



The relationship between depression, anxiety and cognition and its paradoxical impact on falls in multiple sclerosis patients



Alon Kalron^{a,*}, Roy Aloni^b, Gilles Allali^{c,d,e}

^a Department of Physical Therapy, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

^b Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer Street, Tel Hashomer, Israel

^c Department of Clinical Neurosciences, Division of Neurology, Geneva University Hospitals, Geneva, Switzerland

^d Department of Neurology, Division of Cognitive and Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

^e Faculty of Medicine, University of Geneva, Geneva, Switzerland

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ABSTRACT

Although falls, cognitive impairments and mood disorders are very common in people with MS (PwMS) the relationship between these conditions has received scant attention. Therefore, the purpose of the study was to investigate the specific involvement of depression and anxiety on cognition and falls in PwMS. The study included 122 PwMS (75 women) divided into four subgroups according to their manifestation of depression and anxiety assessed by the Hospital Anxiety and Depression Scale (HADS) (i.e. no depression/no anxiety, depression/no anxiety, no depression/anxiety and depression/anxiety). Cognitive performance was evaluated via a computerized cognitive battery of tests. Participants were defined as “fallers” and “non-fallers” based on their fall history recorded during a clinical interview. Thirty-eight PwMS (31.1%) were classified as depressed (mean HADS 11.1, SD = 3.4); 52 (42.6%) were classified as anxious (mean HADS 11.1, S.D = 3.1) and 56 (45.9%) were neither depressed nor anxious. PwMS categorized in the anxiety/non-depressed subgroup were 6 times less likely to fall than PwMS without depression or anxiety (OR = 0.160, 95%CI = 0.040–0.646; *P*-value = 0.010). In terms of global cognitive status, depressed PwMS with anxiety were almost 4 times more likely to experience cognitive impairments compared to PwMS who were not depressed or anxious. Anxiety without comorbid depression is associated with less risk of falling, even when comparing MS patients without depression or anxiety. Future longitudinal investigations should confirm if this phenotype of MS patients with anxiety and without depression fall less compared with other mood groups.

1. Introduction

Depression and anxiety are common in people with multiple sclerosis (PwMS) (Feinstein et al., 2014; Morrow et al., 2016). Recently, a meta-analysis of 87,756 PwMS, found that the prevalence of depression and anxiety in PwMS are 30.5% and 22.1%, respectively (Boeschoten, 2017). Anxiety and depression in PwMS are associated with the level of neurological disability (Butler et al., 2016; Chwastiak et al., 2002) and with poor cognition, especially processing speed, working memory and executive function (Feinstein et al., 2014; Morrow et al., 2016).

Although anxiety and depression are closely related to each other, they depict different mood states. Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior such as pacing back and forth and somatic complaints. Depression is a state of low mood negatively affecting a person's

thoughts, behavior, feelings and sense of well-being (Diagnostic and Statistical Manual of Mental Disorders., 2013). Multiple studies investigated the association between depression, anxiety and self-perceived cognition in PwMS, although there are inconsistent reports in the literature (Akbar et al., 2011; Yasmin et al., 2007).

Previous studies have confirmed that cognitive impairments are associated with falls in PwMS (D'Orio et al., 2012; Gunn et al., 2013; Kalron, 2014). The majority of epidemiological studies have focused on common risk factors, such as mobility, balance or cognitive impairments (Finlayson et al., 2006; Gianni et al., 2014; Nilsagard et al., 2015). Nevertheless, although both falls and mood disorders are very common in MS patients (Feinstein et al., 2014; Boeschoten et al., 2017; Finlayson et al., 2006; Gianni et al., 2014; Nilsagard et al., 2015), the association between falls and mood disorders has received scant attention. In this context, Williams et al. (2005) examined 451 veterans with MS and found that patients who experienced falls were at a higher

* Corresponding author.

E-mail addresses: alonkalr@post.tau.ac.il (A. Kalron), roy.aloni@sheba.health.gov.il (R. Aloni), gilles.allali@hcuge.ch (G. Allali).

risk to suffer from depression compared to those without depressive symptoms (Williams, 2005). However, this investigation did not include anxiety, leaving the question open as to whether an association between anxiety and falls in PwMS exists.

Determining the specific involvement of depression and anxiety with cognition and falls in PwMS can be valuable. Although, anxiety and depression negatively affect daily living, their impact on risk of falling is uncertain in the MS population. For instance, anxiety may relate to a cautious behavior, thus, anxious PwMS may avoid unnecessary risks while walking. On the other hand, PwMS without anxiety may behave the opposite, hence, increasing risk of falls. Therefore, the purpose of the current study was to investigate the specific involvement of depression and anxiety on cognition and falls in PwMS.

Our PwMS were divided into subgroups according to the presence of depression and anxiety. We hypothesized that PwMS suffering from both depression and anxiety would present with the poorest cognition and highest risk of falling, whereas, those without anxiety and depression would exhibit the best cognitive performances and lowest risk of falling. As for MS patients who solely suffer from depression or anxiety, we hypothesized that depression would have a greater impact on cognition and falls compared to anxiety.

2. Methods

2.1. Study design and participants

This cross-sectional study included 122 PwMS (75 women and 47 men) recruited from the Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer, Israel from January 2012 to May 2017. The data were extracted from the Center's computerized database, a population-based registry documenting demographic, clinical and imaging data of all consecutive MS patients followed at the center. The integrity of the data registry was evaluated by a computerized logic-algorithm-questioning process identifying data entry errors.

Inclusion criteria included: (1) a neurologist-confirmed diagnosis of definite MS according to the revised McDonald criteria (Polman, 2011); (2) an expanded disability status scale (EDSS) score of < 7.0 (Kurtzke, 1983); (3) an evaluation of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) questionnaire; (4) a comprehensive neuropsychological assessment (a computerized cognitive test); and (5) the need for the cognitive tests and the HADS questionnaire to be completed within 3 months of each other. Exclusion criteria included: (1) an acute MS relapse; (2) corticosteroid treatment within 90 days before the cognitive assessment; (3) other significant neurologic or psychiatric illnesses and (4) alcohol or drug abuse. All patients gave written informed consent. The study was approved by the local Ethics Committee.

2.2. Anxiety and depression assessments

Anxiety and depression were assessed with the HADS, a validated self-report screening scale used to investigate the prevalence of emotional distress among patients in general medical clinics (Crawford, 2001). The scale consisting of 7 items, rates two components - anxiety and depression. Each question is scored in a simple Likert fashion (0 through 3) yielding a range of scores from 0 to 21 for each item (Honarmand, 2009). The patient is asked how he/she have been feeling during the past week. The questionnaire includes three cut-off scores indicating different levels of clinically relevant distress: a score between 0–7 = normal status, 8–10 = borderline and 11–21 = an abnormal depression rate (Zigmond, 1983). The HADS is widely used in clinical practice and has been validated in the MS population (Honarmand & Feinstein, 2009).

In the present study, we used a cutoff point of 8 to differentiate between MS subjects with and without anxiety/depression (Honarmand

& Feinstein, 2009). Patients with a score ≥ 8 on the anxiety component were defined as anxious and those < 8 were defined as non-anxious. In a similar manner, patients with a score ≥ 8 on the depression component were defined as depressed and those < 8 were defined as non-depressed. According to these definitions, the sample group was separated into four individual subgroups, denoting the presence of anxiety and depression (i.e. non-anxious/non-depressed, anxious/depressed, anxious/non-depressed and non-anxious/depressed).

2.3. Cognitive assessment

The patients completed the computerized cognitive battery of tests (Mindstreams; NeuroTrax Corp., Medina, New York, USA). Outcome measurements encompassed the following cognitive domains: verbal and nonverbal memory, executive function, visual spatial processing, verbal function, attention, information processing speed and motor skills. Each cognitive domain score was normalized and equivalent to an IQ scale (mean: 100, SD: 10) in age and education-specific domains. Cognitive scores obtained from these tests have good test-retest reliability and construct validity relative to paper-based tests in the MS population, including the frequently used Neuropsychological Screening Battery for MS (NSBMS) (Achiron, 2007).

The global cognitive score was divided into two categories: normal and impaired. We used a cut-off score of 1-SD (= 15 points) to differentiate between the two categories. Patients with a score ≥ 90 on the global cognitive score were defined as normal and those with < 90 were defined as cognitively impaired. This cut-off score was based on a large cross-sectional study (n = 1500) identifying cognitive impairments in PwMS. Accordingly, by the 5th and 10th year from disease onset, 20.9% and 29.3% of patients performed below the 1-SD cutoff for cognitive impairment, respectively (Achiron, 2013).

2.4. Fall status

Participants were defined as “fallers” and “non-fallers” based on a clinical interview related to their fall history: “Have you fallen during the past year?” A fall was defined as an event where the participant unintentionally came to rest on the ground or a lower level (Finlayson et al., 2006). Although, this definition does not refer to the reasons for the fall or if it resulted in a serious injury, the advantage is that it is straightforward and minimizes subjective judgment by the researcher and/or participants (Coote et al., 2014). A faller was defined if the patients had experienced at least two falls during the previous year. Two or more falls were selected since it is questionable whether a single fall clearly classifies an individual as a faller (Gunn, 2013).

2.5. Statistical analysis

Descriptive statistics determined the demographic and clinical characteristics of the study participants according to their group allocation. Clinical, demographical, mood and cognitive data were normally distributed according to the Kolmogorov–Smirnov test. Group differences in age and gender distribution were determined using an independent sample-t and chi-square test, respectively. Differences in cognitive parameters between subgroups were determined using the multivariate analysis of variance tests controlling for age, gender and the EDSS score. The Bonferroni correction adjusted multiple comparisons between groups.

Two separate binary logistic regression analysis were performed: the first examined the relationship between fall status (dependent variable) and mood conditions and the second examined the relationship between the global cognitive status (dependent variable) and mood conditions. The following conditions were employed in each one of the binary regression analyses: (1) mood subgroups were entered into the model as categorical covariates; (2) the non-anxiety/non-depressed subgroup was defined as the reference group; (3) the model was

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