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ORIGINAL ARTICLE

Progressive multiple sclerosis and mood disorders

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Abstract Mood disorders are very common among multiple sclerosis (MS) patients, but their frequency in patients with progressive course (PMS) has not been adequately researched. Our study aimed to determine the frequency of mood disorders among patients with PMS compared with those with relapsing-remitting MS (RMS) and to explore the associations with disability and disease duration. The study included consecutive outpatients affected by MS according the 2010 revised Mc Donald diagnostic criteria. Psychiatric diagnoses were determined according to DSM-IV by psychiatrists using structured interview tools (ANTAS-SCID). Demographic and clinical data of patients were also collected. Disease courses were defined according to the re-examined phenotype descriptions by the Committee and MS Phenotype Group. Intergroup comparisons were performed by Chi-square test, while logistic regression analysis was performed to assess possible factors associated with mood disorders. In total, 240 MS patients (167 women) were enrolled; of these, 18 % (45/240) had PMS. The lifetime DSM-IV major depression diagnosis (MDD) was established in 40 and 23 % of the PMS and RMS patients, respectively. Using logistic regression analysis, the presence of MDD was independent from disease duration and disability and dependent on PMS course ($P = 0.02$; OR 2.2). Patients with PMS presented with MDD more frequently than those with RMS, independently from disease duration and physical disability. These findings highlight the importance of considering mood disorders, especially MDD, in the management of PMS patients.

Keywords Multiple sclerosis · Progressive course · Major depression · Quality of life · Multidisciplinary approach

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Introduction

Multiple sclerosis (MS) is a complex autoimmune disease characterized by an inflammatory and neurodegenerative process involving the central nervous system (CNS) [1]. Typically, MS has an unpredictable course, with great variability in clinical presentation, pathological features, and prognosis [2] may lead to permanent disability in young adults [3]. Approximately 85–90 % of patients present with relapsing/remitting disease (RMS) characterized by symptomatic attacks between latent states and secondary progression (SP) after a medium time to conversion of around 15–20 years. Approximately 10–15 % of MS patients present with a primary progressive (PP) form characterized by the steady progressive deterioration of neurological functions from the onset [4].

The clinical subtypes of MS were defined in 1996 by the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials [5]. In 2011, the Committee and the MS Phenotype Group re-examined the 1996 phenotype descriptions to determine a better characterization [6]. Interestingly, analyses of the natural history cohorts

demonstrated that the progression of the disease is uniform for SP and PP MS forms [7, 8]. Imaging measures of progression using magnetic resonance are not definitely established as phenotype descriptors, but number and volume of T1-hypointense lesions and brain volume loss are under consideration [6]. Therefore, definition of progressive disease at present is exclusively based on a steadily increasing, objectively documented neurologic dysfunction without unequivocal recovery, although fluctuations and phases of stability may occur. In light of clinical, pathological, and prognostic similitudes, SP and PP MS forms have been recently considered as a unique entity belonging to spectrum of progressive MS phenotypes, independently from disease activity determined by clinical relapses and/or MRI [6].

The attention of neurologists dedicated to MS is typically focused on early diagnosis and treatment to prevent the physical neurologic disability [9, 10]. Over the past recent years, great progress has been made in the treatment of RMS. Unfortunately, a few drugs have shown limited efficacy to hinder the accumulation of disability in the progressive forms (PMS) to date [11, 12].

In light of this consideration, the management of symptoms and comorbidities of MS, in particular of PMS, became crucial. Further, it has drawn attention to the "invisible symptoms" as fatigue and neuropsychiatric manifestations that may have a major negative influence on health-related quality of life (QoL) as much as physical disability of these patients [13–15].

Major depressive disorder (MDD) is the most considered mood disorder among individuals with MS. Evaluations of the lifetime risk for MDD have reported a range of 27–54 % in the MS population [16, 17]. A limited number of studies regarding the prevalence of other mental illness were also conducted [18–20]. Recently, we reported an association between MS and bipolar disorders (BD) [21]. However, some studies have examined the associations between mood disorders and clinical features of MS, such as disease course, disability, and disease progression, reporting conflicting findings [22, 23].

Considering that management of PMS patients is based principally on a symptomatic approach and that psychiatric comorbidity is one of the main determinants of QoL [24], the knowledge of psychological and pathological process related to comorbid psychiatric disorders, together with the correct diagnosis and treatment, is crucial to improve the global management of PMS patients.

In view of the former considerations the present study aimed to determine the prevalence of mood disorders among patients with PMS compared with those with RMS and to explore the associations between psychiatric affections and MS clinical features.

Materials and methods

Participants

The study included outpatients affected by MS, consecutively referred to the MS Centers of the University of Cagliari.

The MS diagnosis was established according to Poser's classification (Poser 1983) until 2001, and after 2001, the McDonald criteria [25] and its subsequent revisions [26, 27] were used. Clinical onset was established as the occurrence of the first symptom unequivocally related to the disease, and duration of the disease was defined by the year of clinical onset. Disability was assessed using the expanded disability status scale (EDSS) [28]. Disease course was defined as RMS and PMS, according to the re-examined 1996 phenotype descriptions by the Committee and the MS Phenotype Group [6]. All PMS patients included in the study did not experience clinical relapses in the previous 2 years, showed an increased disability of at least one point on the EDSS score in the previous year, and did not show Gd-enhancing lesion at the magnetic resonance imaging scan performed within the previous year.

Demographic (sex, age) and clinical data (course, disease duration, EDSS) of patients were collected by neurologists dedicated to treat MS patients.

Psychiatric assessment

Psychiatric diagnosis according to DSM-IV criteria was made by psychiatrists. The psychiatric interviews were conducted using the "Advanced Neuropsychiatric Tools and Assessment Schedule" (ANTAS) [21, 29], a semi-structured clinical interview derived in part from the non-patient version (SCID-I/NP) for DSM-IV [29, 30].

Subjects with severe cognitive or hearing impairment were excluded to simplify the administration of structured interview tools (ANTAS-SCID). If cognitive impairment was suspected but not clear, patients underwent to neuropsychological evaluation by expert neuropsychologist using BRBN battery [31].

Statistic analysis

Lifetime prevalence of MDD, BD, mood disorder due to general medical condition, substance-induced mood disorder and dysthymic disorder was calculated for PMS and RMS groups.

In the PMS and RMS groups, the differences in sex and prevalence of mood disorders were calculated using the Chi-square test. The comparisons of EDSS scores and disease duration in the study groups were calculated using

the Kruskal–Wallis test. Logistic regression analysis was performed to assess possible factors associated with mood disorders (MS course, disease duration, EDSS score). In all assays, statistical significance was set at $P < 0.05$.

Results

In total, the sample included 45 PMS (female: 26; 57.7 %) and 195 RMS patients (female: 141; 72.3 %). Mean values for the duration of the disease were 14.3 and 10.2 in PMS and RMS patients, respectively, while mean EDSS was 5.8 and 3.0 in PMS and RMS patients, respectively ($P < 0.05$). Four MS patients were excluded for objectively demonstrated cognitive impairment. Demographic and MS characteristics of all patients are given in Table 1. The prevalence of MDD and BD, mood disorder secondary to general medical condition, and substance-induced mood disorders detected by the ANTAS-SCID interview is reported in Table 2. MDD diagnosis was performed in 40 and 23 % of the PMS and RMS patients ($P = 0.02$), respectively. The diagnosis of BD was established in 17.7 and 14.3 % of the PMS and RMS patients ($P = 0.5$), respectively. No differences in the education level, disease duration and EDSS score were reported for PMS patients with or without mood disorders, as well as for RMS patients. In the RMS group, an association was found between MDD and female sex ($P < 0.03$) and BD and male sex ($P < 0.05$) (Table 3).

Logistic regression analysis showed that the MDD presence was influenced by PMS course ($P = 0.02$), while no associations were found between MDD, disease duration, and disability. No association was found between BD and clinical covariates ($P > 0.05$) (Table 4).

Table 1 Clinical MS features in study groups

	MS patients (240)	
	PMS patients (45) Primary PMS 30 (12.5 %) Secondary PMS 15 (6.2 %)	RMS patients (195)
	N (% of total sample)	*N* (% of total sample)
Sex (female)	26 (57.7 %)	141 (72.3 %)
Age (mean ± SD)	43.1 ± 10.9	40 ± 9.5
EDSS (mean ± SD)	5.8 ± 1.2*	3.0 ± 1.8
Disease duration (mean ± SD)	14.3 ± 8.0*	10.2 ± 7.2

PMS progressive MS forms, *RMS* relapsing-remitting MS forms

* $P < 0.05$, PMS vs. RMS patients

Discussion

The accumulating evidence has indicated the high frequency of mood disorders, in particular MDD among MS patients [16, 17]. However, few studies have specifically investigated the presence of mood disorders in PMS. We studied the lifetime prevalence of mood disorders in a cohort of patients, focusing on PMS, and explored the association with clinical variables. About MDD diagnosis, the lifetime prevalence offers a better estimation of this psychiatric comorbidity. The presence of ongoing depression could favor a misdiagnosis of BD; indeed, the presence of depressive symptoms with previous mania, ipomania or mixed episode, irrespective of time expired, meets diagnostic criteria of BD [32].

The study was performed in Sardinia, an island characterized by the high prevalence of MS [33, 34] and a peculiar genetic background [34]. Our previous study reported that MS patients had a higher lifetime prevalence of MDD detected by the ANTAS-SCID interview ($P < 0.0001$), compared to controls (OR 7.9) [21]. In our study we found that the prevalence of MDD is higher in persons with PMS compared with RMS, independently disease duration and physical disability. MDD was reported in 30 of PP (12.5 %) and 15 of SP (6.2 %) patients, hence no difference by use of Chi-square test. Although there were differences in disease duration and disability between the RMS and PMS groups, we did not find associations of these variables with mood disorders. The association of depression with disease course in MS was reported in a paper of Zabad et al. The MDD was reported for 10 % of PMS and 26.4 % of RMS (using a Composite International Diagnostic Interview). Differences between this paper and our data may be due to the small number of patients examined and due the higher disability in RMS group reported by Zabad, compared to our patients [22]. Therefore, the link between MDD, BD, and other mood disorders and the clinical features of MS, remain object of discussion [22, 23, 35, 36].

Several studies examining a population of patients, independently from the phenotype of the disease, were unable to find an association between MDD and duration of the disease [23, 35, 37, 38], while another study reported that patients in the initial period after the diagnosis of MS are more likely to have clinically significant depressive symptoms [39]. In our study, a stratification of the sample for disease duration reported no difference in presence of MDD in patients with short disease duration.

Associations between the severity of the disease and MDD are also conflicting. Higher levels of disability have been associated with more severe depressive symptoms in several chronic illnesses [40, 41]. Our data seem to indicate

Table 2 Lifetime psychiatric diagnoses in PMS and RMS groups

	PMS patients *N* (% of total sample)	RMS patients *N* (% of total sample)
Total sample	45 (18.7 %)	195 (81.3 %)
Unipolar depression	18 (40 %)*	47 (24.1 %)
Major depressive disorder (MDD)	18 (40 %)**	45 (23.0 %)
Dysthymic disorder	0 (0 %)	2 (1.0 %)
Bipolar spectrum disorders (BD)	8 (17.7 %)	28 (14.3 %)
Bipolar disorder I	2 (4.4 %)	3 (1.0 %)
Bipolar disorder II	5 (11.1 %)	14 (7.1 %)
Cyclothymic disorder	1 (2.2 %)	5 (2.5 %)
Bipolar disorder not otherwise specified	0 (0 %)	6 (3.0 %)
Mood disorder due to general medical condition	1 (2.2 %)	10 (5.1 %)
Substance-induced mood disorder	0 (0 %)	10 (5.1 %)

PMS progressive MS forms, *RMS* relapsing-remitting MS forms

* $P < 0.05$, PMS vs. RMS patients

** $P = 0.02$, PMS vs. RMS patients

that severity of illness, as reflected by the EDSS score, was not associated with the prevalence of any mood disorders ($P > 0.05$). Furthermore, the majority of our patients had a moderate disability status, thus minimizing the possible interference of physical disability on the development of mood disorders. Moreover, our findings were consistent with those reported by other studies [42, 43]. We also considered the cognitive symptoms because "invisible disabilities of MS" are often accompanied by emotional symptoms [17]; similarly, mood disorders seem to interfere considerably with cognitive activities in MS patients [44]. For these reasons, we excluded patients with objectively demonstrated cognitive impairment, because such kind of disabilities could interfere with administration of ANTAS interview.

Also fatigue may lead to inflate the estimates of MDD [15]. However, although the absence of a specific questionnaire to detect the presence of central fatigue is a limitation of study design, the use of structured interview to define the MDD diagnosis reduces the risk of over-diagnosis.

After considering the different durations of disease and levels of disability between PMS and RMS in the cohort we studied, logistic regression analysis did not show an association between MDD and the duration and severity of MS, the only determinant being PMS course. These findings did not answer the question of whether the high frequency of MDD in PMS patients is caused by a psychological reaction to the unfavorable outcome or to damage to specific structures and circuits of the CNS. In favor of the first hypothesis, there is the fact that PMS patients experience many disabling symptoms without unequivocal recovery that can result in high emotional burden [45]. The feeling of irreversible accumulation of neurologic dysfunction, as well as the awareness of the lack of treatment capable of hindering their disability progression, may be reasons of frustration for these patients [46]. Additionally, the wide range of symptoms, such as spasticity, ataxia, impaired ambulation, bladder/bowel and sexual dysfunctions, fatigue, cognitive dysfunctions, and pain, are often very challenging to manage with pharmacological treatments [47, 48]. Thus, these symptoms greatly affect the QoL of these patients [49]. Regarding the use of disease modifying treatments, no conclusive data are reported about the association with psychiatric side effects [50]. In anamnesis a previous treatment with first line therapies was reported for 72 % of patients. At interview time were reported the following treatments: interferon beta (33 %); Natalizumab (27 %);

Table 3 Clinical MS features in PMS and RMS with or without mood disorders (MDD, BD)

	MDD (18)	BD (8)	No psychiatric disorders (122)
PMS patients (45 cases)			
Sex (female)	12 (66.6 %)	3 (37.5 %)	11 (57.8 %)
Disease duration (mean ± SD)	14.9 ± 7.2	12.4 ± 7.2	14.6 ± 8.7
EDSS (mean ± SD)	5.9 ± 1.8	5.5 ± 1.8	5.8 ± 1.4
	MDD (45)	BD (28)	No psychiatric disorders (122)
RMS patients (195 cases)			
Sex (female)	38 (84.4 %)*	16 (57.1 %)*	87 (71.3 %)
Disease duration (mean ± SD)	8.7 ± 5.4	10.5 ± 7.2	9.1 ± 7.2
EDSS (mean ± SD)	2.4 ± 0.9	2.5 ± 1.8	2.4 ± 1.3

PMS progressive MS forms, *RMS* relapsing-remitting MS forms, *MDD* lifetime major depression, *BD* lifetime bipolar spectrum disorders

* $P < 0.05$

Table 4 Logistic regression analysis

	OR	95 % CI		*P* value
		Lower	Upper	
MDD				
Progressive course	2.222	1.122	4.4	0.022*
Level of disability	1.282	0.824	1.993	0.270
Disease duration	1.006	0.967	1.046	0.777
BD				
Progressive course	1.29	0.544	3.056	0.563
Level of disability	0.856	0.468	0.856	0.612
Disease duration	1.015	0.967	1.064	0.548

MDD and BD diagnosis in MS patients in relation to the presence of PMS course, level of disability (EDSS score) and disease duration (years)

MDD lifetime major depression, *BD* lifetime bipolar spectrum disorders, *PMS* progressive MS forms, *OR* odds ratio, *CI* confidence interval

* $P = 0.02$

Glatiramer Acetate (11 %); Fingolimod (2 %); no therapy (24 %). No correlation was reported between MDD and the use of disease modifying treatments. However, the Glatiramer acetate has not been associated with neuropsychiatric side effects [51] and the depressive symptoms reported for interferon beta use seem more related to pretreatment levels of depression than to the administration of interferon beta [52]. Because the potential risks of adverse neuropsychiatric events from steroid treatment [53], in our study an exclusion criterion was corticosteroid therapy within the 30 days prior ANTAS interview.

The hypothesis that MDD is sustained by a specific neurodegenerative component is supported by some studies that linked MDD in MS to CNS damage mainly involving the frontotemporal regions [54, 55]. In the PMS form, the neurodegenerative process could be the factor promoting the psychiatric comorbidity. The absence of association between disease duration and MDD found in the present study may suggest that MDD is mainly driven by biological determinants. This is contrary to what occurs in other chronic in which patients with longer disease duration adapt to illness over time using coping strategies [56, 57]. In the present study, MDD was found also in about 1/4 of RMS patients. The occurrence of MDD in these patients could be related to the unpredictable, variable nature of relapses in MS, and to the fear of a possible increased disability over time, added to the distress caused by MS diagnosis in young people [58]. Inflammation is also considered an attractive candidate as a factor promoting depression in particular in studies that found high prevalence rate of MDD in RMS [22]. However, in our RR group, we observed an active disease (with relapses or worsening of lesions in magnetic resonance imaging, and Gd-enhancing lesions, in the previous 6 months) in 31/195 (15 %) patients. No correlation was found between MDD, CMG or other mood disorders, and disease activity.

In a recent study, using a case–control design, we found an association between BD and MS in a cohort of patients [21]. In the present study, we found a higher prevalence of MDD among female patients and of BD among male patients only in RMS patients. In this study results are in accordance with data previously reported in a smaller MS sample [21]. However, we did not find differences in duration of the disease and EDSS score among PMS or RMS patients with and without mood disorders.

Apart from the psychological and pathological processes underlying the development of mood disorders in MS, the management of psychiatric comorbidities is crucial to improve the QoL of MS patients. At time of ANTAS interview, 10.2 % of patients revealed a previous psychiatric examination. Our study was retrospective, then very difficult to estimate the prevalence of MDD and other mood disorders before the onset of MS, especially because the mean values for the disease duration. Retrospective analyses of clinical documentations showed that: 28 % of patients used drugs to treat anxiety; 9 % of patients used SSRI (prescribed by general practitioners or by neurologists/psychiatrists). The use of antiepileptic drugs such as lamotrigine, carbamazepine, topiramate was reported for 18 % of patients, especially to treat neuropathic pain. In light of this consideration, a correct diagnosis and management of mood disorders by psychiatrist is crucial for MS patients [59, 60], as it may be noted by large use of psychotropic drugs in our MS sample. The need for a multidisciplinary approach to MS symptoms has recently been reported in a study aimed to assess what MS patients perceive as shortcomings in the treatment of this condition. MS patients considered it was very important to rely on a multidisciplinary team, composed of neurologists, psychiatrists, and psychologists, for the management of emotional problems, as much as physical and psychosocial problems associated with the disease [61]. In particular, patients with PMS forms are characterized by steady neurological worsening without treatment available to hinder sufficiently the disability progression. Therefore, closer attention to several symptoms, including "invisible problems", such as neuropsychiatric manifestations, may improve the management of these patients.

Conclusions

The findings of this study suggest that MDD may be frequent among patients with PMS. This association may be a step in the study of the pathogenic mechanisms underlying

the development of mood disorders among MS patients, particularly for those with PMS forms. Additionally, our results highlight the importance of considering MDD in patients with PMS experiencing mood symptoms to improve their global care.

Conflict of interest No conflict of interest exists regarding the present paper.

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