



## Depression and fatigue in multiple sclerosis: Relation to exposure to violence and cerebrospinal fluid immunomarkers

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### ABSTRACT

Multiple sclerosis (MS) is a neuroinflammatory condition characterized by chronic dysregulation of immune responses leading to repeated episodes of inflammation in the central nervous system. Depression and fatigue are common among MS patients, even in early disease phases, and the disease course can be negatively affected by stressful events. IL-6 and IL-8 have been associated with depression and stressful life events in non-MS patients. The aim of this study was to examine the relationships between depression, fatigue, and exposure to violence, with IL-6 and IL-8 levels in the cerebrospinal fluid (CSF) of MS patients. Levels of IL-6 and -8 were analyzed in the CSF of 47 patients with relapsing-remitting MS. Correlations between IL-6 and IL-8 levels and self-rated depression and fatigue symptoms, as well as clinician-rated history of being exposed to interpersonal violence, were analyzed with correction for age, sex and MS disability status. IL-6 correlated significantly ( $p < 0.05$ ) with depressive symptoms (adjusted Spearman's  $\rho = 0.39$ ), fatigue ( $\rho = 0.39$ ), and exposure to violence in adult life ( $\rho = 0.35$ ). Depression correlated with both fatigue and being exposed to violence. Associations were not present among patients exposed to disease modifying drugs. In exploratory analyses, the relationship between exposure to violence and IL-6 was non-significant when controlled for depression. Further research should focus on replication of these results, as well as exploring the impact of stressful life events on immune regulation and the clinical characteristics and prognosis of MS patients.

### 1. Introduction

Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) disease that can give rise to a wide spectrum of symptoms, including affection of mood, behavior, and cognition. Clinically significant symptoms of depression, as well as the formalized diagnosis of major depressive disorder (MDD), are common among MS patients (Brenner et al., 2014; Marrie et al., 2015) with a recent systematic review reporting a prevalence of 35% for symptoms and 21% for diagnosis (Boeschoten et al., 2017). Depression and MS appear to have a complex relationship, where common background factors such as stress may exist, but where depression also may be secondary to the MS disease (Arnett et al., 2008). At least part of the underlying variance in this association seems to be explained not by psychosocial factors or coping with disability, but by MS disease activity in itself (Feinstein et al., 2004). However, several criteria in the MDD diagnosis such as restlessness, fatigue, or sleeping problems are also frequently found

among MS patients without depression, and the distinction from the syndrome of MDD may be difficult (Patten, 2010).

MS fatigue, a sensation of physical and mental energy depletion that limits normal activities, is also common and rated as one of the most disabling symptoms by patients (Shah, 2009). While distinct from depression, symptoms do overlap and are highly correlated even when somatic depressive symptoms are omitted (Bakshi et al., 2000; Kroencke et al., 2000). Causality, if it exists, is complex, as depression can predict later fatigue and fatigue can predict later depression (Brown et al., 2009).

Cytokines are signaling proteins central for the immune responses and as such central to the pathogenesis of MS in several ways (Amedei et al., 2012). MS patients have elevated serum levels of both pro- and anti-inflammatory cytokines compared to healthy subjects (Martins et al., 2011). The advancement of multiplex immunoassays seen in later years has led to several mapping studies of cytokines and chemokines in the cerebrospinal fluid (CSF) of MS patients. These studies have shown

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varied and often conflicting results regarding both detectability and dysregulation compared to healthy controls, as well as for specificity for MS clinical disease course (Burman et al., 2014; Edwards et al., 2011; Matsushita et al., 2013). This probably reflects a current lack of knowledge in several areas regarding the mechanisms, variation and detectability of individual cytokines, but also the technical limitations of current analysis platforms. Among a large panel of cytokines reported in MS, interleukin-6 (IL-6) and -8 (IL-8) are among the most consistently up-regulated.

IL-6 plays an important role for adaptive and innate immune responses. It has been implicated both in specific immune processes, such as differentiation of Th17 cells, but also in general systemic effects, such as sickness behavior (Scheller et al., 2011). CSF levels of IL-6 have been reported in several MS materials, however, still with variable results (Malmestrom et al., 2006; Uzawa et al., 2009). IL-8 is a molecule with both cytokine and chemokine-like functions and mainly implicated in innate immune activation processes (Qazi et al., 2011). Detection of CSF IL-8 shows results that are somewhat more consistent and IL-8 has recently been suggested as a biomarker for MS progression (Matejckikova et al., 2015; Rossi et al., 2015). In non-MS subjects, both depressive symptoms and MDD have been rather consistently linked to upregulation of IL-6 and IL-8 in both blood (Baune et al., 2012; Marsland et al., 2007) and in CSF (Dowlati et al., 2010; Kern et al., 2014).

Being exposed to violence as a child or adult seems to increase the sensitivity for developing psychiatric disorders, including depression and suicidality (Devries et al., 2013; Heim and Nemeroff, 2001). Violence is a more specific type of event than the concepts of stress or trauma, and may be less sensitive to recall bias (Lalande and Bonanno, 2011). MS patients have a higher risk than healthy controls for having experienced childhood trauma – although not physical abuse – which is associated with number of relapses, but not with disability (Spitzer et al., 2012). A recent meta-analysis also saw an association with MS onset for some types of violent physical trauma in case-control studies, but not in cohort studies (Lunny et al., 2014), and the authors concluded that further study using validated instruments specifying type of trauma was needed. A growing body of evidence suggests that neuroinflammatory adaptations mediate this connection, including increasing levels of proinflammatory cytokines (Cattaneo et al., 2015). Patients with posttraumatic stress disorder (PTSD), where exposure to a life-threatening event is mandatory for diagnosis, show upregulation of proinflammatory cytokines, including IL-6, in blood (Lindqvist et al., 2017). Thus, IL-6 and -8 have been implicated both in psychiatric conditions in non-MS subjects and as inflammatory markers in MS. However, studies examining the relation between these cytokines and psychiatric symptoms in MS patients are rare.

The aims of this study were to examine the association between CSF expression of IL-6 and IL-8 and a) symptoms of depression, and b) symptoms of fatigue, and c) being exposed to violence as a child or adult, in a clinical cohort of MS patients.

## 2. Materials and methods

### 2.1. Subjects

During the study recruiting period of May 2012 to June 2014, all consecutive relapsing remitting MS (RRMS) patients at the MS outpatient clinic at the Karolinska University Hospital, Solna who met the following criteria were asked to participate in the study: 1. A recent CSF examination for clinical purposes, allowing for an interview session within 90 days of sampling. 2. Being 18–55 years of age. 3. Recent ( $\leq 2$  years) MS diagnosis, or a current switch in drug treatment regime due to relapse and/or side effects. Patients switching treatment could still be treated with their current drug at time of sampling. 4. No known major somatic or psychiatric diagnoses besides MS. 5. No psychiatric or psychotropic medication, including glucocorticoids, within 90 days of

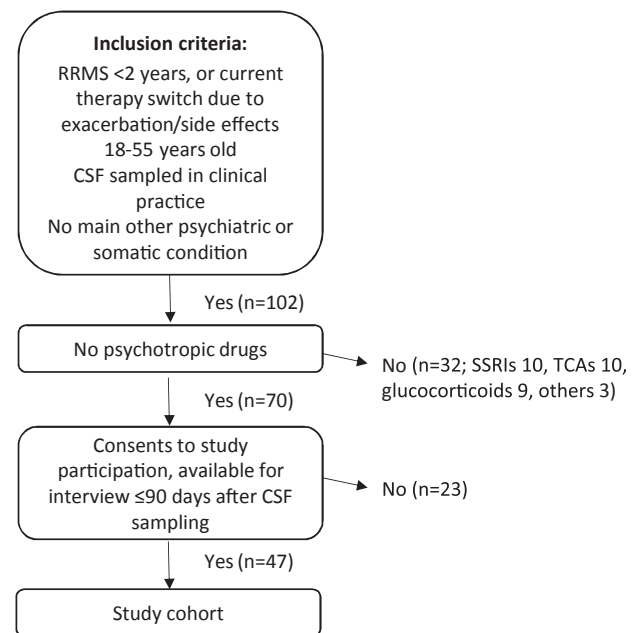


Fig. 1. Study recruitment flow chart. RRMS = Relapsing remitting multiple sclerosis, CSF = cerebrospinal fluid. SSRIs = Selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

sampling. The MS clinic serves a population-based uptake area that includes the central-northern part of Stockholm County corresponding to about 40% of the entire population of approximately 2 million.

Forty-seven subjects who met the criteria and gave informed consent were included in the study. A recruitment flow chart is shown in Fig. 1. Written informed consent was obtained from all patients

and the study was approved by the Regional Ethical Vetting Board of Stockholm (Diary Number: 2012/352- 31/4).

### 2.2. Clinical measurements and covariates

During a single session, participants were subject to two semi-structured clinical interviews conducted by a trained psychiatrist. The Karolinska Interpersonal Violence Scale (KIVS) (Jokinen et al., 2010) includes four subscales, each ranging from 0 to 5, measuring exposure to/used interpersonal violence as a child (6–14 years old) or adult (15 years of age or older). Violence exposure ranges from occasional, low-grade violence (1) up to repeated, serious battering or harm (5). The KIVS has a good interrater reliability (Jokinen et al., 2010). The MINI International Neuropsychiatric Interview (M.I.N.I.) version 6.0.0.b (Sheehan et al., 1998), uses DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) (Association and DSM-IV., 1994) criteria to screen for and clinically validate psychiatric diagnoses, including MDD.

The subjects also filled out the Montgomery-Åsberg Depression Rating Scale, self-report version; (MADRS-S) (Montgomery and Åsberg, 1979), which is a nine item questionnaire for rating of depressive symptoms according to the DSM criteria for MDD. In order not to confound depressive symptoms with common MS-related symptoms such as fatigue or sleeping problems, the five cognitive items in the MADRS-S scale (covering the symptoms depressed mood, anxiety, pessimism, loss of interest and suicidality) were separated for analysis. The Modified Fatigue Impact Scale (MFIS) is modified version of the Fatigue Impact Scale (Fisk et al., 1994) and is a widely used instrument for measuring MS fatigue. Disability was rated at the time of CSF sampling with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) by a trained neurologist.

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