Idiopathic chronic fatigue and chronic fatigue syndrome: a comparison of two case-definitions

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Summary. - The aim of the study was to compare the signs and symptoms of individuals meeting two different definitions of chronic fatigue syndrome (CFS). Ninety-four patients fitting the eligibility criteria for idiopathic fatigue were enrolled into the study. Of the 94 patients, 48 met the 1988 definition of CFS, 20 the 1994 (but not the 1988) definition of CFS, and 26 met neither definition. The 1994 defined cases were more likely than 1988 defined cases, and non-syndromal individuals to be male, married, and high school educated. The 1994 cases were less likely than 1988 cases to present acute onset, self reported sore throat, mild fever, lymphadenopathy, pharyngitis. In conclusion, the 1994 criteria increased the number of patients classified as CFS; however, those who fit only the 1994 criteria were less likely to have an acute symptomatic onset and signs and symptoms suggestive of an infectious process.

Key words: chronic fatigue syndrome, idiopathic chronic fatigue, case-definition, clinical evaluation, diagnostic criteria, epidemiology.


Parole chiave: CFS, fatica cronica idiopatica, definizione di caso, criteri diagnostici, epidemiologia.

Introduction

In recent years, a new syndrome, characterized by prolonged unexplained fatigue and other non-specific signs and symptoms, has been described in the United States and in several other industrialized countries [1-3]. Called chronic fatigue syndrome (CFS), it usually occurs as sporadic cases, and unlike non-syndromal chronic fatigue, it seems to be relatively uncommon [4, 5]. Though there is still no evidence that CFS itself is a communicable disease, the association between CFS and previous occurrence of viral infections has been under investigation [6-8]. Similarly, the relationship between CFS and psychiatric disorders, such as non-psychotic depression, and other symptomatically defined syndromes such as fibromyalgia, remains unclear [3, 9-11].

Several case-definitions have been proposed [12-14], but to our knowledge only few evaluative studies have been conducted [15, 16]. In 1994, the Centers for Disease

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Control (CDC) of Atlanta proposed a new case-definition which remains to be thoroughly evaluated [17]. Here we describe the main results of the analysis of an Italian multicentre study of CFS, performed with the aim of comparing the revised 1994 CFS definition with the 1988 CDC working case-definition.

Patients and methods

Study population and site

Individuals with fatigue lasting for at least six months, who attended six collaborating centres, in the center and in the north of Italy between June 1992 and June 1993, were considered eligible for the study. All the centres, identified by the Istituto Superiore di Sanità (ISS) (the Italian National Institute of Health), had an outpatient facility and were able to provide a multidisciplinary approach to health problems (internal medicine, infectious diseases, immunology consultancy, psychiatric consultancy). To facilitate the recruitment of CFS patients, information on CFS was provided through the national medical press to general practitioners, who were asked to refer the patients to one of the centers. All participants underwent a standardized medical examination and laboratory evaluation.

Two major criteria were used for inclusion in the study: 1) debilitating fatigue lasting at least six months, associated with a 50% self-reported reduction of the individual’s daily activity, and 2) exclusion of other clinical conditions possibly producing similar symptoms (i.e., autoimmune diseases, localized infections, neuromuscular diseases, etc.).

Case-definition

The two case-definitions proposed by the CDC in 1988 and 1994 were used [12, 17]. Firstly, participants were classified with CFS according to the 1988 working case-definition which requires the presence of 2 major criteria, and at least eight of the eleven symptoms, or six of the eleven symptoms and two of three physical examination criteria.

All the participants, both those who fulfilled the 1988 criteria and those who did not, were then reclassified using the 1994 CDC case-definition which does not include the physical criteria and which requires the presence of only four symptoms. Each time, participants with prolonged fatigue who did not fulfill the criteria of case-definition were considered as "non-syndromal cases". The data were collected before 1994 criteria became available; therefore, a post-hoc classification was applied.

Data collection and analysis

Interviews were conducted at each center by a trained physician using a standardized questionnaire to collect data on demographic features and possible risk factors, such as history of previous infectious disease, exposure to toxic substances, and previous problems for which psychiatric or psychologic consultation has been sought. Clinical and laboratory parameters (red cells count, white blood cell count and T-lymphocyte subsets) were also recorded. Participants were seen by a psychiatrist to exclude serious mental disorders. In two centres, a psychiatric evaluation using the ICD-10 criteria [18] was performed on all study participants. Periodic meetings were organized to standardize the psychiatric diagnostic criteria, under the supervision of a senior psychiatrist.

Data input and quality control of the information collected was performed at central level by the ISS. Physicians were contacted to complete missing data. All comparisons were performed between individuals meeting the 1988 CDC definition for CFS, those who did not meet the 1988 but did meet the 1994 definition, and those who met neither definition.

Non-parametric statistics (χ² test or Fisher exact test) were used to compare differences among the different groups for sex, marital status and level of education, the distribution of fatigue characteristics and minor criteria. An association was considered statistically significant if p < 0.05. Differences in age distribution were tested by a t-test. A Mann-Whitney U test was used to compare the distribution of laboratory variables between cases and non-cases.

Results

Of 300 individuals with fatigue referred to the collaborating centres during the study period, 94 met the two major criteria. The others were excluded because they did not fit the inclusion criteria or because they had known causes of fatigue, or serious psychiatric problems. As shown in Table 1, of 94 participants, 48 (51.1%) fulfilled the criteria for the 1988 case-definition, and 66 (70.2%) for the revised case-definition. However, two individuals classified as CFS using the 1988 definition did not fulfill the 1994 criteria; thus, the total number of participants classified as CFS increased from 46 (48.9%) to 66 after changing the case-definition. Of those participants who did not fulfill the 1988 criteria, 20 (43.5%) were reclassified as CFS cases using the 1994 case-definition. The classification of 72 individuals (76.6%) did not change no matter which case definition was used; 46 (48.9%) individuals remained cases and 26 (27.7%) remained non-cases.
Demographic characteristics of cases and non-cases

The frequency distribution of the demographic characteristics of the study participants are shown in Table 2. The 1994 redefined cases were somewhat more likely than 1988 defined cases to be male, married, and high school educated; however, the differences were not statistically significant.

Frequency distribution of symptoms and their characteristics

The clinical characteristics of fatigue among the study participants stratified by diagnostic group are shown in Table 3. The median duration of fatigue was 30 months, ranging from 6 months to 8 years. All participants reported that fatigue started upon awakening.

There was no clear trend among the three groups. Non-syndromal individuals showed a tendency toward an ameliorative effect of amusement and improvement of fatigue with work activities.

Table 4 shows the frequency distribution of other signs and symptoms in the three groups of patients. Individuals meeting the 1988 definition criteria were more likely than those fulfilling only the 1994 criteria to report acute onset, sore throat, mild fever, lymphadenopathy, pharyngitis. The two groups of syndromal cases were similar with respect to headache, myalgia, sleep disturbance, and neuropsychological disorders; these symptoms were more common in the two groups of syndromal individuals than among those who did not meet either definition.

Infectious diseases prior to the onset of fatigue

A history of infectious disease occurring within one month prior to the onset of the fatigue was reported by 39/94 individuals (41.5%). Specific disorders reported by cases were mononucleosis, flu, febrile pharyngitis, varicella, and interstitial pneumonia. Non-cases reported flu-like illness, mononucleosis, pharyngitis, and shingles. Prior infectious diseases were reported by 50% of 1988 cases, 42% of non-syndromal individuals, but only by 20% of 1994 cases. However, the difference was not statistically significant. The interval of time between the occurrence of the antecedent infectious disease and the onset of fatigue was significantly shorter (p < 0.05) among 1988 cases (median 12.5 days) compared to 1994 cases and non-syndromal individuals (median 30 days).

Prior psychological consultation

Psychological consultation before the onset of fatigue had been requested by approximately one fourth of the participants. Eleven (23.9%) of 46 participants meeting the 1988 case-definition, 4 (20.0%) of 20 participants fitting the 1994 criteria, and 8 (30.8%) of the 26 individuals who were not syndromal-cases had sought consultation. Anxiety and depression represented the major reported reason, either by cases or non-syndromal cases, for consultation.

Psychiatric evaluation

A subset of 35 participants from two centres (37.2% of all participants) underwent a detailed psychiatric evaluation. A psychiatric disorder was found in 80% of the 35 participants. The most common diagnoses were dysthymia (67.8%) and generalized anxiety disorders (21.4%). Other individuals presented mixed personality disorders (7.1%) or hypochondrial disorder (3.6%). The proportion of individuals with psychiatric disorders did not differ between 1988 defined cases (78.5%), 1994 cases (87.5%) and non-syndromal individuals (76.9%).
Table 3. - Descriptive characteristics of fatigue

<table>
<thead>
<tr>
<th>Descriptive characteristics</th>
<th>Group 1 (%) (no. 48)</th>
<th>Group 2 (%) (no. 20)</th>
<th>Group 3 (%) (no. 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue always present</td>
<td>56.3</td>
<td>55.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Need of resting during the day</td>
<td>89.6</td>
<td>73.7</td>
<td>72.0</td>
</tr>
<tr>
<td>Fatigue always present (workplace, days off)</td>
<td>97.9</td>
<td>95.0</td>
<td>88.5</td>
</tr>
<tr>
<td>Sport activity reduced or avoided</td>
<td>88.0</td>
<td>80.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Fatigue temporarily resolved with social activity or amusement</td>
<td>21.2</td>
<td>14.3</td>
<td>30.4</td>
</tr>
<tr>
<td>Work activity reduced or suspended</td>
<td>72.9</td>
<td>60.0</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Group 1: 1988-defined cases; group 2: 1994-defined cases; group 3: non-syndromal individuals.

Table 4. - Comparison of frequency distribution of signs and symptoms suggestive of CFS in syndromal and non-syndromal cases using the 1988 and 1994 case-definition

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (%) (no. 48)</th>
<th>Group 2 (%) (no. 20)</th>
<th>Group 3 (%) (no. 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric symptoms</td>
<td>95.8</td>
<td>95.0</td>
<td>84.6</td>
<td></td>
</tr>
<tr>
<td>Unexplained gener. muscle weakness</td>
<td>91.7</td>
<td>75.0</td>
<td>88.5</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>85.4</td>
<td>75.0</td>
<td>38.5</td>
<td>*</td>
</tr>
<tr>
<td>Myalgia</td>
<td>83.3</td>
<td>70.0</td>
<td>42.3</td>
<td>**</td>
</tr>
<tr>
<td>Acute onset</td>
<td>80.9</td>
<td>47.4</td>
<td>61.5</td>
<td>***</td>
</tr>
<tr>
<td>Self-reported sore throat</td>
<td>75.0</td>
<td>40.0</td>
<td>26.9</td>
<td>*</td>
</tr>
<tr>
<td>Self-reported mild fever</td>
<td>75.0</td>
<td>35.0</td>
<td>42.3</td>
<td>**</td>
</tr>
<tr>
<td>Headache</td>
<td>70.8</td>
<td>80.0</td>
<td>23.1</td>
<td>*</td>
</tr>
<tr>
<td>Migratory arthralgia</td>
<td>68.8</td>
<td>40.0</td>
<td>26.9</td>
<td>**</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>54.8</td>
<td>5.6</td>
<td>23.8</td>
<td>*</td>
</tr>
<tr>
<td>Nonexud. pharyngitis</td>
<td>58.5</td>
<td>11.8</td>
<td>33.3</td>
<td>**</td>
</tr>
<tr>
<td>Painful lymph nodes</td>
<td>50.0</td>
<td>30.0</td>
<td>3.8</td>
<td>*</td>
</tr>
<tr>
<td>Fever (taken by a physician)</td>
<td>35.0</td>
<td>12.5</td>
<td>29.4</td>
<td></td>
</tr>
<tr>
<td>Prolonged gener. fatigue after exercise</td>
<td>27.1</td>
<td>10.6</td>
<td>11.5</td>
<td></td>
</tr>
</tbody>
</table>

CFS: chronic fatigue syndrome; group 1: 1988-defined cases; group 2: 1994-defined cases; group 3: non-syndromal individuals.

Laboratory parameters

White cell counts did not significantly vary among the three groups, even though they tended to be lower among non-syndromal individuals. Total lymphocytes and CD4+ cell levels were also similar. CD8+ cell levels were slightly but not significantly lower among participants fulfilling the 1988 CFS criteria than among the individuals belonging to the other two groups (Table 5).

Discussion

The findings of our study show that the use of the 1994 revised case-definition results in the reclassification as CFS cases of 43.5% of individuals with prolonged fatigue who did not meet the 1988 criteria. The pattern of signs and symptoms accompanying the chronic fatigue tended to slightly change after reclassification. These findings suggest that the use of the new definition, which
Table 5. - Main laboratory parameters for CFS cases (using the 1988 and 1994 case-definition) and non-syndromal individuals

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
<th>Group 3 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(no. 48)</td>
<td>(no. 20)</td>
<td>(no. 20)</td>
<td></td>
</tr>
<tr>
<td>White cells M</td>
<td>6099 (4000-10199)</td>
<td>6200 (3700-9000)</td>
<td>5574 (3700-10900)</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lymph. M</td>
<td>1980 (684-3830)</td>
<td>2029 (1156-3299)</td>
<td>184 (1110-3815)</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cells M</td>
<td>828 (212-1647)</td>
<td>788 (295-1169)</td>
<td>835 (437-1307)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8+ cells M</td>
<td>477 (208-1283)</td>
<td>572 (205-1147)</td>
<td>55 (303-1705)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

CFS: chronic fatigue syndrome; group 1: 1988-defined cases; group 2: 1994-defined cases; group 3: non-syndromal individuals; M: median; R: range.

is less restrictive, allows a higher proportion of individuals affected by severe long-lasting fatigue to be classified as CFS.

A recently published paper in which CFS patients were compared with healthy controls, suggests that all the minor criteria of the original CDC case-definition can be used to distinguish patients with debilitating chronic fatigue from healthy individuals [16]. However, symptoms like muscle weakness, arthralgia and sleep disorders were less useful than others for discriminating between cases and controls.

In our study, individuals with chronic debilitating fatigue who fully met the 1988 and/or 1994 case-definition criteria seem to differ not only with respect to non-syndromal individuals. However, symptoms such as neuropsychological disorders and muscle weakness were very common among all the study participants, and were not able to discriminate between the three groups. These symptoms, which seem to be consistently associated to chronic debilitating fatigue “per se”, have been found to be relatively rare in healthy individuals used as control group in other studies [16], but they do not seem useful for distinguishing syndromal and non-syndromal individuals with prolonged fatigue. The high prevalence of these symptoms makes satisfying the need of identifying specific characteristics of CFS patients difficult, as already pointed out by other authors [19, 20].

Individuals fulfilling the 1988 criteria were pretty similar to those meeting only the criteria of the revised definition. However, some symptoms such as acute onset, self-reported fever, pharyngitis and lymphadenopathy, which might be suggestive of an infectious and/or immune process underlying CFS [19, 21], were more common among 1988 defined than among 1994 cases. This may be a consequence of the use of less restrictive criteria, which allows a number of previously non-syndromal individuals to be reclassified as full-blown cases.

The proportion of individuals in our study, who report an infectious disease within one month prior to the onset of fatigue was relatively high (over 40%), but some difference was found among the different groups; the proportion of 1994 cases reporting the event was less than half of those of the other groups, with the limited power of the study being a possible explanation to the lack of statistical significance. Furthermore, the time interval between the previous infectious disease and the onset of fatigue was much shorter among 1988 CFS patients than among the other study participants. These findings may suggest that infections could play a role only in specific subgroups of patients with prolonged fatigue. It should be noted that all participants in our study were affected by prolonged fatigue, and that we lacked a control group of healthy individuals which would have allowed us to test the association between infectious diseases and CFS. However, the results of a prospective study conducted in the UK [7] on the outcome of 1000 symptomatic infectious episodes seem to rule out a strong association between infections and chronic fatigue.

All cases of CFS identified by our sentinel network were sporadic cases. We did not observe CFS clusters nor symptoms suggestive of CFS among relatives or sexual partners (data not shown). This supports the observation that, after the early reports of CFS-like illness outbreaks [22], most cases seem to occur sporadically.

We found that one fourth of all participants had consulted a psychologist before the onset of symptoms, with no significant difference in this behaviour among the three groups. Seventy-nine percent of the participants who underwent a psychiatric evaluation based on ICD-10 criteria had a diagnosis of psychiatric disorder. Depression and anxiety were the most common disorders
as described in studies on chronic fatigue carried out in primary care [23]. Furthermore, the risk of psychiatric disorders in CFS patients compared with medical controls was found elevated in another study [16, 24].

Since the relationship between CFS and psychiatric disorders is still controversial [10, 11, 25–27] we think that a psychiatric evaluation of any fatigued individual should be mandatory.

With regard to hematological and immunological parameters, we did not find striking differences between cases and non-cases, using both definitions. We found that 1988 CFS cases tended to have about 70-100 CD8 cells less than those meeting the revised case definition criteria and non-syndromal individuals. However, this difference was not statistically significant, perhaps due to the limited study power. Most studies performed, up to now, have found no differences in absolute count of lymphocytes and/or T-cells subsets [28–30]. As a limit of our study, we did not perform more detailed immunophenotypic analyses that were found to be modified in other studies [31, 32].

When interpreting the results of our study, certain limitations and biases should be taken into consideration. Firstly, we used a clinical series of individuals presenting with long-lasting fatigue to evaluate the proportion of persons who would meet one of the case-definitions each time. We did not have a control group of apparently healthy individuals; the use of a comparison group represented by individuals with prolonged fatigue but without all signs and symptoms defining a CFS case might have diluted the association between CFS and specific study variables. Secondly, since this study was not designed to define CFS according to the new criteria, only a post-hoc classification of cases was possible. Thirdly, the immunological study was not complete, and the performance of laboratory parameters was not centralized. However, most centres participate in quality control proficiency panels; moreover, the results we found were consistent with those of the international literature. At last, a complete and detailed psychiatric evaluation to identify psychiatric disorders was possible only for a subgroup of participants. However, a basic psychological screening permitted to exclude severe problems for all the other participants.

In conclusion, the fairly drastic changes introduced in the 1994 case-definition may increase the number of patients classified as CFS. There seems to be a considerable overlap between the original and the revised case-definition, with an agreement in 77% of the cases. Patients reclassified according with the new criteria also had many complaints, with the same characteristics of fatigue as others, but are less likely to have an acute onset and signs and/or symptoms suggestive of an infectious disease.

The higher sensitivity of the case-definition, which provides an opportunity for subgrouping the individuals fitting the essential diagnostic criteria for long-lasting idiopathic fatigue, may be useful to help broaden the search for etiology or etiologies of CFS and to evaluate possible therapeutic options.

Acknowledgment

The authors thank Dr. Danino Greco for the useful comments on the study protocol.

Received on 15 February 1999.
Accepted on 8 June 1999.

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