

Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis

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Abstract

Objective To quantify the association between stressful life events and exacerbations of multiple sclerosis.

Data sources PubMed, PsychInfo, and Psychological Abstracts searched for empirical papers from 1965 to February 2003 with terms “stress,” “trauma,” and “multiple sclerosis.”

Review methods Three investigators independently reviewed papers for inclusion/exclusion criteria and extracted the relevant data, including methods, sample statistics, and outcomes.

Results Of 20 studies identified, 14 were included. The meta-analysis showed a significant increase in risk of exacerbation in multiple sclerosis after stressful life events, with a weighted average effect size of $d = 0.53$ (95% confidence interval 0.40 to 0.65), $P < 0.0001$. The studies were homogenous, $Q = 16.62$, $P = 0.22$, $I^2 = 21.8\%$. Neither sampling nor study methods had any effect on study outcomes.

Conclusions There is a consistent association between stressful life events and subsequent exacerbation in multiple sclerosis. However these data do not allow the linking of specific stressors to exacerbations nor should they be used to infer that patients are responsible for their exacerbations. Investigation of the psychological, neuroendocrine, and immune mediators of stressful life events on exacerbation may lead to new behavioural and pharmacological strategies targeting potential links between stress and exacerbation.

Introduction

Most people with multiple sclerosis have a relapsing form of the disease, characterised in part by exacerbations of symptoms which develop suddenly and remit slowly over the course of weeks or months but often can leave some residual impairment.

Numerous triggers of exacerbation have been proposed, including bacterial or viral infections that cause T cells to “mistake” myelin proteins for these antigens, bacterial “superantigens,” physical injury, or stressful life events.¹ Of these, the role of stressful life events in particular has been highly controversial.² More than 100 years ago, Charcot speculated that grief, vexation, and adverse changes in social circumstance were related to the onset.³ Most patients with multiple

sclerosis believe that stressful events can cause or contribute to their exacerbations.⁴ To clarify the present state of empirical research we conducted a systematic review and quantitative meta-analysis to evaluate the hypothesis that stress is associated with subsequent clinical exacerbation in multiple sclerosis.

Methods

Identification of studies

We searched PubMed, PsychInfo, and Psychological Abstracts from 1965 to February 2003 using the terms “stress,” “trauma,” and “multiple sclerosis.” Potential unpublished data sources were obtained in a search on the database of computer retrieval of information on scientific projects (National Institute of Health). On the basis of title and abstract we manually examined reference lists of all articles for other referenced articles not identified in the preliminary search.

Inclusion criteria

We included studies if they used standardised diagnostic criteria for multiple sclerosis; exacerbation was confirmed by a neurologist; they used standardised or standard checklist methods through interview or questionnaire to measure stressful life events; they used case-control or longitudinal design; and they provided enough information about results to allow us to compute an estimate of effect size. We excluded studies if stress could not be distinguished from psychopathology or “temperament”; stress included only physical trauma, as this might be confounded with outcome measurement; there was no clear effect size or test statistic that allowed us to compute an effect size; or the same data were used for two reports.

Coding of studies

Three authors reviewed all eligible studies. They coded studies on design; outcome; type of patients; use of validated *v* unvalidated measure of stress; use of self report *v* structured interview assessment of stress; age; proportion of female patients; and method used to identify exacerbation of multiple sclerosis. We had intended to code for severity of disease, but markers were too variable across studies to be aggregated.

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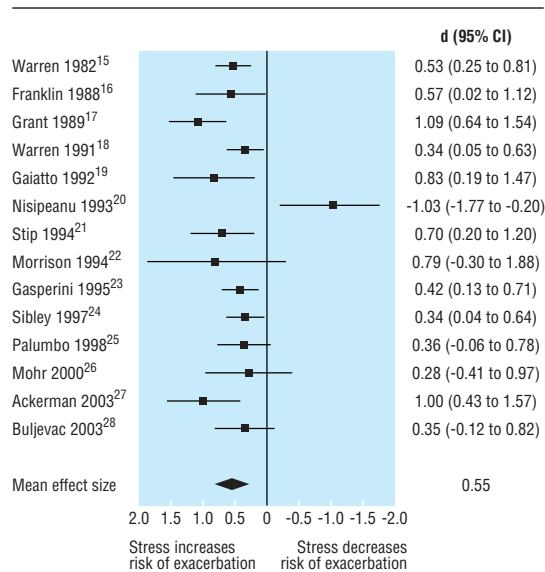
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Effect of stress on exacerbations in multiple sclerosis

Statistical analysis

The dependent variable was occurrence of exacerbation of multiple sclerosis. The primary measure of stressful life events was the independent variable for all studies. Many of the studies report additional subanalyses of the effects of specific areas of stress (such as family, work, bereavement, etc) on exacerbation. However, there was little consistency in how these sources of stress were conceptualised or grouped, making it impossible to code them reliably. We therefore focused only on global stressful life events as the independent variable.

Meta-analytic calculations were conducted as described in Lipsey and Wilson.⁵ We calculated effect sizes from statistics provided in each article. Weighted effect sizes were used for aggregation of effect sizes. The effect sizes and their confidence intervals resulting from the meta-analysis are reported in Cohen's *d*, a standardised effect size measure. We used the *Q* test to test homogeneity of variance, and the *I*² statistic to provide the degree of inconsistency across studies (see bmj.com for details).

Results

The literature search produced a total of 20 articles. Six papers were excluded because they did not meet inclusion criteria. See bmj.com for the general characteristics of the 14 included studies. Seven were case-control studies and seven were longitudinal prospective studies. Two studies examined first exacerbations, which led to a diagnosis of multiple sclerosis, and 12 examined exacerbations after diagnosis.

Outcomes

The figure shows the mean effect sizes and standard deviations for each study. The primary analysis for the main hypothesis found that the weighted average effect sizes for the impact of stress on exacerbation over the 14 included studies was $d=0.53$ (95% confidence interval 0.40 to 0.65), $P<0.0001$. The studies' effect sizes were homogenous ($Q=16.62$, $P=0.22$), with a low degree of inconsistency ($I^2=21.8\%$).

Effect sizes were not significantly affected by any study design characteristics, including the use of longitudinal prospective *v* case-control designs ($P=0.31$), the use of first exacerbation *v* exacerbation after diagnosis as an outcome criterion ($P=0.59$), the use of validated *v* unvalidated assessment of stress ($P=0.12$), the use of self report *v* structured interview in the assessment of stress ($P=0.12$), and the inclusion of relapsing-remitting multiple sclerosis only or relapsing-remitting multiple sclerosis and secondary-progressive multiple sclerosis ($P=0.11$). Regarding sample characteristics, neither the proportions of female participants ($P=0.11$) nor age of participants ($P=0.89$) were significantly related to effect size. None of the methods of determining exacerbation was related to outcomes, including the use of the expanded disability status score *v* neurologist judgment ($P=0.45$), the use of expanded disability status score ≥ 1.0 , or the use of retrospective neurologist verification with standardised data⁶ ($P=0.41$).

Discussion

The results of our meta-analysis support the hypothesis that stress is related to exacerbation of multiple sclerosis, with a weighted average effect size of $d=0.53$.

This effect size is clinically meaningful. As a comparison, a recent meta-analysis of the effects of interferon beta, the principal class of disease modifying drug used to treat multiple sclerosis, showed an overall effect of $d=0.36$ in reducing exacerbations in the first year and $d=0.30$ over the first two years of treatment.⁷ From this we suggest that the negative effects of stress on exacerbation of multiple sclerosis are at least as great as the positive effects of a class of drugs widely considered to produce clinically meaningful results.

Recent neuroimaging data have provided substantial weight to the clinical evidence on which this meta-analysis was based. A prospective study of 36 patients with multiple sclerosis receiving monthly gadolinium enhancing magnetic resonance imaging showed that the occurrence of interpersonal stressors was associated with a significantly increased risk of a new brain lesion eight weeks later.⁸

Is all stress the same?

While our findings were statistically homogenous, the study by Nisipeanu and Korczyn, in contrast to all other published reports, found that stress reduced the risk of exacerbation.⁹ While all other studies examined normal everyday stress, they examined the effects of a traumatic, life threatening stressor—namely, being under one month of missile attacks in Tel Aviv during the first Gulf war. This is consistent with animal models and other biological data. Numerous studies of stress in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, have shown significant reductions in symptoms related to stress,¹⁰ mediated by an increase in the release of cortisol. However, more moderate stressors have been shown to activate experimental autoimmune encephalomyelitis.¹¹

Potential mechanisms

At least one study has found that reducing distress in people with multiple sclerosis can reduce T cell production of γ interferon,¹² a proinflammatory cytokine believed to be vital in the pathogenesis of exacerbation.²

Animal studies have suggested several potential mechanisms. Small increases of cortisol concentrations, similar to concentrations seen in non-traumatic stress, have been shown to enhance the sensitivity of T cells to a number of cytokines and peptides that promote a proinflammatory response.¹³ Alternatively, sustained increases in cortisol concentration in response to chronic stress produce a counter-regulatory reduction in the number, binding capacity, and affinity of glucocorticoid receptors on immune cells,¹⁴ increasing risk of inflammation. Finally, mast cells, which reside in the endothelium, can be activated by increases in corticotropin releasing factor related to stress. Activated mast cells increase the permeability blood-brain barrier and increase inflammation through the release of tumour necrosis factor α , histamines, and tryptase.¹⁵ None of these potential mechanisms has been adequately tested among patients with multiple sclerosis. The absence of a clear biological model is a substantial weakness in the current literature.

Limitations and recommendations

The quality of the studies included varied. Even the best longitudinal prospective designs do not offer absolute evidence of a causal association. Other unmeasured factors may affect both the perception of stress and exacerbation. For example, changes in normal appearing white matter may occur months before traditional neuroimaging markers of inflammation or clinical exacerbation.¹⁶ Thus, we cannot rule out the hypothesis that decreased ability to manage stressors or increased perceived stress may be an early marker of changes in normal appearing white matter.

In summary, while these findings show a significant association between stress and exacerbation in multiple sclerosis, the effect size is modest. This association is not consistent across patients or even within individual patients across time. The potential differential effects of various types of stress or the mechanisms by which stress affects inflammation are not known. Thus, the occurrence of any specific exacerbation cannot yet be linked to any specific stressor. We hope that these findings will open up new investigations, either through stress management or through pharmacological management of potential neuroendocrine or immune responses to stress.

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What is already known on this topic

Most patients with multiple sclerosis believe that stressful life events can cause exacerbations of their illness

The potential role of stressful life events on exacerbation remains controversial among care providers and academics

What this study adds

Non-traumatic stressful life events are associated with an increased risk of exacerbation in patients with multiple sclerosis

The association between stressful life events and exacerbation is complex and cannot currently be determined for any individual patient

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