The effect of war stress on multiple sclerosis exacerbations and radiological disease activity

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Article history:
Received 30 July 2009
Received in revised form 4 September 2009
Accepted 9 October 2009
Available online xxxx

Keywords:
War stress
Multiple sclerosis
Disease activity
Exacerbations
MRI
Gadolinium enhancement

Abstract

Objective: The relationship between stressful life events and multiple sclerosis (MS) exacerbations or radiological disease activity is at best controversial. The aim of this study is to examine the relationship between exposure to war-related events incurred during the July 2006 Israeli-Lebanese war and clinical relapses and MRI disease activity among Lebanese MS patients.

Methods: We studied a group of 216 patients with clinically definite relapsing remitting MS (RRMS), on whom clinical data was available for the war period and for the preceding and following year(s). The number of relapses was determined during the war period and during similar periods over a 3-year span. All patients with brain MRI during the war period had their scans reviewed for evidence of disease activity as defined by the presence of gadolinium enhancing (Gd+) lesions. A group of patients with brain MRI performed outside the war period was used for comparison.

Results: The total number of relapses during the war period (n=23) was significantly higher than during non-war periods (mean = 8.4, SD = 0.86) (p = 0.006). Of the 18 patients with brain MRI during the war, 5/7 with relapses and 1/11 without relapses had Gd+ lesions (p = 0.013). More patients had Gd+ lesions during the war period (33%) compared to controls (13%) (p = 0.075).

Interpretation: Our study shows that exposure to war-related events is likely to lead to an increase in both clinical relapses and MRI disease activity in patients with MS.

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1. Introduction

Evidence that major stressful events may cause exacerbations in patients with multiple sclerosis (MS) is still controversial [1]. Studies in the animal model of autoimmune encephalomyelitis show that certain stressors when administered are associated with disease exacerbation [2]. The animal model of autoimmune encephalomyelitis show that certain patients with multiple sclerosis (MS) is still controversial [1].

In humans, a 1-year prospective study showed that, in comparison to the non-exposed group, MS patients having three or more major stressful events during a four week period had a five-fold increased risk of relapses whereas those having one event had only a three-fold increase in risk [3]. Mohr and colleagues suggest that stress is one of the factors that influence exacerbations in MS [4]. In contrast, a study from Israel failed to demonstrate an increase in the number of relapses during the 1991 Gulf war, suggesting that not all stress conditions are potential causes of increased MS exacerbations [5]. The sample size of this study was, however, too small for a conclusive finding. In addition to increased risk of clinical relapses, stressful events have also been associated with radiological disease activity as evidenced by new Gd+ brain lesions within 8 weeks of the event [6,7].

In July 2006, Lebanon was ravaged by the most devastating conflict in its history. The Israeli war on Lebanon started on July 12 and lasted 33 days, resulting in high casualties’ toll. In addition, almost one third of the Lebanese population was displaced within the country or to neighboring countries [8]. This period was obviously associated with a high degree of psychological stress for all the Lebanese population. A study conducted in Israel during the July 2006 war demonstrated that the relapse rate in patients with MS increased significantly [9]. However, the study lacked validation of the clinical data based on MRI gold-standard evidence of increased disease activity [10]. The aim of our study is to examine the relationship between exposure to war-related events associated with the July 2006 war and MS disease activity both clinically and radiologically.

2. Methods

Data for this study was retrieved from Project MS-Lebanon which is a Lebanese Registry of MS patients developed in 2005 at the American University Hospital (AUH), a tertiary referral center for Lebanon and the Middle East. Using the iMed Electronic Multiple Sclerosis Patient Monitoring System program, data was retrospectively entered before
the year 2005 and prospectively afterwards. The data was retrieved using patients’ hospital and clinic records and included patients who were seen at least once at AUH. Further details on the database are published elsewhere [11]. The diagnosis of MS was based on McDonald’s criteria [12] and disability was evaluated using the Expanded Deficits Status Scale (EDSS) [13]. We analyzed data on all patients with Relapsing Remitting MS (RRMS) on whom clinical data was available between January 15, 2005 and January 15, 2008 (n = 216). These comprised 66% of the total number of patients available in the database. The number of relapses during and up to 1 month after the war (15 July–15 September, 2006) was compared to the number of relapses during consecutive 2-month periods in the year preceding and following the war. Relapses were defined as subjective reporting of new or worsening of old symptoms lasting for more than 24 h in the absence of fever with objective evidence of neurological impairment [14]. Relapses had to cause functional impairment, be confirmed by a neurologist, and require intravenous corticosteroids. All brain MRIs performed during and up to 4 weeks after the war were reviewed (n = 216) and assessed for disease activity defined as the presence of Gd+ lesions [15,16]. These were compared with patients with brain MRIs performed during the same period (July, August, and September) within 2 years preceding or following the war (n = 83) and frequency matched for age, gender, disease duration, baseline disease activity, and EDSS. The radiologists evaluating MRIs were blinded to the time period and study hypothesis. For patients who had Gd+ brain MRI data from brain MRI done up to 6 months before this Gd+ MRI was collected to assess their baseline disease activity. For patients without relapses, brain MRIs were performed on a routine basis. All brain MRIs were performed more than 10 days after the last dose of corticosteroids. A 1.5-T MR imaging unit (Philips, Intera) was used to perform conventional MR imaging. Transversespin-echo T1-weighted (repetition time msec/echo time msec, 603.7/15), T2-weighted (2900/120), fluid attenuated inversion recovery (FLAIR) (6000/150 and TI = 2000) and post contrast T1-weighted (603.7/15) sequences of the brain were performed. The section thickness was 3 mm without any gap, the field of view was 25 cm, and the acquisition matrix was 256 × 192.

Frequencies, means and standard deviations (SD) were used to describe the study sample. Differences in baseline characteristics and in increased disease activity by MRI is necessary to support clinical data. In that respect, our study is the first in the literature to show evidence of increased MS disease activity during severe stress, both by clinical (relapses) and radiological (Gd+ lesions) parameters. Out of 18 patients who had a brain MRI done during the war period, the overwhelming majority of patients (71%) with relapses had Gd+ lesions compared to less than 10% among patients without relapses. These findings provide evidence that the increase in clinical symptomatology during the war period reflects a real increase in disease activity.

To further support the clinical data, we then compared patients with a brain MRI done during the war period to a control group from our database that had an MRI during the same months of the year in brain MRI during that period, 7 of whom had clinical relapses. In the 11 patients without relapses, indication for MRI included routine yearly follow-up, clinical study protocols and headaches. The proportion of patients with evidence of disease activity (Gd+ lesions) was significantly greater among patients with clinical relapses (5/7) than without (1/11), (p = 0.013). We then compared those 18 patients to a comparison group which consisted of 83 patients from outside the war period. There was no statistically significant difference in the mean age, mean disease duration, mean EDSS, gender, baseline Gd+ brain MRI between the two groups. However, patients during the war period had 2.5 times more disease activity on MRI (33%) compared to controls (13%) (p = 0.075) (Table 2).

3. Results

A total of 216 patients had clinical data available between January 2005 and January 2008. The patients’ characteristics and demographics are shown in Table 1. The sample consisted of 86 males and 130 females with a mean age of 39.6 ± 10.9 years, mean EDSS of 3.0 ± 2.4, and mean disease duration of 9.25 ± 7.2 years at the time of the war. The majority of patients (60.6%) were on disease modifying therapy during that period of whom only 2 (1.5%) discontinued treatment during the war period. A total of 23 relapses occurred during the 2-month war period which was significantly greater than the number of relapses in any 2 months during the non-war period (mean = 8.4, SD = 0.86, p = 0.006) (Fig. 1). Importantly, of the 7 patients with relapses during the war period, only one had Gd+ lesions (OR = 5) and none had a relapse in the 6 months preceding the war. To further support our clinical data, we assessed MRI disease activity during the war period in patients with and without relapses. A total of 18 patients performed a

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (years)*</td>
<td>39.6 ± 10.9</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1:1.5</td>
</tr>
<tr>
<td>EDSS (Mean ± SD)*</td>
<td>3.0 ± 2.4</td>
</tr>
<tr>
<td>Mean disease duration ± SD (years)*</td>
<td>9.25 ± 7.2</td>
</tr>
<tr>
<td>Interferon intake*</td>
<td>60.6%</td>
</tr>
</tbody>
</table>

* At time of war.

Table 1

Clinical and demographic characteristics of patients (n = 216).


![Figure 1](image-url)
In conclusion, our study demonstrates for the first time in the literature an increase in both clinical and radiological disease activity in MS patients during periods of severe war stress. Larger prospective studies using clinical, radiological, and biological parameters are warranted to further confirm our findings.

References