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Brief review

ANXIETY AND DEPRESSION AS COMORBIDITIES OF MULTIPLE SCLEROSIS

Filip Mustač[1], Hanna Pašić[2], Filip Medić[3], Borna Bjedov[2], Luka Vujević[2], Maša Alfirević[3], Branka Vidrih[4,5], Katarina Ivana Tudor[2,6] & Marija Bošnjak Pašić[7,8]

[1]Department of Psychiatry and Psychological Medicine, University Hospital Centre Zagreb, Zagreb, Croatia
[2]School of Medicine, Zagreb, University of Zagreb, Zagreb, Croatia
[3]Ministy of Defence of the Republic of Croatia, Zagreb, Croatia
[4]Department of Psychiatry, University Hospital Centre Sisters of Mercy, Zagreb, Croatia
[5]Catholic University od Croatia, Zagreb, Croatia
[6]Department of Neurology, Unit for Headaches, Neurogenic Pain and Spinal Disorders, University Hospital Centre Zagreb, Zagreb, Croatia
[7]Referral Center for Demyelinating Diseases of the Central Nervous System, Unit for Neuroimmunology of Central Nervous System, Clinical Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia
[8]School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

SUMMARY

Multiple Sclerosis (MS), a chronic inflammatory neurodegenerative disease, is accompanied by a number of comorbidities. Among the psychiatric ones, depression and anxiety occupy a special place. It is estimated that the prevalence of anxiety in the MS population is 22.1% verus 13% in the general population; whereas the prevalence of anxiety levels, as determined by various questionnaires, reaches even 34.2%. Systematic literature reviews (SPL) show considerable data variations due to differences in study design, sample size, diagnostic criteria and extremely high heterogeneity (I^2). Among the more conspicuous factors associated with anxiety disorder in MS are demographic factors (age and gender), nonsomatic depressive symptoms, higher levels of disability, immunotherapy treatments, MS type, and unemployment. Depression is the most common psychiatric commorbidity in MS and the lifetime risk of developing depression in MS patients is >50%. According to some research, the prevalence of depression in MS vary between 4.98% and 58.9%, with an average of 23.7% (I^2=97.3%). Brain versus spinal cord lesions, as well as temporal lobe, fasciculus arcuatus, superior frontal and superior parietal lobe lesions in addition to the cerebral atrophy have been shown to be the anatomical predictors of depressive disorder in MS. Hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) and the consequent dexamethasone-insupressible hypercortisolemia, in addition to cytokine storm (IL-6, TNF-α, TGFβ1, IFNγ/IL-4) present the endocrine and inflammatory basis for development of depression. Fatigue, insomnia, cognitive dysfunction, spasticity, neurogenic bladder, pain, and sexual dysfunction have shown to be additional precipitating factors in development of anxiety and depression in MS patients.

Key words: *multiple sclerosis – depression – anxiety - comorbidities*

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INTRODUCTION

Multiple sclerosis (MS) is a complex chronic auto-immune neurodegenerative demyelinating disease of the central nervous system (CNS) (Trapp & Nave 2008). Reaching a peak incidence in patients in their 30s and having a prevalence of over 2.5 million patients worldwide (Owens 2016), MS represents a significant pattern of disability in young adults (GBD 2016 Multiple Sclerosis Collaborators 2019). There has been an emphasis on the comorbidities recently, especially psychiatric (Marrie et al. 2015), in the overall burden of the disease, in addition to their relatively high frequency (Marrie 2016). It has been shown that patients suffering from MS score lower on the HRQOL (Health Related Quality of Life) compared to the general population (Marrie et al. 2012, Berrigan et al. 2016), as well as compared to the patients suffering from other chronic diseases, such as inflammatory bowel disease and rheumatoid arthritis (Rudick et al. 1992). This puts MS patients into a particularly vulnerable group if they develop or are predisposed to a pre-existing psychiatric disorder or illness.

While the simplest and most concise definition of comorbidity is the existence of another disease in addition to the basic, main, dominant disease, that is, the existence of the concomitant disease, but the concept and phenomenon of comorbidity must be considered much broader and deeper (Jakovljević & Ostojić 2013, Jakovljević 2019, Feinstein 1970). At the same time, the question of the difference between comorbidity and multimorbidity also arises. Most of the literature available today argues that comorbidity refers to an additional, concomitant disease or disorder while there is an underlying, major disease that dominates, and multimorbidity refers to the simultaneous presence of two or more diseases or disorders that are in principle independent and cannot be claimed which disease or disorder dominates (Jakovljević et al. 2010, Jakovljević 2009, Valderas et al. 2009, Grumbach 2003). Since multiple sclerosis, despite quite successful modern treatment today, is still a severe disease, which causes

discomfort and impaired quality of life, it is to be expected that certain mental disorders may accompany multiple sclerosis as comorbidities.

The available literature unequivocally indicates an increased prevalence of psychiatric comorbidities, especially depression and anxiety, in MS patients versus the general population (Marrie 2016, McKay et al. 2018). In addition, a more pronounced progression of neurological incidents in the presence of psychiatric comorbidities has also been observed.

Even though psychiatric comorbidities in MS have been the focus of numerous studies, the results are still quite mixed. This is why there is a need for further research and further new studies with the goal of avoiding a reduced level of diagnosing and treatment of the same (Feinstein et al. 2014). The goal of this review article is to look over the recent literature and systemize key facts related to the these significant comorbidities in MS.

ANXIETY - REACTION TO A DISEASE OR UNRECOGNIZED CHRONIC CONDITION

MS patients show a high level of anxiety. Despite it being the subject of numerous studies, its prevalence in this group of patients is difficult to determine accurately given that the results of various studies have been incosistent. Compared to the general population where the prevalence of anxiety disorders is about 13% (Steel et al. 2014), the prevalence of anxiety disorders among MS patients is thought to vary betwen 15% and 31%, with an average of 22.1%; whereas the high level of anxiety as determined by the patient self-report questionnares is at 34.2% (23.2-47.1%) (Boeschoten et al. 2017). In their meta analyses Boeschoten et al. (2017) and Marrie et al. (2015) cite the Hospital Anxiety and Depression Scale (HADS) as the most commonly used objective questionnare in clinical findings. Recent literature additionally positions it as the best tool in assessment of anxiety in terms of senisitivity and specificity (Litster et al. 2016). However, the wide range of results is thought to be the consequence of study design variations, sample size, diagnostic criteria for anxiety, and extremely high heterogeneity (Boeschoten et al. 2017) in systemic literature reviews and meta analyses.

Over time a number of factors that could influence the onset of anxiety have been examined. In their clinical and MRI based study of 95 subjects, Zorzon et al. (2001) were not able to establish an association between lesion locations and the development of anxiety. Furthermore, in their study Janssens et al. (2003) found a pronounced level of anxiety in both newly diagnosed MS patients, and their partners. These findings support the fact that anxiety could be a reactive psychological reaction to an underlying pathology, and not just a consequence of direct impact of a lesion (Jose 2008) or underlying illness per se. Demographic factors, as well as gender and age are thought to be unrelated to the development of anxiety (Wallis et al. 2020, Hartoonian et al. 2015, Brown et al. 2009), although the literature is not very consistent on this issue. Hartoonian et al. (2015) obtained interesting results in their study of 513 subjects that were followed over a 4-month period. In their findings, there was a significant relationship between nonsomatic depressive symptoms and anxiety disorder during T1 or anxious symptoms during T2, 4 months later. In this study, patient's work status was also associated with a significantly higher anxiety after a 4 month period. As opposed to this finding, the average study on 129 individuals highlights the unemployment as a risk factor for the development of anxiety (Tan-Kristanto & Kiropoulos 2015). Such contradictory findings make room for further research which would need to include more socio-demographic indicators as variables and possibly clarify the background for the conclusions from various individual studies.

As for the characteristics of the disease itself and its relationship to anxiety, the results have also been partly contradictory. Some studies have shown the expected connection between higher levels of disability, as well as the non-treatment with immunotherapy with higher levels of anxiety (Wallis et al. 2020, Brown et al. 2009, Garfield & Lincoln 2012). In contrast, in their studies Hartoonian et al. (2015) and Beiske et al. (2008) did not observe the connection between the level of disability, disease relapse or use of immunotherapy and anxiety (Wallis et al. 2020). These findings most certainly indicate a further need for research on this topic. A study conducted in the United Kingdom on >7000 subjects concluded that a relapsing-remitting MS (RRMS) was associated with higher levels of anxiety compared to the primary-progressive MS (PPMS) as well as the secondary-progressive MS (SPMS) (Jones et al. 2012). In another study conducted on 243 subjects, the level of anxiety as well as the mood and the level of self-esteem in MS patients were monitored. It was found that the level of anxiety was the highest in the group of patients who experienced a recent relapse, compared to the patients who were in remission or the general population (Marita 2005). Possible explanation for this conclusion may be in the repeated and unexpected nature of relapse, but also fear of unknown, i.e. not knowing when and how (in what capacity and with what intensity) it is going to have an affect on the patient (Kalb 2007).

Nevertheless, there are objective facts which place anxiety as a significant psychiatric comorbidity in MS. The areas of uncertainty make room for additional research opportunities and the advancement of diagnostic and therapeutic possibilities. Given that twice as much professional literature examines depression in MS versus anxiety (Marrie et al. 2015) it is realistic to expect that further studies in this area will settle a number of ambiguities.

DEPRESSION - IS THE BIOLOGICAL CONNECTION OF THIS BURDEN OBTAINED?

Although it takes center stage in the study of psychiatric comorbidites within MS, depression has still not been a completely explained comorbidity. The exceptional signficance of depression can be explained by its multifactorial genesis as well as its multiple effects on the underlying disease itself and the overall health of the patient. In addition to anxiety, depression is the most common comorbidity in patients suffering from MS (Wood et al. 2013). The lifetime risk of developing major depressive disorder in patients suffering from MS is > 50% (Jose 2008, Sadovnick et al. 1996, Feinstein et al. 2004, Wilken & Sullivan 2007); where depression is also more common in patients suffering from MS than from any other neurological or chronic disease (Wilken & Sullivan 2007).

In the literature, the data on the prevalence of depression in MS patients varies significantly. In their systematic literature review Marrie et al. (2015) state that in all 10 studies which met the qualitative criteria for systematic review and consisted of target and control groups, it was found that depression occurs significantly more often in patients suffering from MS than in the general population. In their review the prevalence of depression was found to be between 4.98% and 58.9%, with an average of 23.7% and a significant level of heterogeneity (I^2=97.3). In their systematic literature review of 57 studies, Boeschoten et al. (2017) found the prevalence of depression to be 30.5%, also with an exceptionally high level of heterogeneity (I2=99.4%). Among the reviewed studies, the most commonly used assessment tools, not in any particular order, were „Center for Epidemiological Studies Depression Scale“ (CES-D), „Hospital Anxiety and Depression Scale“ (HADS), and „Beck Depression Inventory“ (BDI) (Marrie et al. 2015, Boeschoten et al. 2017, Dozeman et al. 2011, Bjelland et al. 2002, Richter et al. 1998). As is the case with anxiety there are numerous reasons for this assortment. The main reasons are non-unified methods of patient assessment, unclear distinction between depression as a diagnosis and depression as a questionnaire assessed symptom, number of subjects, study design, differences in the quality of studies included in the systematic review and/or meta analyses, small number of studies included in the meta-analyses etc.

The theories on the etiology of depression are still not unanimous where different studies provide different approaches in considering this issue. It is possible that just like with anxiety, depression could be a potential reaction to the unpredictable nature of the underlying disease and the disability that ensues (Feinstein et al. 2014, Dalos et al. 1983). The importance of appropriate coping with the disease, use of mature defence mechanisms (such as humor, altruism, sublimation, suppression), social support and lower levels of stress as protective factors, has been shown (Feinstein et al. 2014, Goretti et al. 2010, Feinstein 2011, Chwastiak et al. 2002, Mustač & Marčinko 2020).

Unlike anxiety, for which there is no clear correlation with structural brain changes, when looking at depression there are several parallels. It has been noticed that patients suffering from MS who have lesions predominantly located in the brain are more likely to develop major depression than patients with significant spinal cord involvement (Rabins et al. 1986). Involvement of the temporal lobe of the cerebrum also seems to be a clear risk factor for the development of major depression (Honer et al. 1987). Pujol et al. (1997) linked an increased incidence of depression with the lesions in the left suprainsular white matter - the arcuate fasciculus (fasciculus arcuatus). In their study, this finding accounted for 17% of the depression cases. Bakshi et al. (2000) study on 48 patients concluded that the incidence of depression is statistically significantly more likely to be caused by the superior frontal and superior parietal hypointesive T1 lesions; while its severity was predicted by the appearance of superior frontal, superior parietal, and temporal T1 lesions, as well as the lateral and third ventricular dilatation and frontal atrophy. In the Canadian study, regression analysis identified T2 hyperintensive lesions in the left inferior medial prefrontal cortex and increased cerebrospinal fluid (CSF) in the left temporal lobe (or cerebral atrophy) as the two independent predictive factors for the development of depression (Feinstein et al. 2004). Although the results of the imaging studies look promising, the results included were obtained on a small number of subjects. The unequivocal indication of the importance of the patho-anatomical relationship of the lesions to its surrounding structures, as well as brain atrophy as the basic underlying morphological mechanisms of depression should be further examined and correlated in order to achieve sufficient strenght. The critics should most certainly consider the possibility of major depression development in patients who have met the aforementioned imaging criteria (Feinstein et al. 2014, Jose 2008, Wilken & Sullivan 2007).

In addition to the clear causal relationship between depression and the morphological characteristics of brain lesions, various studies have suggested that endocrine imbalance, especially in terms of hypothalamic-pituitary-adrenal axis (HPA), may also contribute to etiology of depression. Patients suffering from MS are generally thought to show signs of increased activity of the HPA axis, consequently having higher hormone levels, especially of cortisol (Gold et al. 2011). An important feature of this particular hypercortisolemia is that it cannot be supressed with dexamethasone or corticotropin-releasing hormone (CRH) (Fassbender et al. 1998). In addition, there are some indications that

increased HPA axis activity and higher levels of cortisol per se could be associated with depression (Feinstein et al. 2014, Melief et al. 2013).

Recently, other systemic factors which could predispose a patient to or modify the course of depression are increasingly being re-examined. Several studies have found that depressed patients have significantly higher levels of cytokines such as IL-6, TNF- α, TGF-β1, and IFN-γ/IL-4 (Serafini et al. 2013, Kim et al. 2007, Karlović et al. 2012). Moreover, a return of IL-6 and TGF- β1 to initial, lower levels has been reported (Kim et al. 2007). Along with the high levels of IFN-γ (Pokryszko-Dragan et al. 2012), proinflammatory pleocytosis in the CSF as well gadolinium enhancing lesions in MRI (Fassbender et al. 1998) have also been observed as predisposing risk factors.

Although findings like these are an additional gateway in the study of this complex matter, further examination of endocrine-inflammatory etiology of depression is beyond the scope of this paper.

The burden of depression, with all of its ramifications, is further complicated by the presence of comorbidities. Fatigue is considered the most common symptom of MS (Wilken & Sullivan 2007). Its exact interaction with depression is of both causal and consequential nature. Significant fatigue can develop independently, as part of depression, and also as a secondary symptom as part of insomnia (Feinstein et al. 2014). Fatigue can also precipitate depression in patients with relatively low levels of disability (Wilken & Sullivan 2007). Given the proven relationship between psychiatric comorbidities with the progression of MS (McKay et al. 2018), the treatment of fatigue is most certainly an important aspect of the multimodal treatment of depression in addition to being an essential factor in the holistic approach of patient treatment.

Cognitive dysfunction affects 45-60% of patients suffering from MS. It is predominantly manifested by long-term and working memory dysfunctions (Guimarães & Sá 2012). Today we also know that cognitive dysfunction is partially cosequence of depression (Lam et al. 2014). From a clinical perspective it is important to keep in mind the connection between depression and cognitive dysfunction in order to optimize the therapeutic approach, even though there are still many areas of uncertainty realated to the connection between them.

In addition to the explored comorbidities, one should not neglect the others that may also significantly affect the quality of life in patients suffering from MS (Marrie et al. 2012, Berrigan et al. 2016) especially if depression is present as a comorbidity. Fatigue (Feinstein et al. 2014), anxiety (Wallis et al. 2020), spasticity (Fernández et al. 2020), neurogenic bladder (Phé et al. 2016, Tudor et al. 2020), pain (Seixas et al. 2014), and sexual dysfunction (Pašić et al. 2019) play a central role among other comorbidities.

CONCLUSIONS

Even though mortality due to MS has been significantly reduced since the 1990s, the global burden of disease (DALY) has not significantly decreased. With increasing incidence of MS, especially in the developed countries, disability caused by the disease has come into focus more than ever before. A number of factors influencing psychiatric comorbidities in MS patients were examined. The literature is increasingly inclined to view anxiety as a reaction to an underlying disease, while depression is linked to the anatomically specific location of lesions. The association between the more frequent development of depression in patients with brain lesions versus the spinal cord lesions, as well as in patients with lesions in the temporal lobe, fasciculus arcuatus, superior frontal and superior parietal lobes, and cerebral atrophy has been demonstrated. In addition, there have been reports of endocrine abnormalities, especially in terms of increased HPA axis activity and consequent hypercortisolemia. An increased production of pro-inflammatory cytokines IL-6, TNF-α, TGFβ1, IFNγ/IL-4 has also been found. Even though it has been the subject of numerous studies, the influence of a number of environmental and endogenous factors such as demographic, social, inflammatory, epidemiological and numerous others, still needs to be clarified as well as their causal relationship with MS. Given the complexity of this topic, it is clear that further research is necessary so that numerous questions that are present could be clarified, in addition to broadening the horizons in daily work with these patients.

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Contribution of individual authors:

Filip Mustač: concept and design of article, literature searches, writing manuscript.

Hanna Pašić, Filip Medić, Borna Bjedov, Luka Vujević, Maša Alfirević: comments on the concept of article, literature searches, writing some parts of manusrcipt.

Branka Vidrih, Katarina Ivana Tudor, Marija Bošnjak Pašić: critically revising of the manuscript.

All authors approval of the final version.

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Correspondence:
Filip Mustač, MD
Department of Psychiatry and Psychological Medicine, University Hospital Centre Zagreb
Kispaticeva 12, 10 000 Zagreb, Croatia
E-mail: filip.mustac@gmail.com