

Preexisting Psychological Stress Predicts Acute and Chronic Fatigue and Arthritis following Symptomatic Parvovirus B19 Infection

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Background. Psychological stress is thought to be an important factor in the pathogenesis of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Therefore, we sought to examine this relationship in the context of parvovirus B19 infection.

Methods. Thirty-nine patients with laboratory-documented acute parvovirus B19 infection were asked to complete questionnaires on negative life events, perceived stress, and negative affect relevant to the time of onset of parvovirus infection and during the preceding 12 months. These scores were combined into an overall stress index, which was then examined for associations with particular parvovirus-associated symptoms at acute infection and during the ensuing 1–3 years. Additional characteristics monitored included presence of parvovirus antibodies and nucleic acid, cortisol level, dehydroepiandrosterone level, autoantibodies, levels of a range of serum cytokines, and human leukocyte antigen class I and II alleles.

Results. Stress index was significantly associated with development of fatigue during the acute phase of parvovirus B19 infection and also with chronic fatigue and arthritis occurring 1–3 years following acute parvovirus B19 infection. Logistic regression that included all clinical variables indicated that a high stress index at the time of onset of infection was the primary predictor of CFS/ME 1–3 years following acute parvovirus B19 infection (odds ratio, 25.7; 95% confidence interval, 1.7–121.9; $P = .005$).

Conclusions. We report a highly significant association between psychological stress and development of acute and chronic fatigue and arthritis several years following laboratory-documented acute parvovirus B19 infection.

Human parvovirus B19, discovered in 1975 [1] and first linked with human disease in 1981 [2], is a small, single-stranded DNA virus classified as a member of the family Parvoviridae, genus *Erythrovirus*, with tropism primarily for erythroid precursors. Parvovirus B19 infection has been associated with an extremely wide variety of clinical manifestations. Acute parvovirus B19 infection may be asymptomatic in 50% of infected children; in symptomatic persons it is associated classically with childhood rash illnesses, erythema infectiosum, arthralgia, fetal death, transient aplastic crisis in those with shortened RBC survival, and pure RBC aplasia in

immunocompromised persons [3]. Less common clinical associations of parvovirus B19 infection include various skin eruptions, hematologic disorders such as neutropenia, hepatobiliary disease, neurological disease, and rheumatic disease [3]. Parvovirus B19 infection has also been associated with development of acute and chronic fatigue, the latter fulfilling diagnostic criteria for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) [4].

CFS/ME is a disease characterized by severe and debilitating fatigue, myalgia, sore throat, sleep abnormalities, impaired memory and concentration, musculoskeletal pain, stress, and secondary depression [5]. It has been widely reported that the onset of disease coincides with both clinical and laboratory evidence of infection with a variety of viruses and bacteria, but it is unclear why evidence of acute microbial infection is found in some patients with CFS/ME but not in others.

Psychological stress responses result when the demands imposed by events in a person's life exceed cop-

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ing capacity [6]. It is now well established that the immune, endocrine, and central nervous systems interact and that psychological stress dysregulates the immune response via effects on the hypothalamic-pituitary-adrenal axis and the autonomic nervous system [7]. Thus, psychological stress has been shown to predict susceptibility to infection and also to symptomatic courses of infection [8–12].

In the context of CFS/ME, this concept is well illustrated by studies of stress-induced reactivation of Epstein-Barr virus (EBV) infection, in which medical students undergoing academic stress have been demonstrated to experience reactivation of EBV infection with up-regulation of proinflammatory cytokines [13, 14]. However, apart from studies of EBV, there are few data to illustrate this phenomenon for the other virus triggers of CFS.

We have previously reported that parvovirus B19 can trigger CFS/ME [4, 15], that the symptoms in these patients are indistinguishable from idiopathic CFS/ME, and that these patients have increased levels of circulating TNF- α and IFN- γ [16]. In this study, we show that in this small cohort, those who developed chronic arthritis and chronic fatigue 1–3 years after the acute phase, were also those who exhibited significantly higher levels of psychological stress at the time of onset of acute parvovirus B19 infection and in the preceding 12 months.

METHODS

Patient enrollment and clinical characterization. Thirty-nine patients with acute parvovirus B19 infection were identified by detection of serum antiparvovirus B19 IgM. At this time, patients were telephoned and, with their consent, visited at home by one of us (J.R.K.). The procedures of the study were explained to each patient, and the patient was given time to consider whether they wished to be involved. If they were willing to participate, they signed a consent form, which was then witnessed by the visiting doctor (J.R.K.). A detailed history was obtained and a blood sample drawn. Symptoms of acute parvovirus B19 infection and any longer-lasting symptoms in the following months or years were recorded, as previously described [4, 16, 17]. Three stress scales were then administered (see “Stress studies,” in the Methods section). Procedures followed were in accordance with the Central Manchester Research Ethics Committee and with the Helsinki Declaration of 1975, as revised in 1983.

Virological studies, autoantibody detection, and biochemical studies. Serum samples were tested for anti-parvovirus B19 IgM and IgG, parvovirus B19 DNA, autoantibodies, cortisol, dehydroepiandrosterone (DHEA), cytokines (IL-1 β , IL-2, IL-6, IL-10, TNF- α , and IFN- γ), and HLA class I and II alleles, the rationale for which has been described previously [4, 16, 17].

Stress studies. Three measures were used to assess psycho-

logical stress at the time of acute parvovirus B19 infection; number of major stressful life events judged by the patient as having had a negative impact; perception that demands exceeded the patient’s ability to cope; and negative affect. This approach to stress measurement was similar to that used in the study of stress and the common cold [9]. The major stressful life events scale consisted of a list of possible events in the life of the patient (41 items) or in the lives of others who were close to the patient (26 items). The events were a subset of those appearing in the List of Recent Experiences [18] and were chosen on the basis of their potential for negative impact and their relatively high frequency in population studies [18]. Patients were asked which of the items had occurred during the 12 months preceding onset of acute parvovirus B19 infection and to rate each as having had a positive or negative impact on their lives, the score being the total number of negative events identified. The 10-item Perceived Stress Scale (PSS) [19] was used to determine the degree to which life situations in the 12 months preceding acute onset of parvovirus B19 infection were perceived as being stressful. Items in the PSS have been designed to determine how unpredictable, uncontrollable, and overloaded patients perceive their lives [19]. The negative affect scale included 15 items from the list of negative emotions of Zevon and Tellegren [20]. These items included distressed, nervous, sad, angry, dissatisfied with self, calm (reverse scored), guilty, scared, angry at self, upset, irritated, depressed, hostile, shaky, and content (reverse scored). A 5-point (0–4) response format was used to report affect intensity.

Because these 3 stress scales have previously been shown to measure a common underlying concept [9], we combined the 3 into a single stress index, which was used as an indicator of the degree of psychological stress experienced by each subject. As described elsewhere [9], this index was created for each patient by calculating the quartiles for each component stress scale and summing the quartile ranks (with a value of 1 for the lowest quartile and 4 for the highest), resulting in a stress index ranging from 3 to 12. The quartiles divided the patients into groups with the values 0, 1–2, 3–4, and 5–14 for the life events scale; 0–10, 11–14, 15–18, and 19–33 for the PSS; and 0–7, 8–13, 14–20, and 21–49 for the negative affect scale. In each case, a higher score indicated a greater degree of stress.

Statistical analysis. The difference in stress index scores between patients who tested positive and negative for individual symptoms and autoantibodies (at acute infection and follow-up time points) was examined using the Mann-Whitney *U* test (2-tailed), because these data were nonparametric. Multivariate logistic regression analysis was used to determine the independence of association of different clinical features with stress index. In these analyses, the stress index was dichotomized so that a high stress index was defined as a score greater than the median level for this population (index score, >4). Pearson

correlation coefficients were used to assess the correlation of results of the negative life events, perceived stress, and negative affect scales with each other. A *P*-value $\leq .05$ was considered significant.

RESULTS

Parvovirus B19–infected patients. Thirty-nine parvovirus B19–infected patients were studied at 2 time points. Their clinical symptoms and results of virological studies (antiparvovirus antibodies and parvovirus DNA), measurements of cortisol, DHEA, and cytokines, and HLA class I and II alleles have been published elsewhere [4, 16, 17].

Stress measures. Individual components of the stress index (negative life events, PSS, and negative affect) had a high degree of correlation between each other, each pair having a Pearson correlation coefficient of ≥ 0.73 , and all with *P* < .0001.

Acute parvovirus B19 infection. At the time of acute infection, stress index was significantly associated with fatigue and the presence of rheumatoid factor (table 1). Although there were trends towards an increased stress index for arthritis and rash, these were not significant (table 1). The association between fatigue and each of the stress index component scores was significant only for negative life events and negative affect (table 2). There were no significant relationships between stress index and sex, anti–parvovirus NS1 antibody, antiparvovirus VP2 antibody, parvovirus DNA, cortisol level, DHEA level, serum cytokine levels, or HLA class I or II alleles.

Logistic regression analysis that included age, sex, and all clinical features suggested that a high stress index (greater than

the median score of 4) is associated primarily with fatigue (OR, 7.4; 95% CI, 1.5–36.9) (figure 1). Inclusion of cytokine, cortisol, and DHEA levels in the logistic regression analysis suggested that there may also be a weak, independent association with low levels of DHEA, although this was not significant (*P* = .07).

Follow-up of parvovirus B19 infection. A high stress index at acute infection was significantly associated with development of fatigue and CFS/ME at follow-up. All patients who developed CFS/ME had a stress index of 9 or 10 during the acute phase (table 1). Logistic regression analysis that included all clinical variables at the time of acute infection indicated that a high stress index was the primary predictor of CFS/ME at follow-up (OR, 25.7; 95% CI, 1.7–121.9; *P* = .005). The relationship between fatigue and stress index, at both acute and follow-up time points, is illustrated in figure 1.

Higher levels of stress index during the acute phase were also associated with arthritis at follow-up. In patients with arthritis during the acute phase, a stress index >4 was associated with a significantly greater likelihood of having arthritis at follow-up (8 [66.6%] of 12 vs. 3 [21.4%] of 14; OR, 6.2; 95% CI, 1.2–32.5; *P* = .04). There were no other associations between stress index and parvovirus antibodies, parvovirus DNA, individual cytokine levels, cortisol levels, DHEA levels, and HLA alleles at follow-up.

DISCUSSION

This study was an attempt to assess the role of stress in the pathogenesis of fatigue and CFS/ME using parvovirus B19 in-

Table 1. Association between stress index and fatigue, chronic fatigue syndrome (CFS), arthritis, rash, and rheumatoid factor at 2 different time points in 39 parvovirus B19–infected persons.

Factor	Acute infection			Follow-up		
	No. of patients	Stress index \pm SD	<i>P</i>	No. of patients	Stress index \pm SD	<i>P</i>
Fatigue						
Absent	19	3.9 \pm 1.3		26	3.4 \pm 0.6	
Present	20	5.8 \pm 2.8	.046	13	7.8 \pm 1.8	<.001
CFS						
Absent		34	4.2 \pm 1.5	
Present		5	9.8 \pm 0.4	<.001
Arthritis						
Absent	13	4.0 \pm 1.5		28	4.2 \pm 1.8	
Present	26	5.3 \pm 2.6	.1	11	6.6 \pm 2.8	.008
Rheumatoid factor^a						
Absent	25	4.4 \pm 2.2		25	5.1 \pm 2.4	
Present	13	5.9 \pm 2.5	.03	14	4.5 \pm 2.3	.3
Rash						
Absent	21	5.1 \pm 2.6		
Present	18	4.6 \pm 2.1	.6	

^a One patient was not tested for rheumatoid factor at acute infection.

fection and parvovirus B19-associated fatigue and CFS/ME as a model. The 3 stress measures used in this study had a high degree of correlation with each other, providing support for an underlying common component, as has been found previously in the context of viral upper respiratory infection [10, 21]. The association between stress index and fatigue at follow-up was uniformly significant for each of the negative life events, perceived stress, and negative affect scales. However, during the acute phase of infection, only the negative life events and negative affect scales were significantly associated with fatigue; the combined stress index did show a significant association, although it was much weaker than at the time of follow-up.

In this study, we present evidence that psychological stress at the onset of symptomatic parvovirus B19 infection predicts development of fatigue during the acute phase and prolonged fatigue, CFS/ME, and arthritis 1–3 years after the onset of acute infection. Although this is a study with a small sample size, these associations were highly significant.

We have previously reported that the prolonged and chronic fatigue due to parvovirus B19 infection is associated with detectable parvovirus B19 DNA and circulating TNF- α and IFN- γ [16], and that fatigue during the acute phase of parvovirus B19 infection was associated with carriage of the shared epitope [17], which is also a risk factor for development and increased severity of rheumatoid arthritis [22]. However, the association between psychological stress and development of fatigue and arthritis in the present study was independent of these and all other variables studied.

It is now well established that the immune, endocrine, and central nervous systems interact with each other and that this provides the means by which psychological stress can dysregulate the immune response. These interactions are very complex and involve both the autonomic nervous system and the hypothalamic-pituitary-adrenal axis [7]. Psychoneuroimmunology is now an established field involving the study of interactions of these body systems and consequent health implications.

The effect of stress on the immune system and immune control of EBV has been elegantly studied by Glaser et al. [13, 14] over many years. These investigators have demonstrated

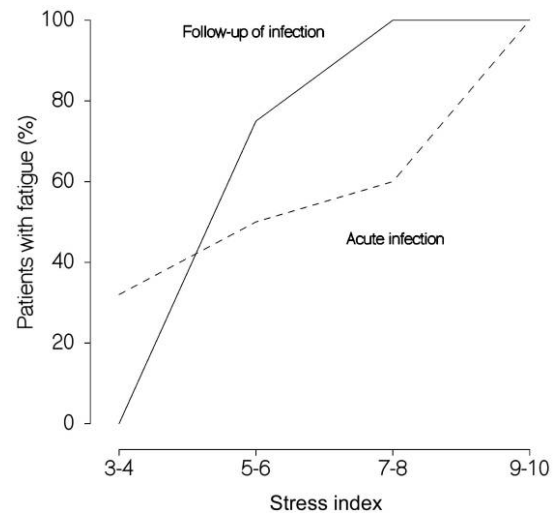


Figure 1. Observed association between the psychological stress index and the rate of fatigue in symptomatic parvovirus B19 infection during the acute phase and at follow-up (1–3 years after onset of acute infection).

that “academic” stress in medical students at the time of examinations results in certain changes in the cellular immune response, including reduction in NK cell activity, reduction in IFN- γ production by concanavalin-A-stimulated lymphocytes, reduction in cells expressing IL-2 receptors, reduction in proliferative responses of peripheral blood lymphocytes to mitogens, reduction in T cell proliferation to EBV polypeptides (memory response), reduction in T cell killing of EBV-transformed autologous B cells (memory response), reduction in antibody and T cell responses to hepatitis B vaccination, and evidence for reactivation of latent herpesviruses (e.g., EBV and herpes simplex virus type 1). There is also evidence that stress can up-regulate transcription of proinflammatory cytokines, which are known to contribute to the pathogenesis of inflammatory disease and CFS/ME [13, 14, 23–25]. Psychological stress has also been associated with infection on challenge with 5 different common cold viruses in ~400 normal volunteers and also with development of symptomatic “colds” during these infections [9].

CFS/ME is known to be associated with a variety of microbial

Table 2. Stress index and component stress indices in 39 parvovirus B19-infected persons with and without fatigue at 2 different time points.

Index	Acute infection			Follow-up					
	Fatigue (n = 20)	No fatigue (n = 19)	P	Fatigue (n = 13)	No fatigue (n = 26)	P	CFS (n = 5)	No CFS (n = 34)	P
Stress index	5.8 ± 2.8	3.9 ± 1.3	.046	7.8 ± 1.8	3.4 ± 0.6	<.001	9.8 ± 0.45	4.15 ± 1.46	<.001
Negative life events scale	1.63 ± 0.9	1.1 ± 0.3	.024	2.08 ± 0.86	1.00 ± 0	<.001	3 ± 0	1.12 ± 0.33	<.001
Perceived stress scale	2.26 ± 1.24	1.6 ± 0.75	.1	3.23 ± 0.60	1.27 ± 0.45	<.001	3.8 ± 0.45	1.65 ± 0.81	<.001
Negative affect scale	1.9 ± 0.88	1.35 ± 0.59	.032	2.46 ± 0.52	1.19 ± 0.49	<.001	3 ± 0	1.41 ± 0.61	<.001

NOTE. All data are index score ± SD. CFS, chronic fatigue syndrome.

infections, including EBV, parvovirus B19, enteroviruses, and *Chlamydia pneumoniae* [26], and is also associated with the presence of psychological stress. This study was performed in light of the known modulatory effect of psychological stress on the efficiency of the immune response and consequent control of virus infection.

In conclusion, we report an association between psychological stress and development of acute and chronic fatigue and arthritis, 1–3 years following laboratory-documented parvovirus B19 infection. This supports a role for psychological stress in the pathogenesis of CFS/ME following parvovirus B19 infection.

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