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INFLUENCE OF SOCIOECONOMIC STATUS ON BEHAVIORAL, EMOTIONAL AND COGNITIVE EFFECTS OF RUBELLA VACCINATION: A PROSPECTIVE, DOUBLE BLIND STUDY

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SUMMARY

A double-blind prospective design was used to investigate the immediate and prolonged psychological effects of a specific viral infection, and the role of immune activation in mediating these effects. Subjects were 240 female teenager girls who were vaccinated with rubella vaccine. Based on analysis of levels of antibodies to rubella, subjects were divided into two groups. An experimental group ($n = 60$), which included subjects who were initially seronegative and were infected following vaccination, and a control group ($n = 180$), which included subjects who were already immune to rubella before vaccination. Compared with the control group and to their own baseline, low socioeconomic status (SES) subjects within the experimental group showed a significant increase in the severity of depressed mood, social and attention problems, and delinquent behavior. Ten weeks post-vaccination there were no differences between the experimental and control groups in serum levels of interleukin-1β, interferon-γ, soluble interleukin-2 receptors (sIL-2r), and cortisol. However, a significant negative correlation was found between fatigue-related symptoms and sIL-2r levels in the experimental ($r = -0.325$), but not the control group ($r = -0.046$). These findings suggest that viral infection can produce prolonged behavioral, emotional and cognitive problems mainly in subjects belonging to the low SES. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords—Virus; Infection; PVFS; Immunization; Rubella; Depression.

INTRODUCTION

Several lines of evidence suggest that viral infections can have short- and long-lasting behavioral, cognitive and emotional effects, which appear after the onset or even the recovery from the infection. Studies on the relatively short term effects of viral infections reported significant impairments in the performance of several cognitive tasks, including psychomotor, attention and memory deficits (Smith et al., 1987a,b, 1988). Prolonged

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effects of viral infections have also been described. For example, an association was found between exposure to influenza virus and psychological and cognitive disturbances, including depression, guilt feelings, obsessions, compulsions, death thoughts and problems in memory, decision making, and concentration, observed after the recovery from the infection (Meijer et al., 1988). Similar virus-induced psychological disturbances, particularly fatigue, depression, and anxiety, have also been reported following infections with herpes viruses, Epstein Barr virus, cytomegalovirus, influenza viruses, rubella virus, Borna disease virus, and the human immunodeficiency virus (Biondi and Zannino, 1997; Bode et al., 1995; Brown et al., 1992; Greenwood, 1987; Hall and Smith, 1996; Hendler, 1987; Jones et al., 1995; Maj, 1996; Smith et al., 1993; White et al., 1995). Many studies in this field focused on the post-viral fatigue syndrome (PVFS), which involves behavioral and physical changes following a viral infection. The PVFS is characterized by fatigue as a primary symptom, and by several other secondary symptoms, including physical problems (e.g. low fever, sore throat, enlargement or pain of the lymph nodes, and generalized muscle weakness) and neuropsychological disturbances (Komaroff and Buchwald, 1991). Viral infection-induced short- and long-term changes in behavior have also been reported in experimental animals. Alterations in ingestive behavior, activity levels, sleep patterns, open-field behavior, startle responses, and learning ability are caused by several viruses, including influenza (Conn et al., 1995), and herpes (Crnic, 1991).

Most previous studies on the neuropsychological effects of infection in general, and the fatigue syndromes in particular, were retrospective and were based on naturally occurring infections. In such studies, it is usually difficult to identify the specific pathogens and the course of the illness. To elucidate more clearly the relationships between viral infections, their physical manifestations, and psychological consequences, we investigated the short and relatively long-lasting physical and psychological effects of an induced and controlled viral infection. The experimental paradigm was based on immunizing female teenagers with rubella vaccine, which is a live-attenuated infectious virus. Immunization with this vaccine is a routine procedure that induces a controlled systemic infection, through which immunity is eventually acquired. Viremia following administration of live virus vaccine has been documented between 7 and 11 days after inoculation (Balfour et al., 1981), peaking at approximately day 11 after vaccination (Detels et al., 1971). A prospective design was used, in which physical, behavioral, cognitive and emotional parameters were measured before, during and following termination of the infection. We hypothesized that following vaccination, subjects who would be immunized (infected), would manifest higher levels of depressed mood, anxiety, somatization, attention and thought problems, social problems, withdrawal, and delinquent behavior.

Several psychosocial variables have been proposed as risk factors for poor health. In particular, low socioeconomic status (SES) has been associated with poorer mental and physical health (Adler et al., 1994; Anderson and Armstead, 1995; Cohen and Williamson, 1991; Ranchor et al., 1996). Differences in SES were found to affect rates of mortality and morbidity from almost every disease and medical condition (Adler et al., 1994). For example, social status was found to be a major risk factor for episodes of depression and other psychiatric disorders in humans (Adler, et al., 1994; Bruce et al., 1991; Murphy et al., 1991). In addition, in a recent study in monkeys, low social status was associated with a substantially greater probability of being infected with an upper respiratory infection (Cohen et al., 1997). Several mechanisms have been proposed to account for the association between SES and health, including material factors such as housing and job conditions, as well as psychosocial factors, such as personality traits, coping styles, stressful life events, and social support. Based on these findings we expected to find a negative relationship between SES and immunization-induced psychological morbidity.

Recent evidence indicates that many of the behavioral effects of infection are mediated by activation of the immune system and the secretion of cytokines (Dantzer et al., 1996; Yirmiya, 1997). For example, studies in experimental animals indicate that antibodies against cytokines or cytokine antagonists block at least some of the behavioral effects of infectious agents and pathogen products (Bluthe' et al., 1992; Dantzer et al., 1996). Moreover, in humans, exogenous administration of cytokines produces marked behavioral and neuroendocrine symptoms that are similar to those induced by viral infections (Fent and Zbinden, 1987; McDonald et al., 1987). In order to elucidate possible mechanisms that mediate the psychological effects of viral infection, we measured serum levels of several cytokines, including interleukin-1β (IL-1β), interferon-γ (IFN-γ), and soluble interleukin-2 receptors (sIL-2r), 10 weeks following rubella vaccination. In addition, we measured the levels of serum cortisol, which is a mediator of neuroendocrine-immune-behavior interactions (Besedovsky and del-Rey, 1996). We hypothesized that in infected, but not control subjects there would be higher levels of cytokines and cortisol, as well as a positive correlation between cytokine levels and psychological disturbances.

METHODS

Subjects

The population study comprised 240 female subjects at the mean age of 12.4 years $\pm$ 2 months. At this age, pupils of this cohort were immunized for rubella, without prior immunization during infancy, as part of the routine immunization program of the Israeli Ministry of Health. The subjects were recruited from eight public schools, in different neighborhoods of Jerusalem, representing different SES.

Procedure

Before the beginning of the study, the research staff informed the school nurses and class teachers about the importance and the various phases of the study. In addition, the research staff met with all the girls who were about to receive the vaccine, and explained to them the importance of vaccination and the various phases of the study. It should be emphasized that throughout the study, the subjects were kept blind to the hypothesis of the study, as well as to any possible effects of rubella vaccination. The parents of each subject filled a SES questionnaire (Lieblich et al., 1972) and a general medical questionnaire, describing the medical history of the subject, including pubertal characteristics and disorders of the immune system. Informed consent was signed by the subjects and their parents.

The first stage of the study (baseline) was conducted 2 weeks before vaccination. At this time, the subjects filled several questionnaires, assessing several psychological and physical variables. These questionnaires provided baseline data, which then enabled assessment of infection-induced changes, in later stages of the study, using within-subjects repeated measures design.

Firstly a health status inventory, that we constructed, which includes a list of symptoms that are part of the CDC diagnosis of the PVFS, and a few symptoms that are observed during rubella infection in particular. These symptoms were clustered into two main syndromes: The rubella and fatigue syndromes. The rubella syndrome includes several physical symptoms often observed in a rubella infection, i.e. rash, sore throat (Coryza) and headaches (Gershon, 1995). The fatigue syndrome includes the main symptoms characterizing the PVFS, i.e., fatigue, weakness, loss of appetite, sleep disturbances, and neuropsychological disturbances, such as confusion, forgetfulness, reduced general interest, and problems in concentration. The subjects were asked to rate the severity of each of these symptoms on a scale ranging from 1 to 7, with 1 representing a very weak symptom, and 7, a profound symptom.

Secondly the Achenbach Child Behavior Checklist (CBCL) for the age group 11–18 years (Achenbach, 1991). This comprehensive questionnaire includes several scales assessing: anxious-depressed mood (e.g. feels lonely, unloved, worthless, cries), withdrawal (e.g. rather be alone, won't talk, secretive, underactive), somatic complaints (e.g. dizzy, tired, headaches, nausea), social problems (e.g. clings, does not get along with others, teased, is not liked), thought problems (e.g. can't stop thinking about certain things, repeats acts, strange ideas), attention difficulties (problems in concentration, confused, day-dreaming, impulsive, poor school performance), aggressive behavior (e.g. fights, attacks, screams, is stubborn) and delinquent behavior (e.g. lies, cheats, runs away, steals). Test–retest reliability, for the average total syndrome score, after a 6 month interval, has been found to be $r = 0.60$ (Achenbach, 1991). The concurrent validity of the CBCL is high, with a correlation of 0.81 between the CBCL and the Quay-Peterson Revised Behavior Problem Checklist (Zilber et al., 1994).

Thirdly the Children's Depression Inventory (CDI) for the age group 8–17 years (Kovacs, 1980), testing emotional-subjective aspects of depressed mood. This inventory includes 27 groups of three sentences. The subject has to mark, in each group of sentences, one sentence that characterizes him the most. Each CDI item is graded from 0 to 2 in the direction of increasing psychopathology. Thus, CDI total scores range from 0 to 54. This questionnaire, as the Achenbach questionnaire, assesses depression, however unlike the Achenbach questionnaire, the CDI does not assess symptoms, but assesses the subjective-emotional aspect of depression. Internal reliability (based on Cronbach's alpha reliability coefficient) was found to be $r = 0.86$, and test–retest, after a period of 3 months, was found to be $r = 0.84$. The validity of the inventory is supported by Friedman and Butler's (Friedman and Butler, 1979) finding that high CDI scorers tend to have low self-esteem (CDI-Piers-Harris correlation = 0.66) (Kovacs, 1980).

In order to define more specific indices of depression, we carried out both statistical and clinical analysis of the CDI. In the first stage an iterated principle factor analysis was carried out, including a principle component analysis with Varimax rotation. The following factors were obtained: (1) an emotional index of depression (e.g. sadness, crying, loneliness); (2) a cognitive index of depression (e.g. self hatred, difficulties in doing things, difficulties in decision making); (3) other characteristics of depression (such as fatigue, sleep-problems and appetite). The items grouped by the factor analysis were submitted to Cronbach's alpha reliability testing. The sub-scale reliabilities were found to be 0.77 for the emotional index, 0.74 for the cognitive index, and 0.68 for the 'other' index. In the second stage, four clinicians, involved in research and treatment of depression, were asked to divide all the questions in this questionnaire into a few categories, so that each category would include questions that assess a specific index of depressed mood. The number of categories was not decided upon before clinical analysis. The clinicians division supported the statistical analysis presented above.

Immediately before vaccination, blood samples were drawn for determination of the initial levels of antibodies to rubella virus. Serum was aliquoted and stored at −70°C.

Two weeks following vaccination (immediately following the assumed peak of viremia) (Plotkin, 1994) subjects again filled the CDI and the Health Status inventory. The Achenbach Child Behavior Checklist was not filled at this time. Ten weeks following vaccination, i.e. after the assumed recovery from the acute rubella infection, subjects filled the Achenbach Child Behavior Checklist, the CDI and the Health Status inventory. A second blood sample was drawn 2–3 days later for assessment of post-vaccination levels of antibodies to rubella virus.

Serum levels of antibodies to rubella, in both blood samples, were determined at the same time by an enzyme linked immunosorbent assay (ELISA), using COBAS/CORE rubella IgG EIA (Hoffman-La-Rosch, Basel, Switzerland). The levels of IL-1β, IFN-γ, and sIL-2r, in the second blood sample, were measured by ELISA kits (Quantikine Immunoassays, R&D Systems, MN). The detection limit of these assays are 0.3, 3.0, 6.0, pg/ml, respectively. Serum cortisol levels, in these samples, were assessed by a radioimmunoassay (RIA) (Coat-A-Count, DPC, Los Angeles, CA). The detection limit of this assay is 0.2 pg/ml.

Statistical Analysis

Statistical analysis was carried out with the SAS package. The results were analyzed by 3-way ANOVAs with the group (experimental vs control) and the SES (high, middle, low) as between subjects factors, and the time (baseline, 2 weeks and 10 weeks following vaccination) as a within subjects, repeated measure factor. After obtaining a significant effect with an ANOVA, we compared the changes from baseline in specific study groups using planned contrasts. An alpha level of 0.05 was considered significant.

RESULTS

Rubella virus infection was evidenced by seroconversion of specific rubella antibodies. After analyzing the two blood samples (at the end of the study) we found that 60 of the 240 subjects were not immune to rubella (seronegative) before vaccination, and as a result of vaccination were infected with rubella virus and seroconverted (exhibited at least a 4-fold increase in rubella antibody titer). Subjects within this group constituted the experimental group, and were expected to manifest more physical and psychological changes compared with the control group. Subjects comprising the latter group were already immune to rubella virus (seropositive) before vaccination, and therefore were not infected (had no appreciable changes in rubella antibody titers). None of the subjects within the control group was re-infected following vaccination. It should be emphasized that neither the subjects, nor the experimenters knew the grouping assignments before the end of the study, when baseline and post-vaccination levels of antibodies to rubella were determined.

Based on the responses to the socioeconomic questionnaire, the population was divided into three socioeconomic status; 24, 55, and 92 subjects in the control group and 7, 18, and 34 subjects in the experimental group belonged to the low, middle, and high SES, respectively (5% of the parents did not fill the SES questionnaire).

Effects of Vaccination on the Rubella and Fatigue Syndromes

The raw scores of the rubella syndrome, are presented in Fig. 1. Subjects within the experimental group had higher average rubella syndrome score, compared with subjects within the control group, 2 weeks following vaccination, however, this finding was not statistically significant. There were no differences between the experimental and control groups in the fatigue syndrome scores, and no differences among the three SES groups with respect to both syndromes.

Effects of Vaccination on Psychological Parameters Examined by the Achenbach Questionnaire

ANOVAs with repeated measures revealed significant group effects for both attention problems ($F(1, 206) = 9.22$, $p < .01$) (Fig. 2), and social problems ($F(1, 206) = 4.31$, $p < .05$) (Fig. 3). In addition a group by SES by time interaction was found for both attention problems ($F(2, 206) = 4.80$, $p < .01$) and delinquent behavior ($F(2, 206) = 4.94$, $p < .01$) (Fig. 4). Planned contrasts revealed that within the low SES, but not middle or high SES, subjects in the experimental group showed significant increases in attention problems ($T = 3.19$, $p < .01$) and delinquent behavior ($T = 3.11$, $p < .01$) compared with control subjects 10 weeks following vaccination. Similar results were obtained using a non-parametric (Wilcoxon) test.

Effects of Vaccination on Depressed Mood

Low SES, but not middle or high SES subjects showed increased depressed mood following vaccination. This result was reflected by significant interaction between the effects of SES and time ($F(4, 195) = 3.00$, $p < .05$), as well as a significant group by SES by time interaction ($F(4,195) = 2.45$, $p < .05$) in the emotional index of depression from the CDI (Fig. 5(A)). Planned contrasts revealed that within the low SES, subjects in the experimental group showed a significant increase in emotional depression compared with control subjects, both 2 and 10 weeks following vaccination ($T = 2.36$, $p < .05$; $T = 2.76$,

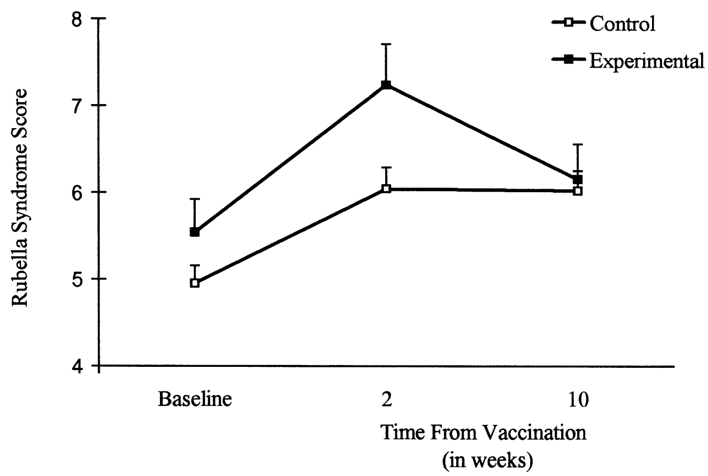

Fig. 1. Effects of vaccination on mean (±SEM) rubella syndrome scores. This syndrome was measured 2 weeks before (baseline) as well as 2 and 10 weeks following vaccination, in control and experimental subjects.

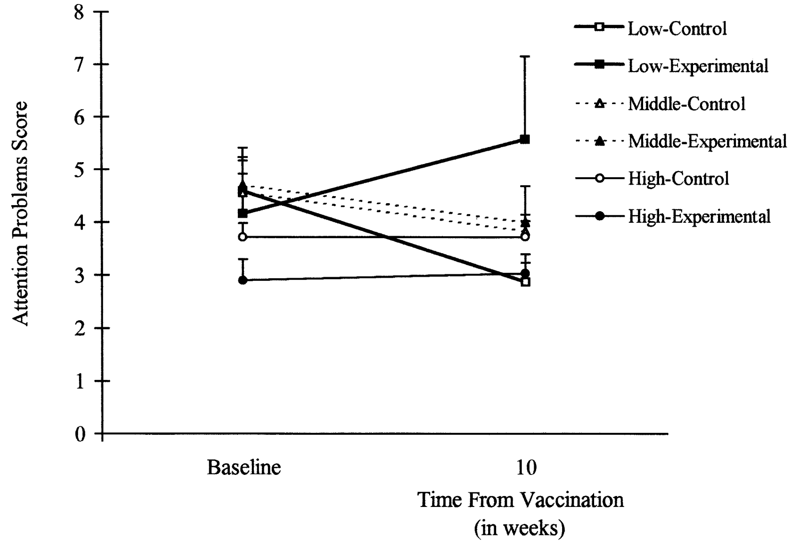

Fig. 2. Effects of vaccination on mean (±SEM) attention problems scores, obtained from the Achenbach Child Behavior Checklist. These scores were measured before and 10 weeks following vaccination, in control and experimental subjects from low, middle, or high SES.

$p < .01$, respectively). Similar, but not statistically significant effects were observed in the total CDI score (Fig. 5(B)), as well as the anxious-depressed mood scale obtained from the Achenbach Child Behavior Checklist (data not shown). Similar results were obtained using a non-parametric (Wilcoxon) test.

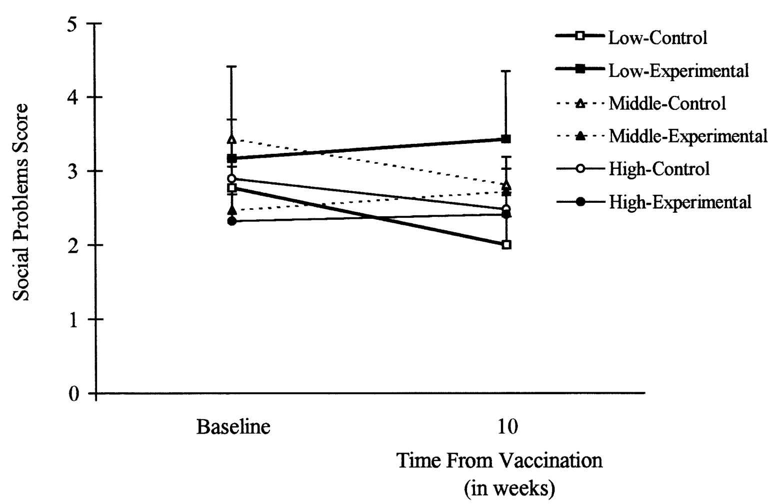

Fig. 3. Effects of vaccination on mean (±SEM) social problems scores, obtained from the Achenbach Child Behavior Checklist. These scores were measured before and 10 weeks following vaccination, in control and experimental subjects from low, middle, or high SES.

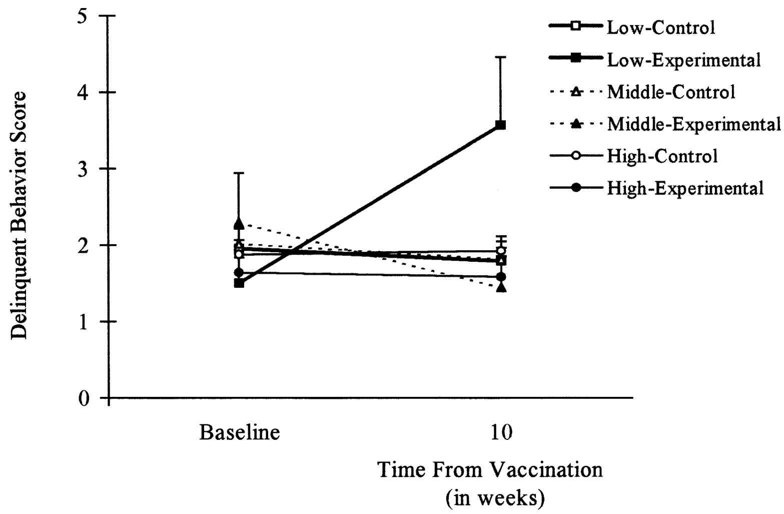

Fig. 4. Effects of vaccination on mean (± SEM) delinquent behavior scores, obtained from the Achenbach Child Behavior Checklist. These scores were measured before and 10 weeks following vaccination, in control and experimental subjects from low, middle, or high SES.

Effects of Vaccination on Serum Levels of Cytokines and Cortisol

Serum levels of IL-1β, IFN-γ, sIL-2r, as well as cortisol levels were analyzed in two sub-groups from the experimental and control groups ($n = 40$/subgroup). All three socioeconomic statuses were represented in these sub-groups. Using a random matching procedure, a subject from the control group was matched for each subject from the experimental group, based on SES, area of residence in Jerusalem, and presence or absence of first menstruation.

The experimental and control groups did not differ in the levels of serum sIL-2r and cortisol, 10 weeks post-vaccination. The levels of IL-1β and IFN-γ were undetectable in both groups (Table I). One subject from the control group was deleted from the analysis due to deviant levels of sIL-2r.

A significant negative Pearson correlation coefficient was obtained between serum levels of sIL-2r and the total fatigue syndrome score, 10 weeks post-vaccination, in the experimental ($r = -.325$, $p = .04$), but not the control group ($r = -.046$, $p = .78$).

Table I. Mean (± SEM) serum IL-1β, sIL-2r, IFN-γ, and cortisol levels in the experimental and control groups, 10 weeks following vaccination

Group	IL-1β (pg/ml)	IFN-γ (pg/ml)	sIL-2 r (pg/ml)	Cortisol (μg/dl)
Experimental	0 (0)	0 (0)	1397 (± 94)	9.88 (± 0.55)
Control	0 (0)	0 (0)	1339 (± 97)	9.29 (± 0.56)

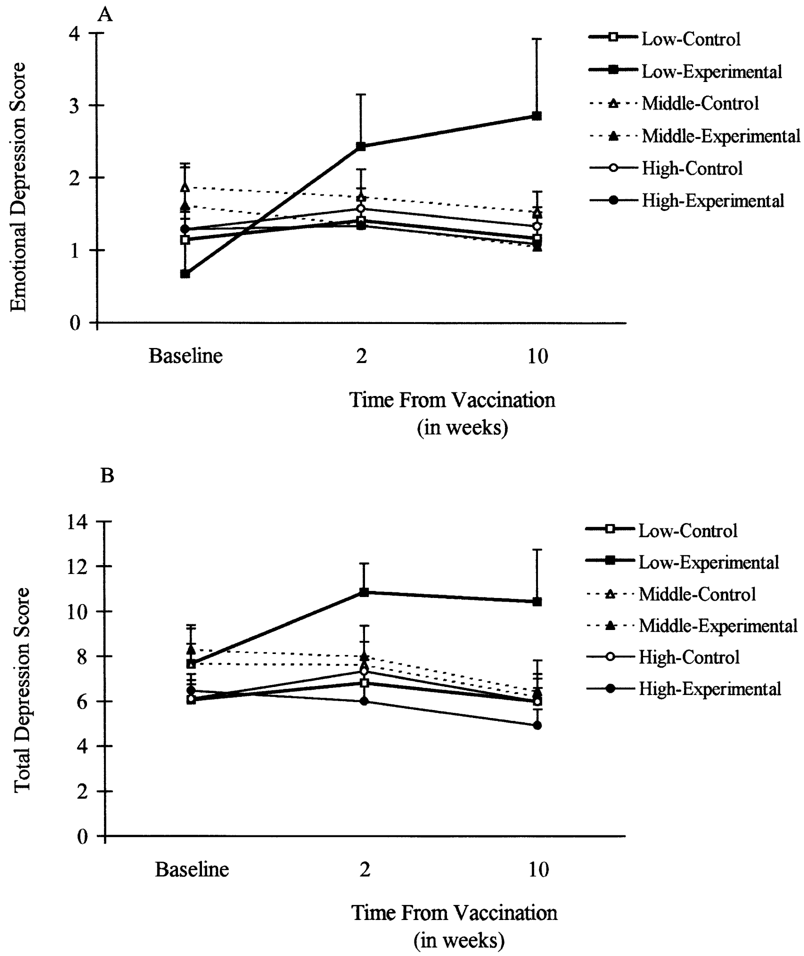

Fig. 5. Effects of vaccination on mean (±SEM) emotional depression scores (A), and total depression scores (B), obtained from the Children Depression Inventory. These scores were measured before, 2 weeks and 10 weeks following vaccination, in control and experimental subjects from low, middle, or high SES.

DISCUSSION

The results suggest that viral infection is associated with both acute and prolonged psychological disturbances, which were reported mainly by low SES subjects. Both 2 and 10 weeks following vaccination, low SES infected subjects reported on increases (from baseline) in depressed mood. Immunization caused several other psychological effects, including increases in problems of attention, social behavior, and delinquent behavior, 10 weeks following vaccination. At this time, subjects within the control group showed a general decrease from baseline symptom levels. Since this time period coincided with the end of the school year, this decrease may be attributed to lower school-related stress levels. In contrast, low SES subjects within the experimental group showed no decrease or even an increase from baseline in various psychological problems. These effects included increases in problems of attention, social behavior, and delinquent behavior.

Previous studies on the prolonged effects of viral infection focused on fatigue as a fundamental concept. Although this concept is vague and subjective, even in the normal population, it is a relatively frequent phenomenon (Woods and Goldberg, 1991). Prolonged fatigue is defined as self-reported, persistent fatigue lasting 1 month or longer. In many patients fatigue persists more than 6 months, and therefore is defined as chronic (Fukuda et al., 1994). One distinction that has empirical support is between physical and mental fatigue. Physical fatigue includes a collection of clinical-somatic symptoms such as tiredness, headaches, poor digestion, drowsiness, and physical pain. Mental fatigue includes cognitive symptoms, including problems in attention, concentration, thought processes and memory, as well as several psychobehavioral symptoms such as difficulties in dealing with other people, decline in libido and desires, irritability, and lack of perseverance (Masuda et al., 1994).

In the present study there were no signs of physical fatigue, possibly because rubella immunization induces a relatively mild viral infection (Plotkin, 1994). However, physical symptoms that appear during more severe viral infections may persist for long periods. On the other hand, the psychological disturbances which were found mainly in a sub-group of experimental subjects, 10 weeks following vaccination, resemble the symptoms of mental fatigue. These symptoms, which were measured by the attention and social problems scales of the Achenbach Checklist, included problems in concentration, confusion, poor school performance, daydreaming, clumsiness, acting young, feelings of rejection and not being liked, not getting along with other children, being teased, clinging, and appearing withdrawn. These findings may indicate that even following a mild infection, some subjects might suffer from prolonged mental fatigue. This conclusion is supported by a previous study on the effects of influenza virus in normal volunteers (Smith et al., 1988). In this study, performance was impaired already during the incubation period. Moreover, the effects of influenza virus on specific cognitive-behavioral tasks was observed in both volunteers showing significant clinical symptoms and in volunteers who were infected, but had no significant clinical illness (Smith et al., 1988). Together, these findings suggest a dissociation between the psychological and clinical effects of infection. The results may have implications for the post-viral fatigue syndrome, which has been described following acute infection with one of many types of viruses, including Epstein Barr virus, entroviruses, herpes hominis type 6, cytomegalovirus, measles virus, rubella virus and others (Behan and Bakheit, 1991; Bell et al., 1991; Klonoff, 1992; Sumaya, 1991; Wessely and Powell, 1989). The present findings, indicating that psychological disturbances that characterize patients with PVFS can be experimentally produced by a mild viral infection, is the first demonstration of this phenomenon in a controlled, prospective study.

Most of the psychological disturbances, induced by the vaccination procedure, were observed in low SES subjects. Although the experimental group in the low SES was relatively small, there are several reasons to believe that the significant effects found within this group do reflect a real vulnerability of low SES subjects: (1) the differences between the experimental and control groups in the low SES subjects were found in several tests, and across different scales within the same test; (2) the subjects comprising the experimental group within the low SES came from different schools, as well as different residential areas in the Jerusalem district. Moreover, the overall design of the study, which controlled for the subject's own performance before the experiment, and which utilized a double blind procedure (in which neither the subjects nor the experimenters knew the group assignment of the subjects until the end of the experiment), makes it unlikely that the significant results in the low SES group were obtained by chance.

One of the more robust findings in the low SES subjects, was the higher levels of emotional depression, in the experimental compared with the control group. This finding is consistent with several previous retrospective studies, which reported that depression is the most consistent psychological disturbance that accompany the onset of, or even the recovery from, viral infections (Bode et al., 1995; Brown et al., 1992; Greenwood, 1987; Hendler, 1987; Yirmiya, 1997). Depression is also a common and prominent symptom in patients diagnosed with the PVFS, occurring in 70–85% of all patients (Abbey and Garfinkel, 1991; Komaroff and Buchwald, 1991). Immune activation-induced depression has been also described in experimental animals (Yirmiya, 1996). The particular vulnerability of low SES subjects to immunization-induced depression is consistent with previous epidemiological studies, demonstrating that people of low SES have higher rates of major depression and depressive symptoms, and are more likely to have chronic or recurrent depression than others, in higher socioeconomic strata (Anderson and Armstead, 1995; Bruce et al., 1991; Hirschfeld, 1995; Murphy et al., 1991). Our results indicated that other immunization-induced psychological disturbances were also more pronounced in low SES subjects, including difficulties in attention and delinquent behavior.

The greater vulnerability of low SES subjects is probably associated with several characteristics of this social class, including higher incidence of stressful life events and fewer sources of social support (Adler et al., 1994; Ranchor et al., 1996; Turner and Marino, 1994). Low SES subjects encounter more stressful life events and more distress compared with their higher SES counterparts (Anderson and Armstead, 1995; Dohrenwend and Dohrenwend, 1970; Dohrenwend, 1973). Stressful life events have been found to suppress immune functions and increase the susceptibility to and severity of infections (Cohen, 1995; Cohen and Herbert, 1996; Cohen et al., 1991; Dorian and Garfinkel, 1987; Kiecolt-Glaser and Glaser, 1991; Stone et al., 1994). Furthermore, the lower levels of social support and social relationships which characterize low SES persons (Anderson and Armstead, 1995; Murrell and Norris, 1991; Ranchor et al., 1996; Turner and Marino, 1994), may also contribute to the SES-health associoation, because social support was found to offer protection against the deleterious effects of stress on disease, possibly by encouraging an ‘active’ strategy of dealing with the stress (Cohen and Herbert, 1996; Dorian and Garfinkel, 1987; Kiecolt-Glaser et al., 1985). Stress and social support were also found to modulate the ability to produce antibodies in response to vaccinations (Glaser et al., 1992; Kiecolt-Glaser et al., 1996). Finally, social status itself was recently found to predict susceptibility to disease in monkeys; monkeys characterized with lower social status were at higher risk of being infected than high social status monkeys (Cohen et al., 1997).

Previous studies indicated that many of the behavioral effects of infection are mediated by cytokines. Studies in experimental animals focused on IL-1 (Dantzer et al., 1996; Yirmiya, 1997), whereas in humans most studies were conducted with IFN (Fent and Zbinden, 1987; McDonald et al., 1987). In the present study, there were no detectable levels of IL-1β and IFN-γ in either the control or the experimental group. In addition, there were no differences between the two groups in the levels of sIL-2r and cortisol, which are usually elevated during the initial phases of viral infection (Griffin et al., 1989; Lewis and Thomas, 1990). These findings do not support a direct relationship between infection-induced secretion of these cytokines and psychological parameters. However, such relationships cannot be ruled out for the following reasons: (1) following infection, cytokines are produced not only in the periphery, but also in the brain (Hopkins and Rothwell, 1995). Although in the present study, the levels of IL-1β and IFN-γ in the periphery were undetectable, they may still be present within the brain. Indeed, previous studies on the presence of elevated IFN levels in the serum of chronic fatigue syndrome patients were controversial (Lloyd et al., 1993), in contrast to the clear indication of elevated IFN levels in the cerebrospinal fluid; (2) in the present study, vaccination-induced elevation of cytokines and cortisol levels may have been associated with the initiation of the psychological disturbances at an earlier time point. However, because the rubella infection was mild, cytokine and hormone levels had already returned to basal levels before the measurement (10 weeks post-vaccination). Thus it is possible that once initiated, infection-induced psychological alterations can persist for longer periods than the immune signals that induced them.

Ten weeks post-vaccination, a significant negative correlation was found in the experimental, but not the control, group, between the fatigue syndrome scores and sIL-2r levels, i.e. infected subjects exhibiting higher fatigue syndrome scores had lower levels of sIL-2r. This finding is consistent with the results of a previous study demonstrating lower levels of sIL-2r in measles patients with complications, including encephalomyelitis and pneumonia, compared with patients without complications (Griffin et al., 1989). Since sIL-2r was found to suppress proliferative responses that occur during infection (Griffin et al., 1989), either by binding free IL-2 (Rubin et al., 1985), or by removing receptors from the cell surface (Diamantstein et al., 1986), our findings suggest that infected subjects exhibiting higher fatigue syndrome scores, have lower levels of this specific immunoinhibitory substance, 10 weeks post-vaccination. Thus, in these subjects there seems to be an impairment in at least one of the feedback regulatory mechanisms, which return the immune system to a state of relative quiescence following an infection.

In conclusion, the present study demonstrates that immunization with live attenuated rubella vaccine is associated with psychological alterations particularly by low SES subjects. Psychological disturbances, including depression, and problems in attention, social and delinquent behaviors, were still reported 10 weeks post-vaccination. These findings suggest the existence of a causal relationship between viral infection and the prolonged mental fatigue that typifies the post-viral fatigue syndrome. The present findings indicate that infection can have psychological effects even when the levels of peripheral cytokines and cortisol, which have previously been implicated in mediating these effects, are either undetectable or not different from control levels. However, in some individuals, altered levels of sIL-2r following infection are associated with fatigue-syndrome symptoms.

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