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Chronic fatigue syndrome following a toxic exposure

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Abstract

Chronic fatigue syndrome (CFS) is a clinical entity characterized by severe fatigue lasting more than 6 months and other well-defined symptoms. Even though in most CFS cases the etiology is still unknown, sometimes the mode of presentation of the illness implicates the exposure to chemical and/or food toxins as precipitating factors: ciguatera poisoning, sick building syndrome, Gulf War syndrome, exposure to organochlorine pesticides, etc. In the National Reference Center for CFS Study at the Department of Infectious Diseases of 'G. D'Annunzio' University (Chieti) we examined five patients (three females and two males, mean age: 37.5 years) who developed the clinical features of CFS several months after the exposure to environmental toxic factors: ciguatera poisoning in two cases, and exposure to solvents in the other three cases. These patients were compared and contrasted with two sex- and age-matched subgroups of CFS patients without any history of exposure to toxins: the first subgroup consisted of patients with CFS onset following an EBV infection (post-infectious CFS), and the second of patients with a concurrent diagnosis of major depression. All subjects were investigated by clinical examination, neurophysiological and immunologic studies, and neuroendocrine tests. Patients exposed to toxic factors had disturbances of hypothalamic function similar to those in controls and, above all, showed more severe dysfunction of the immune system with an abnormal CD4/CD8 ratio, and in three of such cases with decreased levels of NK cells (CD56+). These findings may help in understanding the pathogenetic mechanisms involved in CFS.

Keywords: Chronic fatigue syndrome; Toxic exposure; Pesticides; Ciguatera; Immune system

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1. Introduction

Chronic fatigue syndrome, or CFS, is an illness characterized by a severe and disabling fatigue of uncertain etiology and other non-specific symptoms (Holmes et al., 1988; Fukuda et al., 1994) (Table 1). Several names have been proposed over the years to describe clinical features similar to the syndrome we now call CFS (Acheson, 1959; Behan and Behan, 1988; Poskanzer et al., 1957). The first CFS case definition was formally established in 1988 by the US Centers for Disease Control (CDC) and then revised in 1994 to realize a uniform definition for the syndrome (Fukuda et al., 1994). CDC estimates the minimum prevalence rate of CFS in USA at 4–10 cases per 100 000 adults (Levine, 1997). CFS usually occurs sporadically, but occasionally manifests in epidemics. Most cases occur in women (Behan and Behan, 1988; Behan and Bakheit, 1991) and the age at presentation is usually between 20 and 50 years (Buchwald et al., 1987; Behan and Behan, 1988). The course of the illness differs widely among patients. Typically, the syndrome follows a cyclical course, alternating between periods of illness and relatively good health (Schluederberg et al., 1992). Without knowing the cause of CFS, it is difficult to identify specific diagnostic tests as well as effective treatments. Several etiopathogenetic hypotheses have been formulated over the years: viral infections (Gow and Behan, 1996), immune dysfunctions (Klimas et al., 1990; Landay et al., 1991; Barker et al., 1994), neuroendocrine abnormalities (Demitrack, 1998), psychological, environmental and behavioral factors (Pizzigallo et al., 1998).

However, in at least some subgroups of CFS patients the onset of the illness is well correlated to a previous exposure to specific environmental and/or food toxins: ciguatera poisoning (Gillespie et al., 1986; Pearn, 1995), Gulf War syndrome (Haley et al., 1997; Landrigan, 1997), sick building syndrome (Chester and Levine, 1994, 1997), exposure to pesticides, organophosphates, solvents and other chemicals (Behan and Haniffah, 1994; Bell et al., 1998).

In tropical areas many CFS-like cases follow an episode of gastroenteritis due to the ingestion of certain ciguatoxic fish. Ciguatera consists of a food-chain disease which starts with a reef-dwelling dinoflagellate, *Gambierdiscus toxicus* (Gillespie et al., 1986). The ciguatoxin is heat-stable and tasteless and there is no commercially available practical test for its detection. So individuals can be poisoned from eating fresh or frozen fish, or fish products such as fish soup.

A CFS-like illness has been also described among Gulf War veterans. In fact, 5 years after the Operation Desert Storm in 1991, an estimated 5000–80 000 of the approximately 700 000 Gulf War veterans remain ill with vague symptoms that resemble chronic fatigue syndrome. These veterans were exposed to a wide array of known and potential hazards to health. These risk factors included extremes of heat and cold, blowing dust, smoke from oil well fires, petroleum fuels and their combustion products, pyridostigmine bromide (administered as pretreatment for potential poison gas exposure), anthrax and botulinum toxoid vaccines, depleted uranium (used in certain artillery shells), infectious diseases, chemical warfare agents, pesticides, and pervasive psychological and physical stress

Table 1
CDC CFS case definition (Fukuda et al., 1994)

CFS (chronic fatigue syndrome)
A. Persistent or recurrent fatigue (lasting > 6 months): (1) recent and/or well defined onset; (2) not secondary to excessive physical activity; (3) not resolved by rest; and (4) inducing important reduction of previous levels of physical and mental activities.
B. Presence of more than four of the following symptoms (for a period more than 6 months), not previous to fatigue onset: (1) impaired memory or concentration; (2) sore throat; (3) tender cervical or axillary lymph nodes; (4) muscle pain; (5) multi-joint pain; (6) new headaches; (7) unrefreshing sleep; and (8) post-exertion malaise.
CFS = A + B (> 4)

(Landrigan, 1997). By a factor-analysis, six different syndromes have been identified (Haley et al., 1997): (1) syndrome 1, or the 'impaired cognition' syndrome, greater in veterans who reported wearing flea collars during the war than those who never wore them; (2) syndrome 2, or 'confusion-ataxia' syndrome, mostly reported by veterans involved in chemical weapons exposure (in particular in pyridostigmine bromide exposure); (3) syndrome 3, or 'arthro-myo-neuropathy' syndrome, following the exposure to insecticides applied during the war containing 75% DEET (*N*,*N*-diethyl-*m*-toluamide) in ethanol; (4) syndrome 4, or 'phobia-apraxia' syndrome; (5) syndrome 5, or 'fever-adenopathy' syndrome; and (6) syndrome 6, or 'weakness-incontinence' syndrome. For the latter three syndromes, no well-defined risk factors have been described.

Three apparent outbreaks of sick building syndrome (SBS) were characterized by a symptomatology resembling CFS (Chester and Levine, 1994). In all these cases a potential causal role of environmental factors is highly suggestive because some specific building characteristics were recurrent: all buildings were realized after 1965; the ventilation was inadequate; there were no functioning windows and no efficient air volume duct system of heating and air conditioning (Chester and Levine, 1997).

Furthermore, CFS cases are reported in workers with an exposure to pesticides, organophosphates (Bell et al., 1998). In particular, some clusters of industrial workers exposed to solvents and other chemicals are described: in more than 90% of such cases toxics were represented by DDE (dichlorobischlorophenyletene) and HCB (esachlorobenzene).

On the basis of these previous findings, at Chieti University we started a characterization of CFS patients with a well-documented history of a previous exposure to environmental and/or food toxins. In addition, for a better understanding of pathophysiology mechanisms involved in CFS, we realized a comparative analysis of collected data of three subgroups of our patients: CFS patients with a toxic exposure previous to illness onset, CFS patients with a postviral onset, CFS patients with a concurrent major depression. We prefer to include the latter subgroup in our study even though a diagnosis of major depression should exclude CFS because in our opinion psychological factors play an important role in CFS, both for the illness onset and the clinical course.

2. Methods

Five patients (three females and two males, mean age: 37.5 ± 8.5 years) who developed the clinical features of CFS several months after the exposure to environmental toxic factors (T-CFS) were examined at the Department of Infectious Diseases of Chieti University that is one of the main National Reference Center for CFS Study. Cases consist of ciguatera poisoning in two patients who went in tropical areas for tourism, and exposure to solvents and other chemicals in the other three cases due to working activities. In particular, one young man was exposed to plastics, another one to solvents, dyes and glues in a car industry, and finally a middle-aged lady reported an exposure to air pollution and pesticides. The exposure to such toxics was previous to CFS onset in all five cases with an interval exposure-CFS onset ranging between 3 months and 5 years.

These five patients were compared and contrasted with two sex- and age-matched subgroups of CFS patients without any history of exposure to toxics: the first subgroup consisted of four patients (one male and three females; mean age: 24.2 ± 4.6 years) with a post-viral syndrome following an EBV infection (PV-CFS), and the second of five patients (one male and four females; mean age: 36 ± 12.8 years) with a concurrent diagnosis of major depression (MD-CFS). All subjects underwent medical and psychiatric examinations: laboratory tests including the determination of magnesium in serum, frequently found decreased in CFS (Deulofeu et al., 1991); immunologic studies with a characterization of lymphocyte subsets (CD4 + , CD8 + , CD56 + , CD19 + , CD4/CD8 ratio); neurophysiological investigations — algological evaluation by the application of pressure and electrical pain thresholds, EMG and evoked auditory potentials; and neu-

roendocrine tests, in particular the circadian rhythm of prolactine, TSH, cortisol, DHEA-S and ACTH, and a buspirone challenge test to search for an up-regulation of 5HT1A hypothalamic receptors as reported by many authors (Bakheit et al., 1992). The Student's *t*-test was used for statistical analysis.

3. Results

All CFS subgroups showed low levels of serum magnesium in most of the patients. A similar algological profile with a characteristic reduction of only the muscle pain thresholds and normality of cutis and subcutis pain thresholds was documented in PV-CFS patients and in those with a toxic exposure, while MD-CFS patients showed a reduction of pain thresholds in all the body districts taken into consideration (cutis, subcutis and muscle) as well as a positivity of more than 11 tender points to support the existence in such patients of a concurrent fibromyalgia syndrome (FS). Furthermore, abnormal evoked auditory potentials were reported more frequently by MD-CFS patients than by the other two CFS subgroups.

The patients with a previous exposure to toxics had disturbances of hypothalamic functions similar to those determined in the other two subgroups: most of the patients showed low levels of DHEA-S, a normal profile of the circadian rhythm of the other examined neurohormones. Finally, an abnormal increase of prolactine levels followed the buspirone challenge test, to suggest an up-regulation of 5HT1A hypothalamic receptors in all the three subgroups of patients.

The only comparative analysis that underlined a different behavior of patients with a previous toxic exposure was the lymphocyte subsets characterization (Table 2). Patients with a history of toxic exposure in fact showed a more severe dysfunction of the immune system in a statistically significant way compared both to PV-CFS and MD-CFS patients, and specifically: an abnormal CD4/CD8 ratio; three of such five cases also showed decreased numbers of NK CD56+ cells.

4. Discussion

Chronic fatigue syndrome (CFS) still remains of uncertain definition because of the lack of specific features both clinically and objectively. However, CFS patients complain of some alterations more recurrently than others, such as serum magnesium deficiency, muscle hyperalgesia, impaired activation of HPA axis. In our opinion, the study of the immune system status in CFS patients might help in a better characterization of the syndrome, even if more immunologic studies are required as suggested by literature data. (1) A better characterization of T CD8+ lymphocytes so to differentiate cytotoxic cells from the suppressor ones. In fact many researchers (Barker et al., 1994) report a predominant reduction of CD8+CD11b+ lymphocytes or T suppressor lymphocytes and this agrees with the theory of a persistent immune activation in CFS (Landay et al., 1991). (2) The determination in plasma and, if possible, in CSF of some cytokines frequently found increased in CFS subjects (Patarca et al., 1995; Vollmer-Conna et al., 1998): IL-1, IL-2, IL-6, TNF alpha and beta. Our preliminary findings confirm the presence of a dysfunction of the immune system in CFS patients with an history of

Table 2
Lymphocyte subsets characterization (mean ± S.D.)

	Patients (no.)			Student's *t*-test (*P*)
	T-CFS (5)	PV-CFS (4)	MD-CFS (5)	
CD4 cell count (cell/mm^3)	763 ± 253	921 ± 43	1113 ± 173	n.s.
CD8 cell count (cell/mm^3)	469 ± 256	599 ± 298	607 ± 483	n.s.*
CD56 cell count (cell/mm^3)	65 ± 21*	197 ± 110*	289 ± 132*	< 0.03*
CD4/CD8 ratio	3.0 ± 0.8*	1.8 ± 0.8*	2.7 ± 1.7	< 0.05

toxic exposure previous to CFS onset: an abnormal CD4/CD8 ratio principally due to a reduction of T CD8 + lymphocytes; three of the five examined patients also showed decreased numbers of NK CD56 + cells. So CFS patients with a post-toxic exposure onset might represent a well defined CFS subgroup characterized by specific immune dysfunctions probably precipitated by the toxic exposure itself.

In conclusion, further immunologic studies are needed for a better understanding of the pathogenetic mechanisms involved in CFS, as well as for a better categorization of CFS patients by the immune status.

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