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Predictors of clinically significant anxiety in people with multiple sclerosis: A one-year follow-up study

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ABSTRACT

Background: Mood disorders, such as depression and anxiety, are frequent in people with Multiple Sclerosis (PwMS). Although anxiety has a well-recognized negative influence on family, work and social life, it has received less attention than depression. Thus, it is still under debate which risk factors can predict anxiety, its evolution over time and the extent of its effect on disability progression.

Objective: The aim of this retrospective study was to identify potential demographic, clinical and self-reported predictors that contribute to clinically significant anxiety at one-year follow up, measured by the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS).

Methods: Data was acquired from a cohort of 608 subjects with MS, and included domains potentially meaningful for clinically significant anxiety. Associations between each variable and clinically significant anxiety at one-year follow-up were assessed with univariate and multivariate logistic regression analyses.

Results: Lower educational level, relapsing-remitting disease course, presence of clinically significant anxiety at baseline, higher depression and fatigue perception were significant predictors for clinically significant anxiety at one-year follow up.

Conclusion: Findings confirm the importance of identifying risk factors for clinically significant anxiety in predicting prognosis and planning early intervention.

1. Introduction

Emerging research indicates that in addition to physical and cognitive deficits, people with MS (PwMS) have to contend with various psychiatric symptoms. Among psychiatric symptoms, however, mood disorders, such as depression and anxiety, occur at much higher rates in PwMS than in general population (Feinstein et al., 2014; Butler et al., 2016; Boeschoten et al., 2017). While depression has been associated with cognitive impairments, suicide intent, poor social support and emotion-centered coping (Gay et al., 2010), with a prevalence of 30.5% to 31.7% in the MS population (Sparaco et al., 2019), anxiety has been mostly linked to increased disability (Askari et al., 2014), comorbid depressive symptoms (Gay et al., 2010; Hartoonian et al., 2015) and female gender (Jones et al., 2012). Anxiety has been reported to be present in up to 22.1% of PwMS (Boeschoten et al., 2017; Sparaco et al., 2019), with approximately 30% of them experiencing symptoms consistent with generalized anxiety disorder (Hartoonian et al., 2015; Jones et al., 2012).

Although anxiety has a well-recognized negative influence on family, work and social life in PwMS (Butler et al., 2016), it has received less attention than depression. This observation, not unique to MS, characterizes the neuropsychiatric literature in general, perhaps reflecting a flawed belief that anxiety is of lesser clinical significance than depression (Feinstein et al., 2014). Thus, it is still under debate which risk factors (e.g., demographic or clinical) can predict anxiety, its evolution over time and the extent of its effect on disability progression. Identifying those factors that account for anxiety would be beneficial to patients and clinicians, for predicting prognoses and planning timely interventions. However, only few studies have investigated potential predictors of anxiety in MS.

Korostil and Feinstein (2007), comparing PwMS with or without a diagnosis of an anxiety disorder, found that those at risk for

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experiencing anxiety had a history of depression, excessive use of alcohol, reported higher social stress and had contemplated suicide (Korostil and Feinstein, 2007). Moreover, gender (more often in women) (Jones et al., 2012), age (higher in young/middle age compared to older adults) (Korostil and Feinstein, 2007), MS disease duration (increment with a longer disease duration) (Sparaco et al., 2019; Hartoonian et al., 2015), disease course (more frequent in relapsing-remitting MS than in progressive forms) (Jones et al., 2012), pain and fatigue (Beiske et al., 2008; Fiest et al., 2016) have been reported to be associated with anxiety among PwMS.

The aim of this retrospective study was to extend the scientific literature on anxiety in PwMS by conducting an evaluation of potential demographic, clinical and self-reported variables that contribute to experiencing clinically significant anxiety after a one-year follow-up.

2. Materials and methods

2.1. Study design

The dataset was acquired from a cohort of PwMS consecutively enrolled in the ongoing PROMOPRO-MS initiative (Brichetto et al., 2020). PROMOPRO-MS is a large, multicenter, prospective study, in which PwMS are evaluated periodically with various clinical scales and questionnaires to investigate several aspects including physical, cognitive, psychological, social and quality of life domains. In addition to demographic (gender, age, years of education) and clinical (disease duration, disease course, relapses in the last four months and level of disability as measured with the Expanded Disability Status Scale, EDSS (Kurtzke, 1983) information, Patient Centered Outcomes (PCOs) are also collected. These included: Functional Independence Measure (FIM) (Granger C et al., 1990); Hospital Anxiety and Depression Scale (HADS) (Honarmand and Feinstein, 2009), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005); Life Satisfaction Index (LSI) (Franchignoni et al., 1999); Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977); Symbol Digit Modalities Test (SDMT) (Langdon et al., 2012); Overactive Bladder questionnaire (OAB-q) (Coyne et al., 2006); Modified-Fatigue Impact Scale (MFIS) (Kos et al., 2005) and Abilhand (Simone et al., 2011).

2.2. Participants

Subjects were consecutively enrolled among those followed as outpatients or at-home by the Italian MS Society (AISM) Rehabilitation Services of Genoa, Padua and Vicenza.

Since PROMOPRO-MS inclusion criteria are a definite diagnosis of MS and an age above 18 years, the current cohort was comprised of patients with relapsing-remitting (RR) and progressive (both secondary and primary) MS courses.

Written informed consent was obtained from all subjects prior to study entry. The study was approved by Liguria's region ethical committee.

In order to have an adequate cohort of subjects with complete data at the one-year follow-up (T1) after baseline assessment (T0), evaluations from PROMOPRO-MS collected between January 2014 and December 2019 were considered.

2.3. Primary outcome

HADS consists of two subscales, measuring anxiety (HADS-A) and depression (HADS-D), scored separately. Its usefulness has been validated as a marker of major depression and generalized anxiety disorder in the MS population. In this study, the primary outcome was HADS-A, which is a 7-item measure of anxiety symptom severity, that has been considered the best available tool for detecting anxiety in PwMS (88.5% sensitivity; 81% specificity) (Honarmand and Feinstein, 2009). Items are rated on a 4-point Likert scale, with higher scores indicating greater anxiety. Clinically significant anxiety was defined as a HADS-A score ≥ 8[15].

2.4. Outcome measure

Based on previous evidence, outcome measures in PROMOPRO-MS database, which includes domains potentially meaningful for anxiety, were selected as candidate predictors of clinically significant anxiety at the one-year follow-up. Concerning demographic predictors, age (Beiske et al., 2008), gender (Askari et al., 2014) and level of education (Bjelland et al., 2008) were designated. Disease duration (Hartoonian et al., 2015), disease course (Jones et al., 2012) and EDSS (Janssens et al., 2006) were included as clinical predictors. PCO predictors were MFIS (Beiske et al., 2008; Fiest et al., 2016; Brown et al., 2009) for fatigue, MoCA (Wallis et al., 2020) for cognitive status, HADS-D for depression (Askari et al., 2014; Brown et al., 2009; Wallis et al., 2020) and HADS-A for clinically significant anxiety at baseline.

2.5. Statistical analysis

Associations between each predictor and the clinically significant anxiety at one-year follow up were assessed with simple logistic regression models. Multivariable logistic regression models with predictors that had p-value ≤ 0.1 in simple logistic analyses were used to select potential factors which were predictive of anxiety in MS. Backward variable selection based on the Akaike Information Criterion (AIC) was used to determine the optimal set of predictors (Akaike, 2020; Sauerbrei, 1999). Multi-collinearity of the final model was assessed. A variable was eliminated if the variance inflation factor (VIF) was greater or equal to 10 or the tolerance limit was less than 0.1. The analyses were performed using Stata Statistical Software (StataCorp, 2017).

3. Results

See Table 1 for sample characteristics. In the present study, data from 608 subjects were analysed (females = 408; mean age = 57.9 ± 12.5 years; mean disease duration = 23.2 ± 11.9 years). Progressive MS course was most common (56.7%).

Table 1
Sample characteristics (N = 608).

Age (in years), mean (SD), Min-max		57.9 (12.5) 21–92
Gender, n (%)	Male	200 (32.9%)
	Female	408 (67.1%)
Educational level, n (%)	Primary school	197 (32.4%)
	High school	283 (46.6%)
	University	128 (21.0%)
Disease duration, mean (SD)		23.2 (11.9)
Disease course, n (%)	RR	263 (43.3%)
	SP/PP	345 (56.7%)
EDSS, mean (SD) score		5.1 (2.0)
Median (IQR)		5.8 (3.5–6.5)
MoCA at T0, mean (SD) score		23.2 (4.7)
Median (IQR)		24.0 (21.0–27.0)
MFIS at T0, mean (SD) score		37.5 (18.0)
Median (IQR)		37.0 (25.0–49.5)
HADS-D at T0, mean (SD) score		5.3 (3.7)
Median (IQR)		5.0 (2.0–7.0)
HADS-A at T0, mean (SD) score		6.8 (4.4)
Median (IQR)		6.0 (3.0–10.0)

SD (standard deviation); RR (relapsing-remitting); SP (secondary progressive); PP (primary progressive); EDSS (Expanded Disability Status Scale); IQR (interquartile range); MoCA (Montreal Cognitive Assessment); MFIS (Modified-Fatigue Impact Scale); HADS-D (Hospital Anxiety and Depression Scale - depression subscale); HADS-A (Hospital Anxiety and Depression Scale - anxiety subscale).

Table 2
Predictors of clinically significant anxiety at one-year follow-up: univariate and multivariate logistic regression analyses.

		Univariable OR (95% CI)	*p* value	Multivariable OR (95% CI)	*p* value
Age		1.00 (0.98–1.00)	0.741		
Gender	Male	1			
	Female	1.68 (1.16–2.42)	0.006		
Level of education	University	1		1	
	High school	1.75 (1.08–2.84)	0.022	1.71 (0.96–3.04)	0.069
	Primary school	2.99 (1.81–4.93)	<0.001	2.37 (1.29–4.33)	0.006
Disease duration		0.99 (0.98–1.00)	0.128		
Disease course	SP/PP	1		1	
	RR	1.69 (1.20–2.39)	0.003	1.82 (1.19–2.78)	0.006
EDSS at T0		0.97 (0.89–1.05)	0.470		
MoCA at T0		0.99 (0.96–1.03)	0.685		
MFIS at T0		1.05 (1.04.1.06)	<0.001	1.01 (1.00–1.03)	0.042
HADS-D at T0		1.33 (1.25–1.41)	<0.001	1.16 (1.08–1.25)	<0.001
HADS-A at T0		12.03 (8.10–17.86)	<0.001	6.26 (4.05–9.67)	<0.001

OR (odds ratio); CI (confidence interval); SP (secondary progressive); PP (primary progressive); RR (relapsing-remitting); T0 (baseline assessment); EDSS (Expanded Disability Status Scale); MoCA (Montreal Cognitive Assessment); MFIS (Modified-Fatigue Impact Scale); HADS-D (Hospital Anxiety and Depression Scale - depression subscale); HADS-A (Hospital Anxiety and Depression Scale - anxiety subscale).

At one-year follow-up, 35.7% (217/608) of subjects met the cut-off for clinically significant anxiety: 8.7% (53/608) were new cases of anxiety and 27.0% (164/608) confirmed persistent anxiety. In contrast, 13.2% (80/608) participants reporting anxiety at baseline reduced the score below the clinical cut-off at the follow-up.

The univariate logistic analyses (Table 2) found that female gender, RR course, lower level of education, higher HADS-D, MFIS total scores and HADS-A at baseline were significantly associated with clinical anxiety at one-year follow-up. In the final logistic regression model, lower educational level (OR = 2.37, $p = 0.005$), RR course (OR = 1.82, $p = 0.006$), higher levels of depression and fatigue (OR = 1.16, $p < 0.001$ and OR = 1.01, $p = 0.042$, respectively) and the presence of anxiety (OR = 6.26, $p < 0.001$) at baseline significantly correlated with clinical anxiety at one-year follow-up (Table 2). No collinearity was identified in the final model.

On the contrary, EDSS (OR = 0.97, $p = 0.470$) and MoCA (OR = 0.99, $p = 0.685$) at T0 did not correlate with clinically significant anxiety.

4. Conclusions

Mood disorders, specifically anxiety and depression, are frequent in PwMS. Previous literature has tended to focus on the effects of depression, while less attention has been given to the causes and effects of anxiety, although the prevalence of anxiety is higher (up to 22.1%) in MS (Boeschoten et al., 2017; Sparaco et al., 2019). Anxiety can overlap with somatic (e.g., muscle tension) and non-somatic (e.g., concentrating difficulty) manifestations of the disease, increasing the possibility that the disorder and its causes go under-recognized and, consequently, untreated, impacting other clinical outcomes as well. If untreated, anxiety can reduce quality of life, negatively influence treatment compliance and exacerbate MS symptoms.

The current study identified several risk factors for clinically significant anxiety in MS over one year. These findings corroborate and extend previous evidence suggesting that a lower level of education, relapsing-remitting (RR) disease course, depression, fatigue and the presence of clinically significant anxiety at baseline predict clinically significant anxiety after one year.

The presence of clinically significant anxiety after one year was not related to subjects' age. However, investigating the association between age and anxiety, several authors have found that anxiety tended to decrease across adulthood (Beiske et al., 2008), suggesting that older people have learned increased emotional control so that they are better at dampening negative emotions and enhancing positive emotions. However, a responsible factor for inconsistent results could be age bias in anxiety measurement. Since older people are more likely to report sleep problems, fatigue and thoughts about death compared to mood disorder or anhedonia in general, this may imply that anxiety could be not manifested in exactly the same way in younger and older people. Further, gender did not predict clinically significant anxiety after one year. However, the role of gender is not clear given that some studies have found that females are significantly more anxious than males (Théaudin et al., 2016), while others found no gender differences in those who reported high levels of anxiety (Anhoque et al., 2011).

Further, in line with (Hartoonian et al., 2015; Jones et al., 2012; Beiske et al., 2008), disability level and disease duration did not predict clinically significant anxiety. However, the association between disability level and anxiety deserves further attention. Although some previous studies have shown that individuals with more severe disability report higher levels of anxiety (Askari et al., 2014; Janssens et al., 2006), others did not find a significant correlation between EDSS and anxiety (Beiske et al., 2008). One possible explanation could be that anxiety in PwMS is more associated with the perceived unpredictability of widespread symptomatology rather than with long and persistent disability and reduced ambulation as measured by EDSS. Indeed, anxiety could be most strongly related to psychological factors (e.g., depressive symptoms and fatigue) than disease-related factors (e.g., EDSS), suggesting that the way patients react to the disease (Butler et al., 2016; Wallis et al., 2020) contribute the most to anxiety.

Results did not find a relationship between cognitive functioning and clinically significant anxiety. While anxiety has been shown to negatively impact cognition in PwMS (Wallis et al., 2020; Goretti et al., 2014), specifically affecting executive functioning, memory, and information processing speed (Kalron et al., 2018), cognitive status did not result as a predictor of clinically relevant anxiety. Since our participants showed a preserved cognitive functioning, one possible speculation is that anxiety may act as a protective mechanism for PwMS preventing them to fall on cognitive tasks (Kalron et al., 2018). Thus, consistent evidence indicates that in healthy individuals moderate levels of anxiety can facilitate performance on tests (Owens et al., 2014). Thus, in a update version of the Attentional Control Theory (ACT) (Derakshan and Anxiety, 2009), Eysenck and Derakshan (2011) consider further the possible role of motivation, suggesting that when a task is undemanding and/or the goals are unclear, high-anxious individuals may lack motivation and thus perform worse than when a task is challenging and there are explicit goals (Eysenck and

Derakshan, 2011). Anyway, these results should be interpreted with caution given that clinically significant anxiety and cognitive performance interact each other in complex ways at behavioral, physiological, and neural level (Vytal et al., 2013).

Level of education was included in the analysis as a novel idea to investigate whether it would be a relevant predictor of clinical anxiety. Results indicate that PwMS with less education are at risk for experiencing anxiety over time, in agreement with Bjelland et al. (Bjelland et al., 2008) which found that lower levels of education were significantly associated with higher scores on anxiety/depression measures. Further, higher levels of education are associated with better self-management, defined as an active process of coping with the disease through treatment adherence, self-care, active seeking of information about the illness and emerging treatment options, and emotional balance (Wilski et al., 2016). This could lead to develop more disease awareness and improve the capacity to cope and correctly self-evaluate the disability (Tacchino et al., 2019), thus preventing the onset of clinically significant anxiety.

Furthermore, in a "provocative" way, the relationship between educational level and anxiety could be explained considering the concept of cognitive reserve hypothesis, which show that lifetime intellectual enrichment, commonly indexed by level of education, occupational complexity, engagement in stimulating leisure activities, attenuates the effect of disease burden on cognition (Sumowski et al., 2014). Although it cannot be directly quantified, some surrogates have been explored in MS, such as premorbid intelligence, reading ability and occupational achievement, closely related to education. As consequence, a possible explanation could be that PwMS with a higher level of education (i.e., greater intellectual enrichment) could be protected from the negative impact of disease on cognition and on mental health as well (Sumowski et al., 2014).

RR course was associated with more clinically significant anxiety at the one-year follow up compared to progressive forms. This is in line with the study by Jones et al. (Jones et al., 2012) which found that anxiety was most frequent among RR course (56.5%), whereas depression was recurrent among secondary progressive patients (56.9%). At this early stage of the disease, when PwMS experience a lower level of physical disability, symptoms may be ambiguous, with a variety of manifestations, leading people to question their source and possible evolution, and thus affect work and social roles. Further, the number of relapses over time could significantly increase anxiety levels (Butler et al., 2016). Indeed, PwMS may experience more uncertainty about their future than patients in which progression is more apparent, in the absence of relapses (Hayter et al., 2016). However, results from other studies did not confirm the association between anxiety and disease course (Askari et al., 2014; Wallis et al., 2020). For instance, Askari et al. (Askari et al., 2014) found that progressive PwMS had higher anxiety and depression compared to RR patients. This discrepancy could be due to the choice of different outcome measures, specifically the Beck Anxiety Inventory (BAI) versus the HADS. Since the BAI has been found to have lower sensitivity and specificity than other instruments, this raises the question whether it may overestimate and misclassify anxiety in progressive MS (Marrie et al., 2018). On the contrary, as suggested by Feinstein et al. (Feinstein et al., 2014), the use of HADS-A in clinical routine can help tease out the differences, thereby mitigating the risk that anxiety and its predictors will be ignored.

Anxiety at baseline was a significant predictor of clinically significant anxiety at one-year follow up. Similarly, Janssen et al. (Janssens et al., 2006) found that 69% PwMS with high levels of anxiety at baseline showed significant anxiety at one or two-year follow-up. Also, Hartoonian et al. (Hartoonian et al., 2015) reported anxiety at baseline assessment associated with greater anxiety at a four-month follow-up. A possible explanation could be that the presence of unaddressed anxiety should be a red flag denoting anxiety as a persistent problem. Higher levels of anxiety may persist as individuals continue to experience adverse consequences of MS that may have a negative impact on career, relationships and family planning (Janssens et al., 2006). Lastly, individuals could have difficulty in coping with uncertainty about the type of MS, particularly in the transition phase from RR to a progressive or about the significance of symptoms (Janssens et al., 2006).

Results from the current study confirm the strong association between anxiety and depression in MS (Butler et al., 2016; Hartoonian et al., 2015; Brown et al., 2009). From a clinical point of view, it is well known that when both disorders are present, PwMS usually report greater severity in symptoms, more somatic complaints (e.g., fatigability, irritability, muscle tension, and sleep disturbance), functional impairment and risk of suicide than when anxiety alone is present (Feinstein et al., 2014; Korostil and Feinstein, 2007). However, despite high comorbidity and strong effects in MS, how anxiety and depression are inter-related, either temporally or causally, remains unclear. Recent studies have mainly investigated the role played by anxiety on the genesis of depressive symptoms without taking into account whether depression may predict anxious states. Brown et al. (Brown et al., 2009) showed that anxiety and depression predict each other among PwMS but, in particular, anxiety predicts later depression. Similarly, Gay et al. (Gay et al., 2010) reported that anxiety is a strong predictor of depression by highlighting that its impact is heightened by the presence of alexithymia and a lack of social support. However, as depression and anxiety are inter-related, treating depression could reduce anxiety and other psychological problems in such patients (Askari et al., 2014).

A higher perception of fatigue at baseline predicted clinically significant anxiety at the one-year follow up (Beiske et al., 2008; Brown et al., 2009). As indicated by Fiest et al. (Fiest et al., 2016), anxiety was associated with increased fatigue over time, but this effect was attenuated once depression was accounted for. Beiske et al. (Beiske et al., 2008) found that subjects with fatigue had 5.1 times higher risk for symptoms of anxiety. Also, Brown et al. (Brown et al., 2009) demonstrated that anxiety, depression and fatigue at baseline were better predictors of anxiety over two years than any factors (e.g., disease related, demographics, cognition, stress, psychosocial attributes or lifestyle. Since anxiety, depression and fatigue overlap and often cluster together resulting in an interdependent relationship, it is possible that this association reflects shared underlying pathologic changes (Fiest et al., 2016). Further studies are needed to investigate biological mechanisms between anxiety, depression and fatigue.

In discussing our data, some important caveats need to be considered.

Participants' characteristics may limit the interpretation of our results. Study sample can be considered representative of those clinic-attending PwMS followed as outpatients in rehabilitation centers (i.e., middle-age/older adults and with high proportion of progressive forms) (Tacchino et al., 2017). Thus, results may not generalize to other populations of individuals with MS.

Since the HADS-A is not a diagnostic tool, the current study describes clinically significant anxiety, but not anxiety disorders. An exploration of risk factors for anxiety disorders, as well as differences between types of anxiety disorders, is worthy of future research.

Although an advantage of HADS subscales is that the inclusion of somatic items is limited (e.g., "I feel as if I am slowed down"), distinguishing anxiety from depression in PwMS is difficult since symptoms may overlap (e.g., asthenia, fatigue, energy loss, sleep disorders, and cognitive disorders). Thus, it may be argued that the assessment of depression and anxiety should have used two separate scales.

Finally, to restrict the analysis to a reasonable number of variables, some factors that may also contribute to anxiety were not included, such as marital status, social network, socioeconomic status,

employment, sleep disturbances and personality traits among others. Furthermore, information about any attended treatment (e.g., medications or psychological therapy) should be collected.

The importance of identifying key factors associated with clinically significant anxiety is unquestionable as this problem has been reported to be amongst the most disabling, influencing the general health and quality of life in PwMS (Butler et al., 2016). While some risk factors (e.g., disease course and education) are not modifiable, interventions focusing on other variables that can be addressed (e.g., fatigue and depression) could be effective in successfully treating clinically significant anxiety.

Given the high prevalence of anxiety and depression in PwMS there is a widespread agreement for the need to identify and treat mood disorders at the earliest opportunity. The limited effectiveness of medications alone, their costs and common adverse effects, require the implementation of complementary strategies. Cognitive behavior therapy can be useful in reducing depression and anxiety, and has been shown to help PwMS explore reactions to the unpredictability of the disease, in which anxiety has a key role, as well as modifying dysfunctional beliefs about MS, which may drive the overall anxiety response (Hayter et al., 2016). Similarly, relaxation and mindfulness (Crescentini et al., 2018) strategies have also been found to be effective in reducing anxiety in PwMS by facilitating psychophysiological or emotional changes. While initial results are encouraging, further studies are needed to investigate if and how these psychological therapies could have long-term effects in real world settings.

Credit author statement

Jessica Podda: conceptualization, validation, writing - original draft, review and editing, visualization; Michela Ponzio: conceptualization, methodology, formal analysis, data curation; Michele Messmer Uccelli: writing - original draft; Ludovico Pedullà: investigation, review and editing; Federico Bozzoli: review and editing, Federica Molinari: review and editing; Margherita Monti Bragadin: resources; Mario Alberto Battaglia: supervision; Paola Zaratin: review and editing, supervision; Giampaolo Brichetto: review and editing, project administration, funding acquisition; Andrea Tacchino; conceptualization, validation, writing – original draft, review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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