Chronic fatigue syndrome: clinical condition associated with immune activation

ALAN L. LANDAY CAROL JESSOP EVELYNE T. LENNETTE JAY A. LEVY

There is much conflicting immunological and viral data about the causes of chronic fatigue syndrome (CFS); some findings support the notion that CFS may be due to one or more immune disorders that have resulted from exposure to an infectious agent. In the present study, flow cytometry and several different monoclonal antibodies recognising T, B, and natural killer (NK) cell populations as well as activation and cell adhesion antigens were used to study 147 individuals with CFS. Compared with healthy controls, a reduced CD8 suppressor cell population and increased activation markers (CD38, HLA-DR) on CD8 cells were found. The differences were significant (p=0.01) in patients with major symptoms of the disease. These immunological indices were not observed in 80 healthy individuals, in 22 contacts of CFS patients, or in 43 patients with other diseases. No correlation of these findings in CFS patients with any known human viruses could be detected by serology. The findings suggest that immune activation is associated with many cases of CFS.


Introduction

Chronic fatigue syndrome (CFS) has been reported with increased frequency in the USA, UK, Australia, and other parts of the world. The disorder is characterised by a debilitating fatigue lasting longer than six months with chronic and recurrent low-grade fever, pharyngitis, adenopathy, myalgia, arthralgia, sleep disorders, as well as difficulties in cognition and temperament. In many patients, the syndrome begins with an acute “flu-like” illness. Despite these clinical findings, some physicians question whether there is such a syndrome and have related the observations to depression or stress. The Centers for Disease Control (CDC) have published an epidemiological case definition for CFS, which uses major and minor clinical and laboratory criteria. A viral cause of CFS has been suspected because several viral infections are characterised by a chronic post-infection fatigue and because the onset of CFS often resembles an acute viral illness. However, in other viral infections, in contrast to CFS, the symptoms do not generally persist after several weeks. Initial studies showed that CFS was associated with high concentrations of antibodies to Epstein-Barr virus (EBV). However, subsequent studies suggested that high antibody titres to EBV were not found in all CFS patients, and that polyclonal activation of B cells was a common finding with antibodies to several viruses, especially herpesviruses. Some investigators have reported enteroviral RNA in muscle tissue of people with CFS, but a role for Coxsackie B virus in CFS has not been supported by serological studies. Lately, serological and polymerase chain reaction methods have pointed to an association of a human T-lymphotropic virus-like agent with the syndrome. Nevertheless, no conclusive evidence of a common causative agent in CFS has been presented.

Immunological disorders such as those seen in viral infections have also been described in CFS—eg, decreased function of natural killer (NK) cells and macrophages, reduced mitogenic response of lymphocytes, B-cell subset changes, and activation of CD8 cells. Moreover, infected animals and patients with or recovering from various viral infections often show transient immune abnormalities and chronic fatigue. These findings support the notion that CFS involves immune disorders due most likely to exposure to an infectious agent.

To see whether we could resolve some of these conflicting data we evaluated certain virological and immunological indices in a clinically well-defined cohort of patients with CFS and compared them with control populations.

ADDRESS: Department of Immunology/Microbiology, Rush-Presbyterian-St. Luke’s Medical Center, Chicago, Illinois (A. L. Landay, PhD); Virolab, Berkeley, California (E. T. Lennette, PhD); and Department of Medicine (C. Jessop, MD, Prof J. A. Levy, MD) and Cancer Research Institute (Prof J. A. Levy), University of California, School of Medicine, San Francisco, California, USA. Correspondence to Prof J. A. Levy, University of California, San Francisco, Room S1280, 3rd and Parnassus, San Francisco, California 94143, USA.
Subjects and methods

Subjects

A total of 147 consecutive patients (30 males, 117 females; median age 38 years, range 15–55) who presented with CFS were studied from September, 1989, to November, 1990. Either at the time of evaluation or according to medical history, all patients met the CDC epidemiological case definition for CFS, including symptoms shown in table I. As recommended by the CDC criteria, other conditions that could cause fatigue excluded individuals from the study. The extent of physical activity was assessed in the CFS patients by a self-administered questionnaire that asked the individuals to rate their activity on a scale of 1 (least active) to 10. Additionally, patients were given other questions about their clinical symptoms. (The questionnaire is available from us on request.) Cognitive ability and muscle strength were assessed by history and by mental status and physical examinations. In most cases, neither the physical examination nor laboratory tests were helpful in assessing muscle function. Patients had been ill for one to five years. Most of the patients were caucasian; 20% were Asian. Racial background did not affect the results. Randomly selected control subjects consisted of healthy individuals living in San Francisco, working at the UCSF Medical Center (n = 50), and subjects who were being seen for routine physical examination (n = 30). Immunophenotypic data on these two control groups were not significantly different, so they were combined for this study as one control group (30 males, 50 females; median age 38 years, range 20–55). Racial distribution was similar to the patient group. Additional control populations that were evaluated included patients with acute viral-like illness (n = 15); patients with documented depression (n = 10); spouses and family members of CFS patients (n = 11); medical personnel in contact with CFS patients (n = 11); individuals with prolonged fatigue without other clinical criteria for CFS (n = 6); and patients with systemic lupus erythematosus (SLE) (n = 12) as defined by the American Rheumatology Association. These non-CFS subjects were selected because they were referred by physicians in the San Francisco and Chicago areas. Blood samples obtained from all individuals studied were coded and referred by physicians in the San Francisco and Chicago areas. Blood samples were taken for flow cytometric studies, white blood cell counts, and serological studies. An additional serum sample was taken for viral serological studies.

Viral serology

Antibodies to various viruses (including those proposed as "candidate" agents for CFS) were assayed quantitatively. The CFS patients were subsequently found to represent 23 individuals in group A and 27 individuals in group B as defined in Results. Antibody to adenovirus, Coxackie B4, human herpes virus 6 (HHV-6), human immunodeficiency virus (HIV), human T-cell lymphotropic viruses I/II (HTLV I/II), rubella, papovavirus, and human spumavirus were assayed by indirect immunofluorescence.

Sample preparation and flow cytometric analysis

Lymphocyte and monocyte populations were analysed by flow cytometry with dual colour direct immunofluorescence after whole-blood lysis. The panels of fluorescein isothiocyanate (FITC) or phycoerythrin (PE) monoclonal antibodies used are as follows:

**Table I—Symptoms of Patients with CFS**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Group A (n = 67)</th>
<th>Group B (n = 59)</th>
<th>Group C (n = 21)</th>
<th>Total (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhaustion/fatigue</td>
<td>100</td>
<td>90</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Post exertional weakness</td>
<td>90</td>
<td>88</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>90</td>
<td>93</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>95</td>
<td>30</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>Severe cognitive dysfunction*</td>
<td>92</td>
<td>20</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>Abdominal/gastrointestinal pain</td>
<td>90</td>
<td>88</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Nausea</td>
<td>90</td>
<td>13</td>
<td>13</td>
<td>90</td>
</tr>
<tr>
<td>Neuroirritability</td>
<td>90</td>
<td>68</td>
<td>68</td>
<td>90</td>
</tr>
<tr>
<td>Sleep disorder†</td>
<td>90</td>
<td>42</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>Twitching/myoklonus</td>
<td>90</td>
<td>34</td>
<td>34</td>
<td>90</td>
</tr>
<tr>
<td>Frequent headache</td>
<td>81</td>
<td>51</td>
<td>51</td>
<td>81</td>
</tr>
<tr>
<td>Balance problems</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Depression†</td>
<td>73</td>
<td>32</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>Chills</td>
<td>55</td>
<td>20</td>
<td>20</td>
<td>55</td>
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<tr>
<td>Sore throat</td>
<td>33</td>
<td>10</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Lymph-node pain</td>
<td>30</td>
<td>14</td>
<td>14</td>
<td>30</td>
</tr>
</tbody>
</table>

Data are percent of patients having symptoms at time of evaluation (see text)

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*Short-term memory loss, encoding, stimulus recognition

| Hypersomnia and hypoosomnia

In most cases, onset of depression occurred 6 mo after onset of illness

See Results for definition of patient groups
Markers are known to have a non-Gaussian distribution. The Scheffé test was used to analyse CD8 cell subsets and NK cell populations when comparing control groups to healthy individuals. The McNemar chi square test was used to evaluate viral serology data and for probability analysis.

Results

Clinical evaluation of CFS patients

All the patients had a history of fatigue for more than six months and post-exertional weakness substantially worse than previously observed. Many complained of muscle weakness, myalgias, neurological disorders, frequent headaches, and other symptoms shown in table 1. At the time of evaluation, several patients had improved in clinical symptoms. About half had a medical history of a "flu-like" illness at the onset of this clinical condition. Only 8 patients had depression before the onset of illness, but depression developed in many patients after two years of illness. A full report on the clinical aspects of the patients will be published elsewhere.

After the clinical information had been analysed, we found that the patients could be placed into three groups according to their symptoms. Group A consisted of 67 patients whose illness was so severe that they had less than 25% of their normal daily activity and also had multiple symptoms; group B were 59 individuals with reduced physical activity who continued to have moderate symptoms; and group C consisted of 21 patients who initially had many symptoms and an incapacitating illness like patients in group A, but at the time of evaluation they had substantially improved for at least two months and regained 75% or more of their normal physical activity with only mild symptoms. Healthy controls showed none of the symptoms given in table 1 on a persistent basis.

Viral serology

Healthy controls and CFS patients were generally similar with respect to the prevalence and titres of antibodies to CMV, EBV-VCA, EBNA, rubeola, adenovirus type 2, and the papovavirus (BK virus) (table II). Evaluation of CFS patients by clinical status as defined in table I also showed no differences in these titres compared with controls. No antibodies to HTLV-I/II and HIV were found in any subject. Antibody titres to HHV-6 in the CFS patients were twice as high (p = 0.05) as those in controls. The prevalence of antibodies to Coxsackie B4 virus was also significantly higher in the CFS group than in controls (90% vs 65%, p = 0.001), but the geometric mean titres (GMTs) were similar. Moreover, CFS patients had a significantly higher prevalence of antibodies to EBV-EA than did controls (51% vs 15%, p = 0.001). This finding was specific for EA since the VCA and EBNA seropositivity rates for both groups were identical.

Peripheral white blood cell analyses (table III)

CFS patients and healthy control subjects did not differ significantly with respect to the following indices: white blood cell count (6-10 × 10^3/μl), total lymphocyte, monocyte, and neutrophil populations (irrespective of whether the CFS patients were considered as an entire group or as separate groups) (data not shown); phenotype of major lymphocyte (T, B, NK cell) populations; percentage and absolute number of CD4 and CD8 T cells; mean CD4/CD8 ratio; presence of activation antigens (CD25 and HLA-DR) on CD4 T cells, NK cells, or monocytes; a B-cell subset (CD5/CD20), which we tested because it has been found to be increased in autoimmune disease; and percentage positive or fluorescence intensity of cell adhesion antigens (CD11a, CD18, CD44, CD54) (data not shown). We also assessed CD4/CD8 ratios because previous studies have suggested that CFS patients have alterations in the distribution and ratios of these cells. Most patients had a normal range (table III).

CD8 cell subset analysis

Previous cell surface marker studies in acute viral infections have shown elevation of CD8 cells that express activation antigens (CD38, HLA-DR). With respect to the herpesviruses, these cell numbers return to normal two to four weeks after infection. We evaluated various cell surface antigens expressed on CD8 T cells from the 147 CFS patients and compared them (in total and as separate groups) with the 80 healthy controls.

Three cell surface markers gave noteworthy results. In the total CFS patients evaluated, the population of CD8 cells expressing CD11b was decreased, but not significantly, compared with the normal controls (19 [SD16] vs 25 [10]), indicating a decrease in the phenotypic suppressor CD8 T-cell compartment. Since the total CD8 cell count did not
Percent expression of CD11b, CD38, and HLA-DR on CD8 cells.

Data are mean (SEM). *p=0.01 for group A compared with control (Mann-Whitney U Test). ■ = group A (n=67); □ = group B (n=69). □ = group C (n=21). □ = total CFS (n=147). □ = control (n=80).

change, there was a concomitant increase in the phenotypic cytotoxic (CD8 CD28 CD11b-) population. This result was confirmed in a preliminary study in which there was an increase in the CD8 CD28 population in these patients (data not shown). Compared with controls, CFS patients showed an increase in CD38 (47 [20] vs 35 [12]) and HLA-DR (22 [8] vs 14 [6]) expression. An additional activation antigen, CD25, as well as the CD57 and Leu8 antigens, were expressed on the CD8 cells at a level similar to controls. When the same CD8 cell subset markers were considered in group A patients, the differences compared with healthy controls and group C patients were statistically significant (p = 0.01) (figure). By contrast, evaluation of the CD8 cell antigen expression among the group C patients showed no significant differences from healthy controls (figure). With respect to CD8 cell abnormalities, group B patients were not significantly different from control subjects. Further evaluation of group C patients showed that only 10% of patients had two or more significantly abnormal results among the CD8 CD11b-, CD8 CD38, or CD8 HLA-DR subsets, whereas among the group A patients 85% had two or more abnormal results. These results point to a high probability (90%) (p = 0.01) of having active CFS if an individual has two or more of the CD8 cell subset alterations (McNemar chi square test with improvement fraction).

To control for possible changes in cell-surface antigen expression due to the whole-blood lysis procedure, a subset of patients was evaluated after 'Ficoll-Hypaque' isolation of peripheral blood mononuclear cells. No differences were seen between the whole blood lysis procedure and ficoll-hypaque purified cells (data not shown).

**CD8 cell markers in other control subjects**

To evaluate the specificity of the CD8 cell alteration in CFS patients, the control subjects with other clinical conditions were evaluated with the same panel of monoclonal reagents. Among subjects who had an acute viral-like illness (common cold or flu-like illness), there was an increase in both percentage and absolute numbers of NK cells (CD16/CD56). These NK cells expressed CD8, CD38, CD11b, but not HLA-DR as judged by multiparameter flow cytometric studies (data not shown). In several individuals this initial natural killer response was followed by an increase in activated CD8/CD11b T cells (CD38 HLA-DR). In all these subjects, recovery one to two weeks later was accompanied by a return to normal of all these immunological indices. All other CD8 cell markers were normal in these individuals.

Evaluation of CD8 cell subsets in control subjects with a diagnosis of depression showed no significant differences compared with healthy controls. Furthermore, family members and contacts of CFS patients had normal CD8 cell subsets as did individuals presenting with fatigue other than that associated with CFS (table IV). Laboratory findings among CFS patients have shown low level autoantibodies, which may reflect an underlying autoimmune disease. Evaluation of patients with SLE showed only moderately increased expression of the CD38 marker on CD8 cells (table IV); other cell surface markers were within the normal range.

**Discussion**

We have not found any serological evidence of an aetiological association with CFS of the various human viruses that we tested. Although seroprevalence to Coxackie B4 virus was higher in CFS patients than in controls, the GMT was similar. Moreover, other evidence has not supported a role of this virus in CFS. Anti-EA antibody prevalence was also significantly increased in the CFS patients who in this study were not preselected for EBV serology. Additionally, like other investigators, we found a relatively high GMT for EBV-EA and HHV-6 antibodies; and we also recorded a significantly lower GMT for EBV-EBNA in our cohort of CFS patients. These findings most probably reflect T-cell disorders in these patients.

Immunological testing of CFS patients has resulted in conflicting reports about abnormalities in T-cell subsets, monocyte responses, and cytokine production. Also, seen between the whole blood lysis procedure and ficoll-hypaque purified cells (data not shown).

**TABLE IV—CD8 CELL SURFACE MARKERS AND NK CELLS IN CONTROL POPULATIONS**

<table>
<thead>
<tr>
<th>Cell subset</th>
<th>Acute viral (n=15)</th>
<th>Depression (n=10)</th>
<th>Family members* (n=11)</th>
<th>Contacts† (n=11)</th>
<th>Chronic fatigue alone (n=6)</th>
<th>Autoimmune disease (n=12)</th>
<th>Healthy controls (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8 cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD11b</td>
<td>42 (12)</td>
<td>28 (10)</td>
<td>27 (12)</td>
<td>27 (8)</td>
<td>30 (12)</td>
<td>28 (6)</td>
<td>25 (10)</td>
</tr>
<tr>
<td>CD38</td>
<td>63 (10)†</td>
<td>26 (8)</td>
<td>28 (7)</td>
<td>32 (6)</td>
<td>25 (6)</td>
<td>45 (12)</td>
<td>35 (12)</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>12 (3)</td>
<td>10 (5)</td>
<td>10 (6)</td>
<td>12 (6)</td>
<td>9 (3)</td>
<td>15 (4)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>NK cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD16/CD56</td>
<td>24 (7)</td>
<td>12 (4)</td>
<td>8 (2)</td>
<td>11 (4)</td>
<td>10 (5)</td>
<td>12 (6)</td>
<td>14 (8)</td>
</tr>
</tbody>
</table>

Data are % cells (SD) expressing surface markers shown
*Spouses or family members of CFS patients.
†Contacts are medical personnel in contact with CFS patients.
Statistically significant (Schiffe test) compared with healthy controls, p = 0.01
changes in B-cell immunity associated with autoantibody production, high antiviral antibody titres, circulating immune complexes, and increased numbers of CD5/CD20 B cells\(^5\) have been noted, as have decreased function of NK cells and changes in NK cell numbers.\(^6\)\(^,\)\(^7\) Finally, monocytes from CFS patients have been reported to have decreased HLA-DR cell-surface antigen expression and decreased phagocytic activity.\(^8\)\(^,\)\(^9\)

Our study centred on the use of flow cytometry to define immunological alterations in patients with CFS. Our CFS patients had a female to male ratio of 3 to 1 and a characteristic median age for CFS of 38 consistent with other studies.\(^10\) That most of our CFS patients had a normal percentage and number of CD4 and CD8 cells, also accords with others.\(^11\) When all CFS patients were considered, we found a state of immune activation specifically among the CD8 lymphocyte population. Moreover, the suppressor subset of CD8 (CD11b) was reduced in many patients, significantly so in patients with multiple symptoms and severe incapacitating illness (group A). These results agree with those reported by Klimas et al,\(^12\) who demonstrated in 30 patients an elevation in CD8 cells expressing related markers (HLA-DR and CDw26). In that study, however, patients were preselected for high EBV titres. Unlike in CFS, an elevation of cells expressing CD11b or CD57, usually NK cells, is a common finding in acute viral illness.\(^13\) Our data confirm this observation; within one to two weeks, the immunological indices in our subjects with acute viral illness returned to normal. Our findings suggest that in CFS patients, the NK cell number is normal, the CD8 CD11b population is reduced, and the CD38 and HLA-DR markers remain persistently raised.

The reason for this immune activation is not known, but we have seen it in individuals who have had symptoms for one to five years. Moreover, the abnormalities have persisted in 6 patients followed for more than a year. In 2 other cases, an improvement in symptoms was accompanied by a return to normal of some immunological markers (data not shown). Our results with CFS patients whose symptoms have improved (group C) support these observations. The immune disorder in CFS does not seem to reflect an underlying autoimmune disease or depression (table IV). A possible explanation is that the NK dysfunction,\(^14\) or the decreased CD11b CD8 suppressor cell population (our findings), leads to a persistent hyperimmune response of the remaining CD8 cells. The activation might lead to an outpouring of cellular products and cytokines (eg, interferon, tumour necrosis factor, interleukin-1) that are characteristically associated with myalgia, fatigue, neurological signs, and other signs and symptoms associated with acute viral infections.\(^15\) Unless the immune system is brought back into balance, however, this chronic activation affects the individual further and might eventually lead to other clinical illnesses.

Although not diagnostic of CFS and not observed in all individuals with a history of CFS, the immunophenotypic data presented here indicate that many individuals with symptoms of CFS have CD8 cell immune activation. Additionally, many have a reduced level of CD8 cells with a suppressor phenotype (CD11b) and an increase in CD8 cells of the cytotoxic type (CD11b\(^+\)). Further functional studies of these CD8 cell subsets may provide insights into CFS pathogenesis. Most noteworthy is the statistical evidence that an individual with two or more of the CD8 cell subset alterations (increased CD11b\(^+\), CD38, and HLA-DR) has a high probability (90%) of having active CFS.

findings are consistent with chronic stimulation of the immune system perhaps by a virus, although evidence for a common agent has not been found.

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REFERENCES

Role of psychosocial stress in recovery from common whiplash

Bogdan P. Radanov  Giuseppe di Stefano  Ayesha Schindrig  Pietro Ballinari

It is widely accepted that psychosocial factors are related to illness behaviour and there is some evidence that they may influence the rate of recovery from post-traumatic disorders. The abilities of psychosocial stress, somatic symptoms, and subjectively assessed cognitive impairment to predict delayed recovery from common whiplash were investigated in a follow-up study. 78 consecutive patients referred 7-2 (SD 5-1) days after they had sustained common whiplash in car accidents were assessed for psychosocial stress, negative affectivity, personality traits, somatic complaints, and cognitive impairment by semistructured interview and by several standardised tests. On examination 6 months later 57 patients were fully recovered and 21 had persisting symptoms. The groups' scores for the independent variables assessed at the baseline examination were compared. Stepwise regression analysis showed that psychosocial factors, negative affectivity, and personality traits were not significant in predicting the outcome. However, initial neck pain intensity, injury-related cognitive impairment, and age were significant factors predicting illness behaviour. This study, which was based on a random sample and which considered many other possible predictive factors as well as psychosocial status, does not support previous findings that psychosocial factors predict illness behaviour in post-trauma patients. Lancet 1991; 338: 712-15.

Introduction

The importance of psychosocial factors in relation to illness behaviour is widely accepted. 23-26 Two psychosocial factors thought to be related to illness behaviour are negative affectivity (defined as a wide range of aversive mood states, including anger, disgust, scorn, guilt, fearfulness, and depression) 26 and neuroticism—a broad dimension of individual differences in the tendency to experience negative, distressing emotions and to possess associated behaviour and cognitive traits. 26

Despite this established relation, no empirical study has examined it for the illness behaviour of patients with post-traumatic disorders. The few non-experimental studies of this issue suggest secondary gain as the principal mechanism by which illness behaviour persists. There have been no follow-up studies of predictive relations between psychosocial factors and the course of recovery of post-trauma patients with random samples. This study attempts to fill this research gap.

Our primary aim was to evaluate the predictive significance of psychosocial factors, negative affectivity, and personality traits in the recovery of patients with common whiplash. We also studied the predictive abilities of somatic symptoms and self-reported cognitive impairment. The disorder is considered to be a medical trauma leading to cervical sprain or strain due to hyperflexion/hyperextension. 27-30 The trauma occurs most commonly in car accidents involving frontal or rear-end collisions. 27-30 It is commonly followed by symptoms such as neck pain, headache, 31-32 and cognitive impairment. 33 If patients do not recover within 2-3 months, the symptoms are increasingly likely to persist. 33-35 Symptoms persisting beyond 6 months are known as late whiplash syndrome. 36 In contrast to mild head injury, common whiplash is a non-contact trauma that does not result in a traumatic loss of consciousness.

Patients and methods

We asked primary care physicians to refer patients who had lately incurred common whiplash as soon as possible after trauma. We offered no treatment to participants; this remained the responsibility of the referring physician. Our inclusion criteria were injury mechanism that accorded with the above definition, German native language, and age 55 years or younger. Of 104 consecutive

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