · Magnetic resonance · Multiple sclerosis · Organic lesions

Introduction

Multiple sclerosis (MS) is a demyelinating neurodegenerative disease that affects central nervous system (CNS). Depression is one of the most common neuropsychiatric symptoms of MS: studies have suggested that mood disorders are more frequent among people with MS than in the general population or in many other chronic illnesses [1–6].

Emotional disturbances in MS might be determined by an understandable psychological reaction to the diagnosis and progression of the disease [7], or they could be associated with cortical lesions and structural damage in brain networks involved in emotional processing [8, 9].

In MS depression, neuroimaging studies showed an involvement of fronto-temporal lobes and hippocampus [10–14]. In particular, structural and functional disconnections between limbic and frontal regions were found [15–17]. Other studies showed cortical atrophy and white matter (WM) lesions in frontal areas [18–21]. MS depressive disorder was also associated with hippocampal atrophy [21–23]. These cerebral alterations seem to be related to motor, sensory, visual disability and cognitive deficits [24, 25]. In addiction the cortical hypoperfusion and/or hypometamobilism consequential to subcortical lesions in MS patients seem to be indirectly linked with depressive disorder [26, 27].

This review explored the correlation between brain lesions (BL), structural damage (SD) and depressive symptoms (DS) in patients with MS. In particular, we have investigated if specific cerebral areas are involved in the onset of DS in MS patients.

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Methods

Search strategy

A descriptive review was conducted on the specificity of BL or SD related to DS in MS patients. Studies were identified by searching on PubMed (1954, year of the first-related published article–January 2018) and Web of Science databases (April 1997–January 2018). The search combined the following terms: functional[All Fields] AND ("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND ("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]).

The search terms were identified as title and abstract. We selected only English texts. After duplicates had been removed, all articles were evaluated based on title, abstract and text. We included studies that examined the correlation between BL or SD and DS, after they fulfilled the following criteria:

1. Published peer-reviewed research
2. The sample population included MS patients.
3. Studies specifically assessed the relationship between BL or SD and DS.
4. Images for the evaluation of BL and SD were acquired by magnetic resonance imaging (MRI) o functional magnetic resonance imaging (fMRI).
5. We excluded case studies.

Results

Of the 745 identified studies, only 9 met inclusion criteria (Fig. 1) and investigated the relationship among BL, AFA and DS in MS patients. All studies conducted research on 389 patients with MS associated with DS and 120 Healthy Controls (HC) (Table 1). Studies found a positive correlation between depressive symptoms and limbic system, hippocampus and other networks.

In 1996, Sabatini et al. [41] hypothesized that impaired function of the limbic system could be related to complex pathophysiologic changes. The authors showed a disconnection between subcortical and cortical areas linked to the function of limbic system. Their study, on 20 MS patients (whose 10 depressed), investigated the association of depression with anatomic and cerebral blood flow (CBF). A different regional CBF (rCBF)%A in limbic cortex between two groups was found: a relatively higher rCBF on the left side in depressed patients and on the right side in non-depressed subjects. These perfusion asymmetries seem to be linked (significant correlation by ANOVA) with depressive test scores but not with regional and total MRI asymmetry. So, they did not find an association between CBF asymmetry in the limbic system and depression.

Riccelli et al. [32] have assessed altered models of functional connectivity of the limbic system in 77 MS patients. Research methodology has analysed MR images while patients were categorizing 30 greyscale pictures of emotional faces (angry, sad and neutral faces posed of different actors for gender). The study have examined functional connectivity patterns in "seed" regions usually associated to pathophysiology of depressive symptoms (right and left amygdala and hippocampus) [43]. The authors showed that individual differences in depression in MS patients were significantly associated with altered regional activity and functional connectivity patterns of key limbic fronto-temporal circuits. Berg et al. [40] affirmed the important role of the main projection areas of the limbic system in DS. Depressed MS patients had a significantly larger temporal lesion load than non-depressed MS patients on the right side. A trend of difference was detected for lesions of right parietal and frontal lobe, cerebellum and total lesion load. They found that depression in MS patients was associated with an increased lesion load of the projection areas of the basal limbic system.

Pujol [39] showed that lesions in the left arcuate fasciculus region are associated with the core of depressive syndrome rather than marginal symptoms: these findings suggest that this left suprainsular brain region involves white matter tracts relevant to mood regulation.

In 2002, Zorzon et al. [44] found that disability score and right temporal brain volume were correlated to depressive symptoms in 90 MS patients. Disability, cognitive performances, depressive and anxiety symptoms have been assessed at baseline and after 2 years. The authors assessed the relationship among the development of depressive symptoms score, quantitative changes of regional and total lesion load (LL) and brain atrophy performed on a T_1-weighted SE sequence measuring brain parenchymal volumes (BPV). There were no difference in LL between depressed and non-depressed patients at baseline, and after 2 years, brain atrophy was significantly more conspicuous in the left frontal lobe, and an association between depressive symptoms and LL or BPV was found in three patients who became depressed in the follow-up. Similarly, Nunnari et al. [9] have found that the presence of depressive symptoms represents an important determinant of cognitive

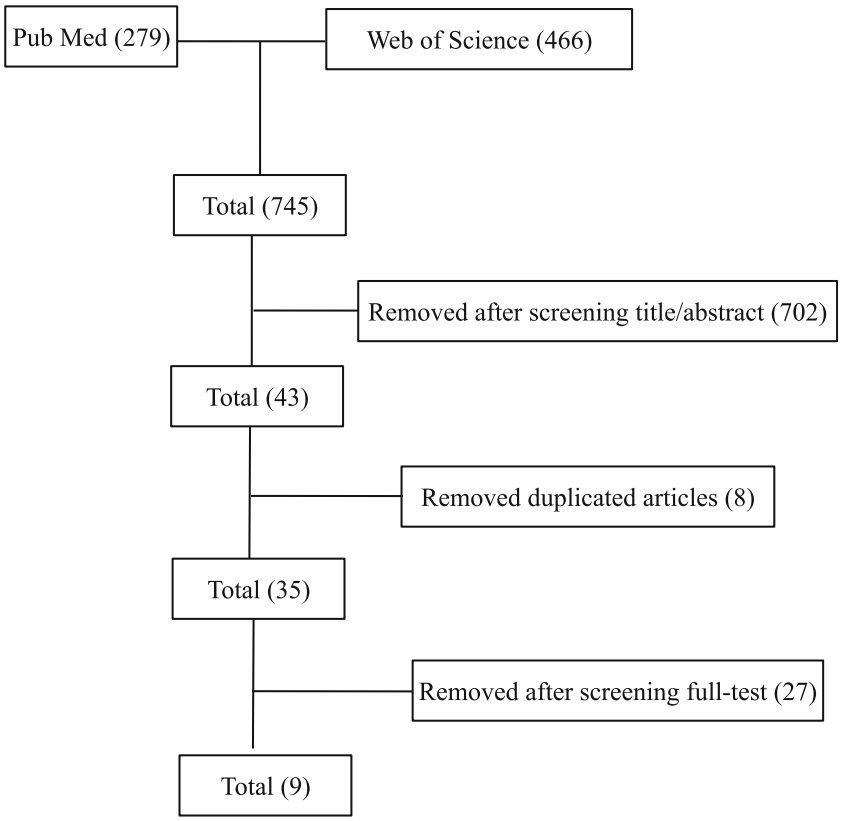

Fig. 1 Search and selection of eligible articles

performance in MS patients, more than disability, disease duration and cortical atrophy.

The involvement of hippocampus in pathophysiology of depressive symptoms in MS patients requires consideration of memory impairments related to this brain area. Kiy et al. [5] proposed a study of 72 MS patients, by measuring left and right temporal horn volumes, which was regarded as an indirect measure of hippocampus volume, in memory performance and mood status. This study, however, did not exhaustively elucidate the brain mechanisms involved, limiting a generic description of the results. A marginally significant correlation between consolidation of information in memory and right temporal horn volume was found. Several studies [45, 46] have shown that consolidation of information is a major function of hippocampus but there is not a clear explanation why it is present a lack of correlation between left temporal horn volume and consolidation.

Rocca [33] has assessed the relationship between abnormalities of hippocampal resting-state (RS) functional connectivity with brain lesion volumes (LV) and depression in 69 MS patients. The authors have considered the role of the hippocampus in default mode network (DMN) RS functional connectivity (FC), a system that is involved in the hierarchical organization of all brain networks and it is linked in patients with major depression [47–51]). A significant association between depression and reduced RS FC in the OFC, middle temporal gyrus (MTG) and precuneus was found. This implicates the involvement of neural network associated to mood and affect regulation, memory, attention and other cognitive aspects related to depression and cognitive deficit. Hippocampal RS FC disruption was correlated to the severity of disability and to focal WM lesions related with other DMN regions. Disconnection might be related to the disease duration and the severity of disability, but considering the post mortem investigation [52], the authors tend to exclude that is caused by depression and attribute the cause of the RS FC abnormalities to the presence of WM focal brain lesions. The relationship between hippocampal involvement and DS in MS patients has recently been investigated by Colasanti et al. in a study including 22 healthy control subjects and 13 patients with relapsing–remitting MS who underwent MRI and [18F]PBR111 PET scans [28]. The authors have observed a higher [^{18}F]PBR11 binding in hippocampus. This parameter was considered to quantify activation of hippocampal microglia. The analysis found a close correlation between hippocampal [18F] PBR11 binding and BDI scores. Hence, the neuroinflammation process that alters the

Table 1 Studies assessing anatomical–functional abnormalities and brain lesions related to depressive symptoms in MS patients

Authors, published	Year	Aim	Sample (*n*)	Image acquisition	Clinical assessment	Outcomes
Colasanti et al. [28]	2016	To assess strength of hippocampal functional connectivity (HFC) and hippocampal microglia activation and depressive symptoms	11 MS (RR) 22 HC	[^{18}F]PBR111 PET Resting-State Functional MRI	Expanded Disability Severity Scale (EDSS) [29] Beck Depression Inventory-II (BDI-II) [30] Fatigue Severity Scale [31]	MS > HC for [^{18}F]PBR111 DVR in the hippocampus for those MS with recent major depressive episode (MDE). Correlation with the strength of functional connectivity and regions in PFC, parietal and occipital cortices. MS = HC for HFC of whole-brain statistical contrasts.
Riccelli et al. [32]	2016	To assess changes in brain activity and functional connectivity patterns in depressed MS while executing a "face task" (for probing brain emotional regions)	77 MS (RR) 20 HC	fMRI	EDSS [29] BDI-II [30] FSS [31]	MS > HC for increased activation in the right ventrolateral PFC (VLPFC) Depression scores in MS are negatively correlated with: 1) activity in the right subgenual cingulate cortex 2) the functional connectivity between the left hippocampus and orbitofrontal cortex (OFC) as well as DLPFC; 3) the functional connectivity between the left amygdala and left VLPFC/DLPFC.
Rocca et al. [33]	2015	To assess the relationship between abnormalities of hippocampal resting-state (RS) functional connectivity (FC) with brain lesion volumes (LV) and depression	69 MS relapse-onset 42 HC	MRI RS fMRI	EDSS [29] Montgomery and Asberg Depression Rating Scale (MADS) [34]	Correlation between reduced hippocampal RS FC and depression. MS > HC for reduced RS FC between the L and R hippocampi and several regions located in the frontal, temporal and parietal lobes, the cingulate cortex, insulae, thalami, caudate nuclei and cerebellum MS > HC significantly decreased RS FC was located within default mode network (DMN).
Nunnari et al. [9]	2015	To investigate the influence of demographic and clinical variables, such as depression, fatigue and quantitative MRI marker on cognitive performances in a sample of patients affected by multiple sclerosis (MS)	64 MS	MRI	EDSS [29] FSS [31] BDI-II [30]	Depression is more influent than disability, disease duration and brain volume decrease on cognitive performance. According to multiple regression analysis, the BDI-II represents a significant predictor for most of the neuropsychological tests
Kiy et al. [5]	2011	To evaluate the correlation of ventricular volume of the temporal horn (indirect measure of hippocampal volume) and memory or depressive mood differentiating	72 MS (64 RR 8 PP) 16 HC	MRI	EDSS [29] BDI [30] FSS [31]	MS > HC larger left temporal horn and right temporal horn volume. MS < HC retrieval performance. MS > HC on fatigue severity and on somatic BDI items HC > MS more correct responses on the PASAT. Correlation between the left temporal horn with memory performance (consolidation) and depression.

Table 1 (continued)

Authors, published	Year	Aim	Sample (*n*)	Image acquisition	Clinical assessment	Outcomes
		between psychic and somatic symptoms				
Zorzon et al. [10]	2002	To evaluate pathological abnormalities caused by MS that can contribute to the development of depression	90 MS	MRI	EDSS [29] Functional Independence Measure (FIM) [35] Mini Mental State Examination (MMSE) [36] Hamilton Depression Rating Scale (HDRS) [37] Hamilton Anxiety Rating Scale (HARS) [38]	Correlation of depression with disability and right temporal atrophy. At baseline and at 2-year follow-up no differences between depressed and non-depressed MS regard a calculation of regional and total lesion load (LL). At baseline, depressed MS showed a trend for decrease in BPV in the R temporal lobe, in both temporal lobes and in the L frontal lobes; at second time-point, a significant decrease in BPV in L frontal lobe and in both frontal lobes of depressed MS; a trend of difference in the R frontal lobe an in both temporal lobes.
Pujol et al. [39]	2000	To establish the significance of the previously reported association between depressive symptoms and demyelinating lesions in the region of the left arcuate fasciculus in MS	45 MS	MRI	BDI [30]	After exclusion of neurologic symptoms and cognitive distortions: left arcuate fasciculus lesions accounted for 26% of the remaining BDI symptoms
Berg et al. [40]	2000	To assess if a specific lesion pattern or changes of the basal limbic system as seen in primarydepression and depression associated with neurodegenerative disorders might be identified in depressive MS patients	78 MS	MRI	BDI [30] FSS [31] MADRS [34] HDRS [37]	Depression in MS patients is not associated with an alteration of the basal limbic system
Sabatini et al. [41]	1996	To investigate the relationship between depression and both anatomic and cerebral blood flow (CBF) abnormalities	10 MS depressed 10 MS non-depressed for HC	MRI ^{99m}Tc HM-PAO SPECT	BDI [30] HDRS [37] Zung Anxiety Scale [42]	Regional CBF (rCBF)%A in the limbic cortex > on the left side in depressed MS and on the right side in non-depressed ones. Perfusion asymmetries in the limbic cortex are correlated with both depression test scores but not with regional and total MRI asymmetry.

function and connectivity of hippocampus may cause depression. Specifically, this process causes alterations of gamma-aminobutyric acidergic transmission [53], a similar condition observed in depressive conditions [54] in animal model studies.

Discussion

The comorbid occurrence of psychiatric conditions in patients with MS may be also due to several factors a relationship between immune function and depression and anxiety, possibly side effects of certain treatments. Psychiatric comorbidity can decrease adherence to disease-modifying therapy, increase fatigue and decrease overall quality of life. Depressive symptoms could represent a psychological reaction to the diagnosis as a consequence to loss of function or changes in social or occupational roles. Numerous studies analysed cortical brain areas implicated in depression. In particular, some authors described the involvement of limbic system and brain abnormalities mainly in fronto-temporal areas [18] or structural and functional disconnection of the hippocampus from several brain networks [17]. In addition, a reduced grey matter volume in the right prefrontal cortex seems to predict a future worsening of DS in SM patients [55].

In MS, depression is a common disorder; however, pathophysiology is still debated.

Some research aimed to understand the pathophysiological mechanism underlying the relationship between depression and multiple sclerosis studying the adaptive capacity of neuronal mechanisms In the Riccelli et al. [32], altered activity of the prefrontal cortex could be interpreted as an adaptive mechanism to compensate neuronal brain damage in patients with MS.

Donald Hebb [56] had intuited how the compromised neuronal communication paths were substituted by others; more recent studies have shown that the plasticity of the brain also affects structural aspects in addition to functional ones [57]: the observation of the proliferation of cortical tissue in adult subjects, reported by Gomez [58], is a clear example of the ability of neurons to generate themselves. It might be interesting to study both the functional and structural aspects of brain plasticity in the emotional regulation system when it is compromised by process of demyelination in MS patients.

In the genesis of depression are involved biological and psychosocial factors [6]; however, affective disorders seem to be an intrinsic part of this neurological disorder rather than an independently co-occurring psychiatric disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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