Does the presence of multiple sclerosis impact on symptom profile in depressed patients?


**Objective:** Major depressive disorder (MDD) is common in patients with multiple sclerosis (MS) but may remain unrecognized because of overlapping symptoms and different presentation due to its specific MS-related neurobiological aetiology. We aimed to investigate the clinical profile of MDD in MS.

**Methods:** In a sample of MDD patients with MS (n = 83) and without MS (n = 782), MDD characteristics, 30 depressive symptoms, and sum scores of cognitive, somatic, atypical and melancholic symptom clusters were compared using logistic regression analyses and analysis of co-variance.

**Results:** MDD in MS was characterized by older age of onset (p < 0.001), and fewer comorbid anxiety disorders (37% versus 72%; p < 0.001). The symptom ‘future pessimism’ was more common in MS patients (OR = 1.62; 95%CI = 1.02–2.59). ‘Diminished capacity for pleasure/enjoyment’ (OR = 0.44; 95%CI = 0.24–0.78), ‘increased appetite’ (OR = 0.40; 95%CI = 0.19–0.85), ‘arousal symptoms’ (OR = 0.49; 95%CI = 0.26–0.84), and ‘panic/phobic symptoms’ (OR = 0.49; 95%CI = 0.29–0.84) were less common in MS patients. Twenty-five symptoms (83%) out of 30, including depression's core symptoms (sadness and loss of interest) were not differentially associated with MS and no differences existed for the symptom clusters.

**Conclusion:** Only subtle differences in depressive symptom profiles existed between MDD patients with and without MS. The clinical profile of depression remains valid among MS patients, although it presents with diminished anxiety distress and comorbidity.

**1. Introduction**

Major depressive disorder (MDD) is common in multiple sclerosis (MS) and its prevalence is substantially higher compared with the general population [1,2]. Depression is associated with cognitive dysfunction [3], suicide intent [4], and decreased adherence of MS treatment regimens [5]. Although depression has enormous impact on the quality of life of MS patients, it is often not adequately diagnosed and treated [6–8]. This might be partly due to overlapping psychiatric and neurological symptoms such as fatigue, psychomotor slowing, and sleeping problems. Recognizing depression and selecting appropriate treatment could therefore be a major improvement for MS patients and their clinicians [6,7].

The underlying neurobiology of MS may play an important role in the increased prevalence and expression of depression in MS patients. Structural brain changes, elevated Hypothalamic-Pituitary-Adrenal (HPA)-axis activity and immune-inflammatory dysregulations are related to the presence and severity of depression in MS. Abnormalities in both the limbic and endocrine system may be more closely related to affective (e.g. mood alterations) and cognitive depressive symptoms in MS, whereas MS-inflammatory markers showed stronger correlations with neurovegetative symptoms [9–11]. Inflammatory dysregulations and elevated HPA-axis activity also play a significant role in atypical and melancholic subtypes of MDD [12]. One might therefore expect more atypical and melancholic features in depressed MS patients due to shared pathophysiological pathways.

Research concerning the clinical profile of MS-related MDD is still scarce. Symptoms as pervasive mood change, diurnal variation in mood, and suicidal ideation are suggested to be important indications of depression in MS [13–15]. One study found depressed and non-
depressed MS patients to be best differentiated by symptoms of ‘sadness’, ‘ pessimism’, ‘sense of failure’, ‘guilt’, ‘disappointment’, and ‘changes in appetite and/or weight’ [16], whereas another recent study showed depressive symptoms measured with the Beck Depression Inventory-II to be similar in moderate or severe depressed MS patients compared with MDD patients without MS [17]. So, earlier conclusions have been inconsistent, and were generally based on small samples and self-reported depression. Examination of the depressive symptom profile in a larger representative MS sample with a clinical diagnosis of MDD is therefore a subsequent step to substantiate whether the concept of depression is similar in patients with and without MS.

This study aims to compare 30 depressive symptoms and four symptom clusters (cognitive, somatic, atypical, melancholic) in a sample with moderate or severe MDD, including patients with or without MS, taking into account clinical characteristics. Furthermore, the presence of comorbid anxiety disorder(s) will be addressed since MDD and anxiety disorders often co-occur. Research on comorbid MDD and anxiety disorders in MS received little attention yet which is unfortunate since co-occurrence of depression and anxiety in the general population has been associated with worse clinical outcomes than in MDD alone [18]. By combining a well-defined MS sample and a large cohort with clinical MDD diagnoses, this study makes a significant contribution to the understanding of the clinical phenotype of MS-related depression.

2. Method

2.1. Study sample

Data were derived from i) a randomized controlled trial (RCT) investigating the effectiveness of internet-based cognitive behaviour therapy for depressed MS patients [19], and ii) an ongoing multi-center cohort study ‘the Netherlands Study of Depression and Anxiety’ (NESDA) examining the long term course and consequences of depression and anxiety disorders in patients with current or remitted depressive and/or anxiety disorders as well as healthy controls [20]. Both study protocols were approved centrally by the Ethical committee of the VU University Medical Center, and for NESDA subsequently by the review boards of the University Medical Center Groningen and Leiden University Medical Center. All patients provided written informed consent.

MS patients (n = 178) participating in the RCT were recruited at several MS centres throughout the Netherlands, and through calls in MS newsletters and Internet-sites. The methods have been described previously [19]. Participating patients were 18 years or older with sufficient command of Dutch language, and were not receiving psychotherapy. Patients with prescribed antidepressant medication were included if they were on medication for > 6 weeks with stable dosage. Psychiatric comorbidity other than MDD was no reason for exclusion. Baseline assessment took place between August 2011 and September 2015. Patients completed the self-report Inventory of Depressive Symptomatology (IDS-SR) [21] in addition to other baseline assessments.

The NESDA sample consisted of 2981 adults aged 18 to 65 years who were recruited from the general population, primary health care, and specialised mental health care facilities in the Netherlands, and completed baseline assessment between September 2004 and February 2007. Exclusion criteria were insufficient command of Dutch language, and a primary clinical diagnosis of an obsessive compulsive disorder, bipolar disorder or severe addiction disorder. Psychiatric treatment was allowed. A detailed description of the NESDA study design and sampling procedures can be found elsewhere [20].

From both study bases, we included the following participants for the present study: those with a) a current (i.e. past 6 months) MDD diagnosis according to DSM-IV criteria assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization version 2.1 [22], and b) a score ≥ 26 on the self-report IDS-SR indicating moderate to (very) severe depressive symptoms [21,23]. By excluding patients with no or mild depressive symptoms, sufficient depression severity and amount of variation were warranted in order to enhance comparison of symptom profiles. This selection resulted in a sample of 865 patients (782 from NESDA, 83 from the RCT). MS patients were only included from the RCT sample as all 6 patients from the NESDA sample with MS did not have a MDD diagnosis.

2.2. Assessment

2.2.1. MS and patient characteristics

MS diagnosis was based on self-report and a confirmed diagnosis by the neurologist of each patient. Self-report data on sociodemographic characteristics including age, sex, and education level were collected. Also self-report antidepressant use was assessed since this can introduce bias in interpreting the clinical depression profile. Different types of antidepressants could have different effects on depressive symptoms and its side effects could change the MDD profile by influencing specific symptoms as weight gain or constipation [24]. Patients were classified as antidepressant users if antidepressant medication was taken 6 weeks or longer. For patients from the NESDA study, besides self-report, antidepressant use was also obtained by drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical classification [25].

In the MS sample, MS-specific questions were self-reported medication use, MS duration and disease course (confirmed by the neurologist). The telephone version of the Expanded Disability Status Scale [26] was used to assess the physical disability level. The EDSS score ranges from 0 ‘normal neurological examination’ to 10 ‘death due to MS’. Questions assess for example the ability to walk (in meters) with or without (uni- or bilateral) walking-aid, use of wheelchair, and (independent) transfers in and out of bed. When walking ability is good, the estimated EDSS score is most likely between 0 and 4. The EDSS score was categorized from 0 to 1.5 (no experienced restriction by MS in daily life, no complaints), 2–4 (restriction by MS in daily life, low to moderate complaints), 4.5–6 (moderate to severe complaints), and ≥ 6.5 (very severe complaints). Although findings on the relation between depression and MS-related factors such as disease course, duration and physical disability are inconsistent [7,27], disease-related factors could be of importance for a better understanding of MS-related depression. We therefore investigated the relation between disease-related factors (disease course, duration, disability level, medication) and depression severity in the MS-sample additionally.

2.2.2. Depression characteristics and depressive symptoms

Age of depression onset, information on the current episode (recurrence) and presence of a co-morbid dysthymic and/or anxiety disorder in the past six months were assessed with the CIDI [22] by trained research staff. Anxiety disorders involved panic disorder with or without agoraphobia, social phobia, generalized anxiety disorder and agoraphobia.

Depression severity was assessed with the 30-item IDS-SR [21], a self-report instrument that assesses all DSM-IV criteria for MDD, plus commonly associated symptoms (e.g. anxiety, irritability) and symptoms relevant to melancholic and atypical features over the past week. Each item has four answering options from 0 (no problems) to 3 (severe problems). The total severity score of the IDS-SR is calculated as the sum score of all items with a higher score indicating a higher severity. The IDS-SR showed good psychometric properties and was recently validated for MS patients [23,28].

To determine the presence of individual depressive symptoms, IDS-SR items were recoded into dichotomous variables; a score of 0 or 1 means the symptom is absent, a score of 2 or 3 indicates its presence [29]. The separate items on appetite increase and decrease were
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