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## **Abstract**

Chronic and life-threatening neurodegenerative diseases may be associated with Post-traumatic stress disorder (PTSD). We investigated the prevalence of PTSD in Multiple Sclerosis (MS) patients, and then we identified significant determinants of PTSD.

Two hundred thirty-two MS patients were consecutively recruited and screened for the presence of PTSD with the Impact of Event Scale-Revised (IES-R), corroborated by the Structured Clinical Interview for DSM-IV. Furthermore, participants were administered the Hospital Anxiety and Depression Scale and the Fatigue Severity Scale.

Twelve patients (12/232, i.e. 5.17%) were diagnosed as suffering from PTSD.

The levels of education, anxiety and depression were significant determinants of the presence of PTSD.

The roles played by the levels of education, anxiety and depression in determining the presence of PTSD has been highlighted. Further research on the psychological features of neurodegenerative diseases are urgently needed in order to plan appropriate treatments and improve patients' quality of life.

**Keywords:** Anxiety, depression, multiple sclerosis, neurodegenerative diseases, post-traumatic stress disorder.

## 1. Introduction

Post-Traumatic stress disorder (PTSD) is a disabling condition typically characterized by the re-experiencing of the traumatic event; voluntary avoidance of stimuli associated with the event; and increased physiological arousal for at least one month from the event (American Psychiatric Association, 2000). A traumatic event is defined as one in which the person “experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of others” (Criterion A1) and the person’s response involved “intense fear, helplessness, or horror” (Criterion A2) (p. 467).

Chronic and potentially life-threatening illnesses have been identified as significant stressors potentially triggering PTSD. This has demanded allow the acknowledgement of the significant emotional consequences of the diagnosis of a serious medical condition, such as cancer, myocardial infarction, and stroke (Cordova et al., 2007; Kangas et al., 2002; Tedstone & Tarrier, 2003). It is now well established that people with chronic neurological illnesses appear to demonstrate poorer psychological functioning and quality of life compared to people in the general population (e.g., Behari, Srivastava, & Pandey, 2005; McCabe & McKern, 2002). However, patients differ in terms of how they react to the medical illness, and how they face their problems during the course of the clinical condition (Mohr et al., 1999). It would appear that coping strategies, social supports and ways of approaching the illness may be important in shaping adjustment to the illness among both patients and caregivers (McCabe, McKern, & McDonald, 2004). Thus, to date it appears clear that suffering from a chronic neurological condition has a significant impact on the emotional, professional and social aspects of patients’ lives. In addition, depending on the individual

characteristics of the patients and on the availability of adequate social support, the impact of the chronic condition differs among patients.

In recent years some studies have started to focus on the possible association between PTSD and neurological diseases, fostering our knowledge about the existence and the nature of this association. For example, it was shown that suffering from PTSD lead to an increased risk of developing dementia in a large cohort of U.S. Veterans (Qureshi et al., 2010; Yaffe et al., 2011) and Holocaust survivors (Sperling et al., 2011). Thus, the possible connection between traumatic stress and neurodegenerative disorders supports the necessity of carefully screening for PTSD in these conditions, in order to verify its possible presence and to plan treatments accordingly, when needed (Esch et al., 2002; Possemato, 2011).

Amongst neurodegenerative diseases, a condition that has been recently investigated in terms of its association to PTSD is Multiple Sclerosis (MS). MS is an inflammatory disease of the central nervous system that affects both the brain and the spinal cord. It is the most common cause of non-traumatic neurological disability amongst young and middle-aged adults, and it is typically characterized by significant motor impairment and additional neuropsychiatric and cognitive symptoms (Beiske et al., 2008; Chiaravalloti and DeLuca, 2008; McCabe, 2006). Chronic and potentially life-threatening illnesses have been indicated as significant stressors triggering PTSD. This has allowed underlining of the significant emotional consequences of the diagnosis of a serious medical condition, such as cancer, myocardial infarction, and stroke (Cordova et al., 2007; Kangas et al., 2002; Tedstone and Tarrier, 2003).

~~In recent years some studies have started to focus on the association between PTSD and neurodegenerative diseases (mainly dementias), to foster our knowledge about the existence and the nature of this association. Interestingly, it has been shown that suffering from PTSD leaded to an increased risk of developing dementia in a large cohort of U.S. Veterans (Qureshi et al., 2010; Yaffe et al., 2011) and Holocaust survivors (Sperling et al., 2011).~~

~~Thus, the connection between traumatic stress and neurodegenerative disorders supports the necessity of carefully screening for PTSD in these conditions, in order of clarifying the clinical picture and planning treatments accordingly (Esch et al., 2002; Possemato, 2011).~~

~~Amongst neurodegenerative diseases, a condition that has been recently investigated in terms of its association to PTSD is Multiple Sclerosis (MS). MS is an inflammatory disease of the central nervous system that affects both the brain and the spinal cord. It is the most common cause of non-traumatic neurological disability amongst young and middle-aged adults, and it is typically characterized by significant motor impairment and by additional neuropsychiatric and cognitive symptoms (Beiske et al., 2008; Chiaravalloti and DeLuca, 2008; McCabe, 2006).~~

PTSD in MS has some peculiarities: it is not related to a single event ~~that~~ occurred in the past, but rather to the expected course of the degenerative condition, and ~~then~~ the intrusive symptoms are typically oriented to the future (i.e. fear of being confined to a wheelchair, fear of relapsing episodes, fear of the progression of the disease, and so on). These features of PTSD in MS have already been identified by Chalfant et al. (2004), which was the first study that investigated the presence of PTSD due to the diagnosis of MS in a small sample of patients. They found a relatively high rate of patients presenting with PTSD (N = 9/58, i.e. 15.5%). However, it remains unclear whether a significant proportion of patients with MS actually suffer from PTSD, and, most importantly, what are the possible determinants of PTSD in this clinical population.

In the present study, our goal was to assess the rate of patients presenting with PTSD in a large sample of MS patients, in order to estimate the expected rate of PTSD due to the presence of MS. In addition, we aimed to identify the possible contribution of demographic and clinical variables to the presence of PTSD in patients with MS. The implications of these findings for clinical treatments were briefly discussed.

## 2. Methods

### 2.1. Ascertainment of participants.

Two hundred thirty-two patients with MS (68 males and 164 females) were consecutively recruited from May 2010 to June 2011 from the CRESM (Regional Reference Centre for Multiple Sclerosis, affiliated with the University Hospital “San Luigi Gonzaga” of Orbassano, Italy, an Italian center for the diagnosis and treatment of MS patients). All of the patients underwent detailed neurological, biological and neuroimaging investigations, and received a definitive diagnosis of MS according to the standard international criteria (Polman et al., 2011) from neurologists expert in the diagnosis of MS. In terms of MS status, 209 participants (i.e. 90.08%) were classified as relapsing-remitting, 7 (3.02 %) as primary progressive, and 16 (6.90%) as secondary progressive.

Inclusion criteria were as follows: age between 18 and 65 years; definitive diagnosis of MS; corticosteroids free for at least 30 days before the evaluation; fluent in Italian. Exclusion criteria were as follows: presence of severe psychiatric disorders such as psychosis or bipolar disorder; presence of severe medical conditions other than MS such as diabetes, strokes or traumatic brain injuries; drug or alcohol abuse; suicide attempts; and overt dementia.

Informed consent was obtained from all of the participants. The study was granted approval by the local Research Ethics Committee.

### 2.2. Procedure.

All of the clinical interviews were conducted at the University Hospital “San Luigi Gonzaga” of Orbassano by psychiatrists with a significant clinical experience (at least 5

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~~years) psychiatrists with significant experience in the diagnosis of PTSD.~~ To evaluate the presence of PTSD in MS we followed the proposal of previous studies (Chalfant et al., 2004; Hathaway et al., 2010; Dell’Osso and Carmassi, 2001): the Criterion A2 (subjective experience) was modified by asking participants if they felt intense fear or helplessness due to the presence of MS. It is crucial to note that our request was aimed at investigating whether during the last month the patients felt intense fear or helplessness due to the presence of MS, not just that whether they were scared or worried about it in the past. The ~~diagnostic~~ assessment process comprised of the administration of the clinical tools detailed below, which allowed the clinicians to identify the presence of MS as the patients’ most significant source of stress.

All of the participants were first screened via the Impact of Event Scale-Revised (IES-R, Horowitz et al., 1979; Weiss and Marmar, 1997), a 22-item self-report measure consisting of three subscales (8 items investigate intrusions, 6 items pertain to hyperarousal, and 8 items are related to avoidance) that assesses subjective distress caused by traumatic events. Each item is rated on a 5-point scale ranging from 0 (“not at all”) to 4 (“extremely”). A reliable capacity of this measure to distinguish between traumatized and non-traumatized individuals has been demonstrated (Briere, 1997). According to the DSM-IV three-factor structure of the definition of PTSD, we considered as potentially affected by a significant trauma related distress, those patients that presented at least one item of intrusion  $\geq 3$ , two items of hyperarousal  $\geq 3$ , and three items of avoidance  $\geq 3$ . This way we were confident that all participants with the possible presence of PTSD would be admitted to the following assessment stage. Participants with an IES-R score suggesting the possible presence of a significant traumatic disorder were thus specifically interviewed by an experienced psychiatrist using the PTSD module of the Structured Clinical Interview for DSM-IV (SCID, First et al., 1996), in order to corroborate the diagnosis of PTSD.

Only participants with both the IES-R and the PTSD module of the SCID indicating the presence of a significant post-traumatic disorder were considered as suffering from PTSD, whereas participants with only the IES-R as indicative of a significant disorder were not considered as suffering from PTSD.

Patients diagnosed as suffering from PTSD were then administered the Clinician Administered PTSD Scale (CAPS, Blake et al., 1995), a clinical semi-structured interview based on the DSM IV-TR considered the gold standard in assessing PTSD.

To conclude, all of the participants recruited for the study (regardless of their PTSD status) were administered the following two measures: the Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983; [Honarmand & Feinstein, 2009](#)), a 14-item self-assessment scale that provides a valid and reliable measure of severity of anxiety and depression and the Fatigue Severity Scale (FSS, Krupp et al., 1989), a nine-item one-dimensional questionnaire assessing the severity of fatigue.

Patients received a score on the Expanded Disability Status Scale (EDSS, Kurtzke, 1983) from their neurologist, to monitor the level of disability presented at the time of the current psychiatric assessment.

### 2.3. *Statistical analyses.*

Statistical analyses were performed using SPSS<sup>®</sup> (Statistical Package for the Social Sciences) version 18.0 for Windows<sup>®</sup>. Given the large sample size available, and, as the graphical explorations of the data by means of Q-Q plots indicated an acceptable distribution of the variables of interest, parametric tests were used. The analyses were run as follows:

First, the demographic and clinical variables were reported for the following groups: the overall group of participants (i.e. “overall group”, N = 232); the subgroup of participants



with both the IES-R score and the SCID-PTSD module indicating the presence of PTSD (i.e. “PTSD group”, N = 12); the subgroup of participants with the IES-R score but not the SCID-PTSD module indicating the presence of traumatic symptoms (i.e. “IES-R + group”, N = 24); and the subgroup of participants with the IES-R score not indicating the presence of PTSD (i.e. “IES-R – group”, N = 196).

Secondly, as the IES-R was used as a screening tool, we performed a multiple regression analysis in order to identify the significant predictors of the IES-R score.

Lastly, we performed simple and multiple logistic regression analyses in order to detect the possible influence of demographic and clinical variables to the presence of PTSD.

A  $p$  value  $< 0.05$  was accepted as statistically significant throughout all of the analyses.

### 3. Results

Figure 1 shows the number of participants at each assessment stage. The overall group included 232 participants, only 12 of who (i.e. 5.17%) satisfied the diagnosis of PTSD as indicated by both the IES-R score and the SCID-PTSD module. A small subgroup of patients (N = 24, 10.35%) presented with an IES-R score suggesting the presence of significant traumatic symptoms, but this was not corroborated by the SCID-PTSD module. Interestingly, the vast majority of participants (N = 196, 84.48%) did not show a significant presence of traumatic symptoms. Regarding the HADS and the FSS, four patients did not perform the former tool and one patient did not perform the latter tool due to time constraints. Table 1 shows the demographic and clinical characteristics of the groups of participants.

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Figure 1 around here

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Table 1 around here

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Furthermore, in order to clarify the contribution of the demographic and clinical variables to the IES-R score, a multiple regression analysis was run. The contribution of the predictors to the IES-R score is shown in Table 2. The level of formal education and the HADS-anxiety measure reached a statistically significant contribution to the IES-R score (level of formal education: standardized  $\beta = -0.113$ ,  $p = 0.037$ ; HADS-anxiety: standardized  $\beta = 0.481$ ,  $p < 0.001$ ), while all of the other variables included in the statistical model did not reach a significant contribution. The final model yielded a satisfactory proportion of variance explained (adjusted  $R^2 = 0.425$ ).

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Table 2 around here

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Simple and multiple logistic regression analyses were performed in order to detect the influence of demographic and clinical variables on the presence or absence of PTSD.

Simple regression analyses showed the presence of PTSD was significantly associated with lower education ( $p < 0.001$ ), higher level of anxiety ( $p < 0.001$ ), higher level of depression ( $p < 0.001$ ) and higher level of fatigue ( $p = 0.03$ ). In the multiple regression analyses only education ( $p = 0.019$ ), level of anxiety ( $p = 0.016$ ) and level of depression ( $p = 0.022$ ) remained significantly associated with the presence of PTSD (Table 3).

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Table 3 around here

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#### 4. Discussion

The investigation of the nature and prevalence of psychological comorbidities in neurodegenerative diseases is an important clinical issue. In fact, it is essential to clarify whether significant psychological problems such as anxiety, depression and PTSD complicate patients' medical conditions, in order to plan appropriate and effective treatments accordingly.

The current study is one of the first investigations of the possible presence of PTSD in a large sample of patients with MS. Interestingly, our findings suggest that the prevalence of PTSD in this clinical population is not as large as expected: in fact, only 12 out of 232 MS patients (i.e. 5.17%) actually fulfilled the diagnostic criteria for PTSD as required by the IES-R and the SCID-PTSD module. A previous study (Chalfant et al., 2004) identified a higher proportion of MS patients (9/58, i.e. 15.5%) as presenting with PTSD.

A possible explanation for the discrepancy between our findings and the previous ones is the different clinical tools used to make a diagnosis of PTSD (i.e. IES-R, SCID-PTSD

module and CAPS versus CAPS alone, respectively) may result in a different capacity of detecting the presence of PTSD. Alternatively, as our sample was four times as large as the sample used in the previous study, it is possible that our findings represent a more reliable estimation of the actual prevalence rate of PTSD secondary to MS. However, future studies should clarify between these (or other) possible explanations.

We were also interested in investigating the demographic and clinical predictors of the IES-R score. Only the level of formal education and the HADS-anxiety score were significantly related to this measure. Our results showed the lack of a significant relationship between the duration of MS, the degree of disability (as measured by the EDSS), and the level of fatigue (as measured by the FSS), and the presence of relevant traumatic symptoms as measured by the IES-R. This lack of significant relationships implies that factors different from the clinical indices of MS are involved in determining the presence of substantial traumatic symptoms. This is in agreement with the evidence suggesting that PTSD seems to be associated more to individual factors pertaining to the patient than to the precipitating event *per se* (Brewin et al., 2000).

Regarding the significant relationship of the HADS-anxiety score to the IES-R score, this is in line with previous findings suggesting that anxiety in MS patients is an important and frequent comorbidity that needs to be recognised and treated appropriately (Beiske et al., 2008). Furthermore, our findings suggest that anxiety symptomatology is also significantly related to the IES-R score. In other words, anxiety in MS is not an important neuropsychiatric factor *per se*, but it may play an additional role in increasing the possibility of developing a traumatic disorder that would complicate significantly the clinical condition of the patients.

We were still interested in investigating the contribution of demographic and clinical factors to the presence (or absence) of PTSD. Regarding this important issue, simple logistic regression analyses allowed us to identify a lower level of formal education, a higher score on

the HADS-anxiety and depression measures and a higher level of fatigue (as measured by the FSS) as significant predictors of PTSD. Furthermore, multiple regression analyses combining these significant predictors allowed us to identify the level of education and the levels of anxiety and depression as significantly related to the presence of PTSD. The levels of anxiety and depression may exacerbate the post-traumatic symptomatology and may be related to the fear of the progression of the disease.

In this study, we also found in MS patients a significant relationship between PTSD and the level of education, previously found in other clinical populations (Vasterling et al., 2002; Ullman and Filipas, 2001). At this point in time, no clear explanation for this finding exists, so it is only possible to speculate about it. For example, this relationship could be explained by the fact that the level of education might be involved as a 'protective' factor against the development of PTSD. In other words, higher levels of education might support patients' understanding and acceptance of the diagnosis of MS (Chiovetti, 2006) and might reinforce patients' ability to cope with the challenges of this chronic disease (Patti et al., 2007).~~For example, this relationship could be explained by the fact that the level of education, a proxy of 'cognitive reserve' acting as a protective factor against cognitive impairment in neurodegenerative diseases such as Alzheimer's disease and MS (Stern, 2006; Sumowski et al., 2009), might be involved as a protective factor against the development of PTSD as well. In other words, higher levels of education might support patients' understanding and acceptance of the diagnosis of MS (Chiovetti, 2006) and might reinforce patients' motivation towards the treatment during the course of the disease. Moreover, higher cognitive levels may help to cope with the disease more adaptively.~~ However, future studies should specifically clarify this issue.

The present study has some important strengths. It involved a large sample of patients with MS, allowing us to be very confident about the reliability of the results obtained. Also,

both the neurologists and the psychiatrists involved in the study were very experienced ~~in the diagnosis of MS and PTSD, respectively~~. Furthermore, to the best of our knowledge, this is the first study that highlighted the possible factors related to PTSD in MS patients, corroborating the important role played by the level of education and the levels of anxiety and depression.

The study also has some limitations. As the vast majority of patients presented with the relapsing-remitting form of the disease, we did not perform a comparison between different types of MS due to the lack of adequate sample sizes. Moreover, we did not investigate the influence of the MS on patients' quality of life, which is affected by the diagnosis and the course of the neurodegenerative condition.

To conclude, it is still interesting to note that PTSD in patients with MS may have some peculiarities: the criterion of re-experiencing the event is likely to be different for MS and for chronic diseases in general, as the stressful event (i.e. the medical condition) is not confined to the past but is still present and will be present for the rest of their lives, as already noted by Chalfant et al. (2004). Thus, phenomenologically speaking, in chronic diseases the psychological symptoms could be more tied to the future than related to the past. However, the possible validity of this suggestion has to be specifically investigated in further research.

~~To conclude, in our study we found some peculiarities of PTSD in patients with MS, as already noted by Chalfant et al. (2004): the criterion of re-experiencing the event is likely to be different for chronic diseases, as the stressful event is not confined to the past but is still present and will be present for the rest of their lives. Thus, symptoms are likely to be more tied to the future than related to the past.~~

Overall, our findings support the necessity of taking into account multiple clinical dimensions when making a diagnosis and planning a long-lasting treatment for patients with MS, including a careful investigation of the possible presence of PTSD. In fact, the

psychological aspects related to MS (e.g., depression, anxiety, and PTSD) should be seriously taken into account, in order for the clinicians to plan efficient treatments devoted to reduce the levels of psychological symptoms that often complicate the clinical picture. This may help in improving social adjustment, reducing the negative implications of stress, and ultimately enhancing patients' quality of life (Esch et al., 2002). In order to verify this hypothesis, our group is currently treating the MS patients affected by PTSD involved in the present study. More precisely, we are currently treating them with Eye Movement Desensitization and Reprocessing (one of the most efficient psychotherapy methods for the treatment of post-traumatic stress disorder together with Trauma-Focused Cognitive Behaviour Therapy), which has recently started to show a beneficial effect on the quality of sleep, anxiety, and depressive symptoms too (Raboni et al., 2006; van der Kolk et al., 2007). Our aim will be to demonstrate that the adjunctive planning of a short-term treatment specifically tailored to patients' psychological needs can significantly improve the level of functioning and the quality of life of patients with MS.

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