



Opinion paper

Possible role for early-life immune insult including developmental immunotoxicity in chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME)

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Abstract

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) in some countries, is a debilitating disease with a constellation of multi-system dysfunctions primarily involving the neurological, endocrine and immune systems. While substantial information is available concerning the complex dysfunction-associated symptoms of CFS, environmental origins of the disease have yet to be determined. Part of the dilemma in identifying the cause(s) has been the focus on biomarkers (hormones, neurotransmitters, cytokines, infectious agents) that are contemporary with later-life CFS episodes. Yet, recent investigations on the origins of environmental diseases of the neurological, endocrine, reproductive, respiratory and immune systems suggest that early life toxicologic and other insults are pivotal in producing later-life onset of symptoms. As with autism and childhood asthma, CFS can also occur in children where the causes are certainly early-life events. Immune dysfunction is recognized as part of the CFS phenotype but has received comparatively less attention than aberrant neurological or endocrine function. However, recent research results suggest that early life immune insults (ELII) including developmental immunotoxicity (DIT), which is induced by xenobiotics, may offer an important clue to the origin(s) of CFS. The developing immune system is a sensitive and novel target for environmental insult (xenobiotic, infectious agents, stress) with major ramifications for postnatal health risks. Additionally, many prenatal and early postnatal neurological lesions associated with postnatal neurobehavioral diseases are now recognized as linked to prenatal immune insult and inflammatory dysregulation. This review considers the potential role of ELII including DIT as an early-life component of later-life CFS.

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Keywords: Early-life immune insults (ELII); Developmental immunotoxicity (DIT); Chronic fatigue syndrome (CFS); Myalgic encephalomyelitis (ME); Immune dysfunction; Inflammation; Infections; Prenatal; Neonatal; Neurological system; Endocrine; Postnatal stress

1. Introduction

Chronic fatigue syndrome (CFS) is a multi-factorial disease (Prins et al., 2006; Devanur and Kerr, 2006) primarily affecting the neurological (de Lange et al., 2005), endocrine (Segal et al., 2005) and immune systems (Klimas et al., 1990; Landay et al., 1991; Racciatti et al., 2004; Klimas and Koneru, 2007) but frequently influencing other systems as well (Peckerman et al., 2003; Meeus et al., 2007). It is very often accompanied by fibromyalgia (FM) (Teitelbaum et al., 2001). CFS is persistent

and debilitating when in an acute episode. However, even when not acute, chronic persistence of symptoms of a lesser degree causes patients to drastically alter their lifestyle to minimize the risk of relapse (Richardson, 2002; Soderland and Malterud, 2005; Larun and Malterud, 2007). Both genetic relationships and common environmental experiences influence the incidence of CFS (Underhill and O’Gorman, 2006).

Recent research has made progress in describing the dysfunction associated with CFS and some potential approaches to therapy have shown promise (Teitelbaum et al., 2001; Vermuelen and Scholte, 2006). However, attempts to decipher a root cause of CFS generally have been unsuccessful. This may be due in part to the lack of a single causative agent responsible for inducing the full spectrum of CFS cases. It seems more likely that

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multiple environmental factors targeting sensitive developmental processes may be important for the induction of later life CFS among susceptible genotypes. This is consistent with the emerging concept that many stress-related later-life diseases have a fetal origin (Kajantie, 2006).

Recent evidence suggests that many childhood neurobehavioral conditions such as autism (Cohly and Panja, 2005; Ashwood et al., 2006; Ponzio et al., 2007; Smith et al., 2007), autism spectrum disorders (Molloy et al., 2006) and schizophrenia (Meyer et al., 2005; Fortier et al., 2007) are linked to prenatal–perinatal immune inflammatory insult. Additionally, prenatal exposure to endocrine disrupting chemicals can wire both the immune and endocrine systems for aberrant later life responses (Fenaux et al., 2004). The developing prenatal immune system is particularly sensitive to toxicants, maternal infections and stressors making it an easy target for functional disruption. Because the immune system is responsible not only for host defense but also for homeoregulation of tissues and organs, prenatally induced insults can alter later-life function of non-immune systems (neurological, endocrine and reproductive tissues).

This paper examines the possibility that early-life immune insults (ELII) including developmental immunotoxicity (DIT) can: (1) produce immune dysfunction with immune-inflicted injury of neurological and endocrine tissues and (2) play an important role in the risk of later-life CFS. Research has shown that ELII/DIT is induced by a wide range of environmental contaminants, drugs, maternal and neonatal infections and prenatal stressors; no single environmental factor is responsible for ELII/DIT. The proposed paradigm linking ELII/DIT to CFS argues that the immune dysfunction evident in most CFS patients is not simply an outcome of this complex disease, but rather a reflection of an early-life immune insult that contributed to postnatal neurological and endocrine problems. If causative, this would suggest that better preventative protection against toxicants and other agents would be helpful and that correction of underlying ELII/DIT-associated problems should be a component of corrective therapies for CFS.

2. Age-relationships and implications for early-life CFS risk factors

Chronic fatigue syndrome is not only a disease of adults but also occurs in children and adolescents (Garrald and Rangel, 2004, 2005; Saidi and Haines, 2006; Colby, 2007). Additionally, problems in diagnosing CFS in the pediatric setting may delay recognition and treatment for children (Jason et al., 2006). Colby (2007) has discussed the problems in adequately recognizing and treating CFS in children. By definition, pediatric CFS involves early-life causative factors. Therefore, the existence of early life environmental inducers of CFS seems clear in spite of the lack of precise identification of those factors. At issue is whether the same environmental insults that cause pediatric CFS may also contribute to adult onset of the disease. If so, then those prenatal and neonatal exposures should be factored into the search for causes of adult CFS.

3. Early life link to CFS and other chronic diseases with immune-inflammatory dysfunction

One of the difficulties in deciphering cause–effect relationships among environmentally induced diseases concerns the timeline of sampling. Infectious agents and/or environmental contaminants and drugs may be important in the multifactorial etiology of CFS (Vojdani and Lapp, 1999). As a result, studies have evaluated these potential environmental factors in the context of CFS (Racciatti et al., 2001; reviewed in Devanur and Kerr, 2006; Appel et al., 2007). Frequently, the easiest measurements to obtain for investigating exposure to toxicants or infectious agents are those contemporary with CFS diagnosis and/or treatment. However, presence of a toxicant, virus or bacterium at this time may be very misleading relative to an original instigating agent for CFS. Instead, toxicant levels and/or presence of infectious agents found after disease onset may reflect one of the many outcomes of the disease rather than point toward a cause. The literature suggests that even for some neonatal-onset diseases, the most likely causative environmental event occurred earlier in life. This is one area where prospective studies that include a determination of cord blood levels of environmental chemicals and drugs can be particularly useful when paired with postnatal biomarkers of CFS. Two examples of such studies and analyses follow for the heavy metal, lead, and for polychlorinated biphenyls (PCBs). In these examples, the analyses showed that the critical window of vulnerability to the toxicants was during prenatal development as opposed to later childhood.

Much research has gone into the association of low-moderate level exposure to the heavy metal, lead, and childhood neurobehavioral toxicity including reduced I.Q. Contemporary blood lead sampling when neurobehavioral deficits are detected is obviously the most convenient and this prompted a focus on childhood exposure to lead. However, recent studies suggest that critical developmental windows for lead-induced neurological and immune toxicity occur prenatally and/or near birth (Snyder et al., 2000; Bunn et al., 2001; Annesi-Maesano et al., 2003; Ronchetti et al., 2006; Schnaas et al., 2006).

In a similar example, exposure to PCBs was found to adversely impact childhood vaccine responses in children up to 7 years of age causing a significant percentage of exposed children, in the Faroe Islands, to be effectively unprotected. But the best predictor of PCB exposure–health risk outcome was not childhood PCB levels. Instead, it was cord blood PCB levels rather than contemporary blood levels of PCBs obtained near the time of vaccination (Heilmann et al., 2006). Again, this suggests that contemporary evaluation for environmental causes of many neurological and immune-related postnatal diseases may be insensitive, at best, since the causative agent and/or its metabolites may not be among the most prominent factors detected. At worst, the later-life analysis may point in the wrong direction as per the actual risk factors for the disease.

Other examples where early-life environmental insults appear to be critical for later life diseases include: Parkinson's disease (Cory-Slechta et al., 2005; Barlow et al., 2007), autism and autism spectrum disorders (Kolevzon et al., 2007), atherosclerosis (Srivastava et al., 2007; Alkemade et al., 2007),

type 1 diabetes (Larsson et al., 2004; Peng and Hagopian, 2006), alcohol-related diseases (Ping et al., 2007; Spohr et al., 2007), asthma and other respiratory diseases (Pincus-Knackstedt et al., 2006; Yeatts et al., 2006; Penn et al., 2007), obesity (Newbold et al., 2007), hypertension (Gardner et al., 2007), kidney disease (Woods, 2007) and childhood leukemia (Pombo-de-Oliveira and Koifman, 2006; Greaves, 2006).

In the case of CFS, one or more early life events seem to be important for risk of later life CFS episodes. Heim et al. (2006) showed that early life physical or emotional trauma is a risk factor for CFS. While it is unclear if this experience alone is a cause, the finding should drive investigation of causes toward an early timeframe of vulnerability. Genetic background may also be important in determining susceptible individuals for early-life environmentally induced dysfunction. Carlo-Stella et al. (2006) found that specific polymorphisms for immune cytokine genes involving inflammation and Th cell functions were more prevalent among CFS patients than in the general population. The authors suggested that CFS patients are more likely to mount inflammatory responses to one or more environmental insults. This is significant in an early life induction scenario since mid-directed immune inflammation and aberrant homeoregulatory function of immune cells in host tissues could precipitate damage to multiple systems.

4. Environmentally induced origin of CFS dysfunction: immune, neurological and/or endocrine?

For more than two decades, immune dysfunction has been recognized as a prominent feature of CFS (Caliguri et al., 1987; Komaroff et al., 1988; Shor, 2003; Racciatti et al., 2004). Because immune cells play a critical homeoregulatory role in neurological and endocrine tissues, early life alteration of macrophages, dendritic cells or microglial cells can create dysfunction in other physiological systems. Additionally, lymphoid–epithelial secretory cell components are active in many fetal tissues as early as the second trimester of gestation (Gurevich et al., 2002). Lorton et al. (2006) describe the ability of immune cytokines such as IL-1beta and TNF-alpha to impact the neuroendocrine systems affecting neural activity, hormone release as well as sleep behavior. Additionally, examples of DIT producing neurological (Gottesfeld, 1998; Lian et al., 2004; Wang et al., 2007a,b), endocrine (Nussdorfer and Mazzocchi, 1998; Ye et al., 2004) and reproductive system (Pace et al., 2005) damage have recently come to light. Therefore, it remains a question precisely where one or more early-life environmentally induced dysfunctions arise that predispose to CFS.

Certainly neuroendocrine factors can dramatically impact immune development and function (Bellinger et al., 1992; McDade et al., 2001; Solomou et al., 2002; Land and Darakhshan, 2004). In turn, early-life timed immune inflammatory dysfunction can inflict damage on the developing neurological and endocrine systems resulting in postnatal dysfunction (Duggan et al., 2001; Stene et al., 2004; Niklasson et al., 2006; Fan et al., 2007; Wang et al., 2007a,b; Gotsch et al., 2007). However, with CFS it is not known whether early-life xenobiotic exposures target multiple physiological systems

simultaneously or whether one physiological system is targeted first and then produces a cascade of dysfunctional effects. Cleare (2004) points out that in some prospective studies of CFS, the HPA-dysfunction seen with later CFS episodes was not observed during the earliest stages of the disease. The following sections outline the evidence that prenatal–neonatal immune insults including developmental immunotoxicity is likely to be an important factor in CFS.

5. The immune insult profile linked with CFS

5.1. Overview

CFS patients have a specific immune dysfunction profile featuring enhanced baseline activation of lymphoid populations but suppression for certain immune responses. Increased baseline lymphoid activation markers (e.g. HLA Class II molecules) were reported among CFS patients in several studies (Landay et al., 1991; Barker et al., 1994). Patients' systems react as if they are continually combating an infection regardless of whether an infectious agent is actually present at the time. But when patients are challenged with stressors such as infections, production of anti-inflammatory cytokines can occur and immune responses may be blunted (Klimas et al., 1990). This pattern of dysfunction comprising a hyperinflammatory resting state and targeted immunosuppression of responses is supported by Mihaylova et al. (2007). They found that *ex vivo* mitogen stimulation of lymphocytes from CFS patients resulted in reduced expression of the T lymphocyte-Natural Killer (NK) cell activation marker, CD69. So despite the heightened baseline state of lymphocytes, the actual effectiveness of immune responses can be problematic particularly if they are Th1-driven (e.g. antiviral and anti-tumor responses) (Lloyd et al., 1992). The primary problem arising from the cytokine dysfunction is that baseline IL-6 is significantly elevated. This alone, or supported by elevated IL-1beta and possibly TNF-alpha production, induces the sickness behavior-fatigue phenotype so prevalent in CFS. But the actual profile of cytokine dysfunction seen in CFS patients is influenced, in part, by the stress/infection status of the patient at the time of sampling.

Based on the literature to date, the immune dysfunction reported in CFS patients can (1) facilitate dysfunction across physiological systems connected to immune inflammatory cell damage in early life and (2) result in numerous unintended host responses to postnatal stimuli, stress and/or infections. Chief among the inherent problems are mid-directed and mis-regulated immune inflammation. As will be discussed in more detail in following sections, the problematic inflammation is associated with tissue macrophages, as well as dendritic cells and other hematopoietically derived cells (microglial cells, Kupffer cells, alveolar macrophages, neutrophils, mast cells). These cells exhibit overproduction of anti-microbial metabolites including reactive oxygen and nitrogen intermediates which, as endogenous toxins, can oxidize macromolecules, mutagenize DNA, impair mitochondrial function and destroy bystander cells in various tissues (Espey et al., 2002; Kennedy et al., 2005; Maes et al., 2006a,b, 2007a,b; Pall, 2007). Monokine misproduction

(IL-1 β , TNF- α , IL-6) can affect many tissues, regulating both neuropeptide production (Cragnoli et al., 2006; Guo et al., 2006a) as well as adrenal function (Goshen et al., 2003; Dantzer, 2004). Dysfunctional arachidonic acid metabolism by macrophages contributes to inappropriate production of cyclooxygenase mediators of inflammation (Ben-Baruch, 2006; Olsson and Sundler, 2007; Triggiani et al., 2007; Maes et al., 2007a). This is combined with reported mast cell dysfunction and increased sensitivity for airway hyperresponsiveness (rhinitis and bronchial hyperresponsiveness) (Baraniuk and Ho Le, 2007; Nijs et al., 2003) all contributing to mis-directed inflammation at the tissue level.

5.2. Myelomonocytic cells and specific inflammatory mediator production

Numerous findings support the existence of inflammatory dysfunction as a part of CFS (Snell et al., 2005). CFS has been associated with aberrant oxygen and nitrogen radical generation and scavenging (Richards et al., 2007; Pall, 2007). With the increased free radical generation, status macromolecular targets for oxidation (DNA, cell surface lipids, etc.) should be examined. For example, lipid peroxidation has been reported to be increased in CFS (Kennedy et al., 2005). Richards et al. (2000) also reported elevated oxidative stress among CFS patients. Note that increased oxidative damage may explain the observation that heart disease and cancer are two of the three major causes of death among CFS patients (Jason et al., 2006). Increased oxidation of DNA and lipids would be expected to contribute to an increased likelihood of tumor cell formation. But this is further compounded by the likelihood of CFS-associated reduction in anti-tumor defenses. Pall (2002) found that citrulline, a product of arginine conversion to nitric oxide (NO) (via nitric oxide synthase) is elevated in the serum of CFS patients. Consistent with this observation, Fremont et al. (2006) found that inability to molecularly down-regulate chronic NO production may be a critical part of CFS. Additionally, cyclooxygenase production of prostaglandins is increased in CFS (Maes et al., 2007a). This may be due in part to reduced availability of omega-3 polyunsaturated fatty acids (Maes et al., 2005), which influence the arachidonic acid content of macrophage membranes.

6. CFS and baseline immune activation

Problems with immune activation as well as targeted immune dysfunction are common in CFS patients. Kaushik et al. (2005) point out that genes involved in immune activation were found to have altered patterns of expression in three separate studies of CFS patients. This supports an earlier report on CFS and the dysfunctional appearance of immune activation markers (Landay et al., 1991). Robertson et al. (2005) found that CFS patients had normal levels of T cells, B cells and NK cells. However, specific subsets of these immune cells were altered in representation. Resting T lymphocytes were decreased in frequency while autoantibody-associated populations of B lymphocytes were increased. Additionally, exercise performance in CFS patients has also been related to immune dysfunction (Nijs et al., 2005).

The immune activation state associated with CFS has been used as a treatment target by Vermuelen and Scholte (2006). These investigators reported success in treatment approaches designed to counter the dysfunctional activation of the immune system.

7. The inflammation–anti-inflammation dysfunctional cycle of cytokines

Cytokine perturbations are commonly observed with CFS with the most frequent observations indicating that CFS patients are elevated in production of proinflammatory cytokines particularly if they exercise significantly or encounter infections. Elevated serum tumor necrosis factor- α (TNF- α) was reported in CFS patients vs. controls by a number of investigators (Patarca et al., 1994; Moss et al., 1999; White et al., 2004). Interleukin-1 (IL-1) was also seen as elevated in both the serum of CFS patients vs. controls (Cannon et al., 1997) as well as from *ex vivo* cultures of adherent monocytes (Gimenez et al., 1999). Consistent with these observations, Chao et al. (1991) reported that *ex vivo* stimulated peripheral blood mononuclear cell (PBMC) cultures from CFS patients produced significantly increased levels of three proinflammatory cytokines TNF- α , IL-1 and IL-6 vs. controls, and Gupta et al. (1997) found similar *ex vivo* elevations for TNF- α and IL-6.

However, there are also observations suggesting that anti-inflammatory cytokines are misregulated in CFS patients. Both Chao et al. (1991) and White et al. (2004) reported dysfunction involving transforming growth factor- β (TGF- β) in CFS patients. In the first study, PBMCs from CFS patients vs. controls had elevated TGF- β production in unstimulated cells. But after LPS stimulation *ex vivo*, TGF- β production was decreased relative to that from control cells and in opposition to the pattern seen for TNF- α . Similarly, in the study by White et al. (2004), CFS patients had elevated serum levels of TGF- β vs. controls when at rest. But after exercise, CFS patients produced a prolonged increase in serum TNF- α above controls without the same magnitude of increase in TGF- β . Taken together, these results support the model that CFS patients have a propensity for overproduction of proinflammatory cytokines, particular when stressed, coupled with a misregulation of anti-inflammation cytokines. The relationship of chronic over-production of proinflammatory cytokines to the “sickness behavior” phenotype is discussed in the next section.

8. Immune cytokine-induced sickness behavior and CFS symptoms

Cytokine-induced sickness behavior is a well-recognized ramification of immune dysfunction/misregulation (Dantzer and Kelley, 2007). Gaab et al. (2005) reported that CFS patients had a misregulated pro-inflammatory cytokine response to lipopolysaccharide (LPS) where cytokine levels decreased in the stress cycle in CFS patients while they were increasing in controls. Additionally, Vollmer-Conna et al. (2004) found that both IL-1 β and IL-6 were the cytokines released *in vitro* from peripheral blood monocyte cultures in patients with “sickness behavior” following acute Q fever viral infection. Fatigue itself

appeared to be most closely associated with IL-1beta, TNF-alpha as well as IL-6. Mast cells have been suggested as a possible source of IL-1, IL-6 and TNF-alpha that could mediate HPA-axis alteration and inflammation (Theoharides et al., 2005). Haack et al. (2007) reported that IL-6 is closely associated with sleep disorders and related pain. The connection between inappropriately elevated IL-6 production and fatigue extends well beyond CFS. Transitory overproduction of the same cytokine has been associated with periods of fatigue in endurance athletes (Robson-Ansley et al., 2007).

9. Potential T helper bias

Many of the immune alterations reported for CFS are consistent with a prominent pattern of dysfunctions arising from environmental insult of the developing immune system. One of these concerns is T helper polarization. Th1-driven cell-mediated immunity has been reported to be impaired in CFS patients while Th2 cytokines are in abundance (Patarca, 2001; Skowera et al., 2004) and inflammatory cell dysfunction is prominent (Kennedy et al., 2004; Maes et al., 2007a,b). Likewise with DIT induced by certain categories of xenobiotics such as heavy metals, environmental tobacco smoke and estrogenic compounds, Th1-dependent functions and/or cytokines are suppressed relative to Th2-dependent function (Miller et al., 1998; Snyder et al., 2000; Guo et al., 2005; Cary et al., 2006; Wang and Pinkerton, 2007; Wang et al., 2007).

ter Wolbeek et al. (2007) reported that CFS patients have a Th2 biased anti-inflammatory cytokine profile with elevated IL-10 and low gamma interferon production. Th1-related cytokine production (e.g. IFN-gamma) (Visser et al., 1998) as well as reduced perforin content of NK and T cells (Maher et al., 2005) was found to be depressed in CFS patients. Additionally, the Th1-dependent delayed type hypersensitivity response is suppressed (Lloyd et al., 1992). This suggests that some anti-viral and anti-tumor responses may be reduced. Clinical improvement of CFS patients was reported in association with isoproinosine induced increases in IL-12 production as well as NK cell activity (Diaz-Mitoma et al., 2003).

The similarity between the CFS-associated immune dysfunctions and those seen in some cases of DIT (Holladay and Smialowicz, 2000; Dietert et al., 2000; Dietert and Piepenbrink, 2006; Dietert and Dietert, 2007) is striking. In the case of DIT, the pregnancy state itself helps to determine part of the immune vulnerability to *in utero* immune disruption (Lim et al., 2000). Th1 function is delayed in development due to the semi allogeneic nature of the pregnancy (Lim et al., 2000; Holt and Jones, 2000; Protonotariou et al., 2003). Among the potential outcomes seen with DIT is a postnatal Th2 bias where dendritic cell support to promote Th1 responses is blocked (Mainali and Tew, 2004; Mainali et al., 2005; reviewed in Dietert and Dietert, 2007).

Part of the Th bias reported with CFS is likely connected to dysregulated myelomonocytic metabolism and cytokine driven responses. Macrophages and dendritic cells are easy targets for early life immunotoxic disruption with the result having impact not only on innate and acquired immune responses but

also on other physiological systems (reviewed in Dietert and Piepenbrink, 2006; Dietert and Holaspple, 2007; Dietert and Dietert, 2007). Table 1 illustrates the various immune dysfunctions and problems with host resistance that are found in common between ELII/DIT and CFS. The environmental contaminants, drugs or other environmental conditions (infectious agents, stress) producing specific ELII/DIT-induced dysfunction are also indicated.

Th skewing in CFS may not be the only T cell functional alteration warranting attention. It should be noted that two important recently identified T lymphocyte populations (T regulatory cells and T17 cells) (Evans et al., 2007; Wei et al., 2007; Reynolds et al., 2007) have yet to be examined in the context of CFS.

10. Innate immunity-NK cells

Innate immunity is also affected with CFS (directly or indirectly via cytokines and immune metabolites). Alteration of NK cell numbers and/or functional activity is a common observation among CFS studies. Because NK cells are important in immune regulation as well as in innate anti-viral and tumor immunity, a reduction in NK cell activity can have implications for host resistance to certain infections as well as cancer.

NK cell cytotoxic activity is usually decreased with CFS although NK cell populations are not necessarily lower in incidence (Barker et al., 1994). Among the observations for CFS and NK cells, Ogawa et al. (1998) reported a decrease in NO-related activation of NK cells among CFS patients. Whiteside and Friberg (1998) also reported that CFS patients have low NK cell activity vs. controls. Ojo-Amaize et al. (1994) reported a correlation of low levels of NK cell activity with the severity of CFS disease. In a large multi-locale study, Stewart et al. (2003) found that NK cell incidence was significantly reduced in CFS patients. In one of the earliest CFS-immune studies, specific NK cell subsets appeared to be deficient in CFS patients (Caliguri et al., 1987).

Despite differences among studies in whether the incidence of NK cells is lower in CFS patients, most studies report that NK functional activity is depressed. This may be linked, in part, to the cytotoxic capacity among the intracellular granules of the NK cells. Both NK cells and cytotoxic T lymphocytes (CTLs) from CFS patients were found to have reduced perforin levels (Maher et al., 2005).

11. Virus infection and reactivation: CFS inducer, episode trigger, or reflection of immune status?

Many studies have reported the association of viruses with CFS but the implications relative to early-life causes of the disease are unclear. Several different types of viruses have been detected in CFS patients, but the presence of some of them may reflect that immune surveillance is depressed in CFS patients. For example, Chapenko et al. (2006) found a high incidence of herpes virus (HHV7) reactivation among CFS patients and detected dual infections with both HHV-6 and HHV-7 only in CFS patients. Similarly, Kondo (2007) suggested that herpes

Table 1
Early-life immune insults (ELII) including developmental immunotoxicity (DIT) and later-life immune dysfunctions in common with CFS

Immune-host resistance dysfunctions common to ELII/DIT and CFS	Environmental inducers of prenatal–neonatal immune dysfunction	ELII/DIT references for agent-dysfunction	CFS references for immune dysfunction
- Increased susceptibility to viruses - Reduced vaccine responses	TCDD Dexamethasone, Neonatal stress PCBs	Voderstrasse et al., 2004 Burleson et al. (2008), Avitsur et al. (2006), Heilmann et al. (2006)	Chapenko et al., 2006 Komaroff (2006), Hickie et al. (2006), Sairenji and Nagata (2007), Chia and Chia (2007)
- Impaired innate immune defenses	Maternal alcohol use Neonatal stress LPS	Gauthier et al. (2005) Avitsur et al. (2006) Hodyl et al. (2007)	Siegel et al. (2006) Iwakami et al. (2005) Kennedy et al. (2004)
- Increased risk of autoimmunity	TCDD DES Maternal infection	Mustafa et al. (2007) Brown et al. (2006) Hodyl et al. (2007)	Maes et al. (2006a) Margutti et al. (2006) Staines (2006, 2004)
- Suppressed delayed-type hypersensitivity (DTH) response	Lead TCDD	Bunn et al. (2001) Gehrs and Smialowicz (1999)	Lloyd et al. (1992)
- Suppressed cytotoxic T lymphocyte (CTL) activity	Maternal smoking TCDD Dexamethasone	Ng et al. (2006) Voderstrasse et al. (2004) Burleson et al. (2008)	Maher et al. (2005) Mihaylova et al. (2007)
- Th2 bias for cytokines/immune responses	Lead Mercury Environmental tobacco smoke	Miller et al. (1998) Silva et al. (2005) Wang et al. (2007)	Patarca-Montero et al. (2001)
- Reduced NK cell activity	Cadmium Alcohol	Pillet et al. (2005) Arjona et al. (2006)	Maher et al. (2005) Mihaylova et al. (2007), Stewart et al. (2003), Suhadolnik et al. (2004)
- Myelomonocytic dysfunction and inflammation (ROI, NO, PGs)	Pesticides Lead LPS Maternal infection Alcohol Maternal smoking	Theus et al. (1992) Miller et al. (1998) Boisse et al. (2004) Pang et al. (2005) Ping et al. (2007) Noakes et al. (2007)	Kennedy et al. (2005) Maes et al. (2005) Maes et al. (2007a,b) Kennedy et al. (2004) Richards et al. (2000) Jammes et al. (2005)

PCBs, polycyclic chlorinated biphenyls; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LPS, lipopolysaccharide; DES, diethylstilbesterol; NK, natural killer; ROI, reactive oxygen intermediates; NO, nitric oxide; PGs, prostaglandins.

virus7 (HHV-7) reactivation is a biomarker in CFS patients. Epstein–Barr virus latency has been suggested as a feature of CFS (Glaser and Kiecolt-Glaser, 1998) and Glaser et al. (2005) suggested that Epstein–Barr virus-encoded proteins may induce the specific cytokines and the sickness behavior symptoms observed with CFS. Lane et al. (2003) reported that a high proportion of CFS patients have enterovirus sequences in their muscle tissue and Chia (2005) recently reviewed the association of enteroviruses with CFS. Among other viruses, parvovirus B19 has also been reported in CFS patients (Kerr et al., 2002). Finally, co-infection of several agents in CFS patients was reported by Nicolson et al. (2003).

The detection of a diverse range of viruses including herpes virus reactivation with CFS is reminiscent of the proposed relationship between forms of childhood leukemia and viral infections. In those cases, common infectious agents have been suggested as a trigger for childhood leukemia brought about through a dysfunctional immune response to the agent. It is the dysfunctional immune response that is key rather than a truly novel infection (Greaves, 2006).

It seems likely the situation is similar with CFS where infectious agents are either a postnatal trigger of a CFS episode, as discussed by Chapenko et al. (2006), or, in the case of HHV 6 reactivation, this can occur with targeted immunosuppression (Humar et al., 2002; Deborska et al., 2003; Hentrich et al., 2005) and may be a reflection of immune dysfunction in CFS patients. But that does not imply that an original infection was necessarily the early-life cause of CFS. Komaroff (2006) found HHV 6 in a subset of CFS patients. Therefore, the question remains whether HHV 6 reactivation may trigger CFS episodes in a subset of patients or that viral reactivation is yet another outcome of a CFS episode triggered by other environmental agents or conditions.

12. Multi-factorial inducers of CFS—a possible model

Childhood trauma seems to be important in the development of CFS (Heim et al., 2006). This trauma frequently takes the form of violence/abuse among susceptible genotypes (Crofford, 2007). Fig. 1 illustrates a proposed model for CFS risk factors

Risk Factors for Chronic Fatigue Syndrome

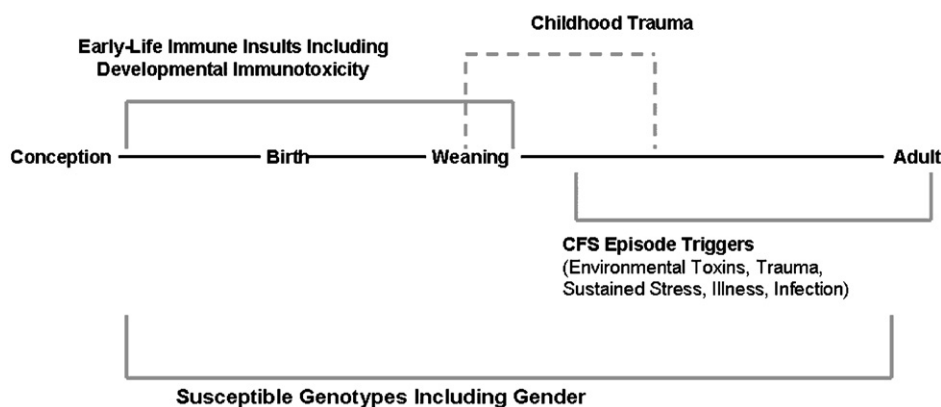


Fig. 1. Proposed model for risk factors of chronic fatigue syndrome (CFS) incorporating early life immune insults (ELII) including developmental immunotoxicity (DIT). Potential multi-factorial risk factors for CFS are shown above the developmental timeline. *In utero* or postnatal exposure to environmental chemical, drugs, infectious agents or other stressors induces adverse immune alterations. A major postnatal stress such as childhood trauma would fix the earlier life physiological disruption in the form of CFS. Additional childhood or adult triggers such as exposure to infectious agents, toxicants, or other stressors are necessary to elicit disease onset. Genetic background including gender plays a role as shown below the developmental timeline. This would determine the susceptible subset of the population where exposure to the risk factors would manifest as this disease.

which includes a prenatal or neonatal immune insult (toxicant, infectious agent, stress) followed by a childhood trauma event that fixes the aberrant immune, endocrine and neurological system responses in the form of CFS. The potential importance of a prior prenatal–neonatal immune insult is a new feature. Certainly not all children who experience trauma develop CFS. In this proposed model, early immune disruption via ELII/DIT would set the palette for a CFS outcome in certain genotypes. Post-trauma exposure to precipitating environmental factors (De Becker et al., 2002) would then instigate the CFS episodes in the child or adult.

13. Conclusions

As detailed in this paper, an increasing number of later-life diseases with dysfunction of the immune, neurological and/or endocrine systems have been found to have early-life origins. An accumulation of information suggests that CFS may have an early-life risk component similar to those found with autism, schizophrenia, Parkinson’s disease, type 1 diabetes, childhood asthma and allergies and childhood leukemia. Prenatal and early postnatal exposure to various environmental factors (environment contaminants, drugs, infectious agents, physical stressors) can produce several adverse immune outcomes of potential importance for CFS. It seems likely there is no single environmental “cause” of CFS.

Many early life exposures result in a continuation of a “fetal type” of immune balance in the offspring, often with misregulated inflammation (reviewed in Dietert and Dietert, 2007), and/or can produce a latent immune dysfunction in which the immune system has been completely rewired by the prenatal insult (Fenaux et al., 2004). In the latter case, later-life environmental exposures or stressors will trigger aberrant and unpredicted immune responses. As shown in Table 1, the spec-

trum of immune alterations associated with CFS bears a striking resemblance to those reported in many cases of DIT (Holladay, 2005; Ng et al., 2006; Luebke et al., 2006; Dietert and Dietert, 2007) as well as for other environmental factors (Boisse et al., 2004; Avitsur et al., 2006; Hodyl et al., 2007). These include misdirected and misregulated inflammation, innate immune alterations, cytokine skewing as well as skewing of T-dependent immune responses. Among the categories of xenobiotics shown in Table 1 and of particular interest relative to CFS are: heavy metals, pesticides, halogenated aromatic hydrocarbons, alcohol, environmental tobacco smoke, estrogenic compounds and corticosteroids.

Most of the research concerning environmental factors and CFS has focused on agents and biomarkers identified contemporary with CFS diagnosis. But this has potential pitfalls in determining disease origin. Recent lessons from PCB-associated immunotoxicity in children (Heilmann et al., 2006) and toxicant-induced neurobehavioral alterations (Schnaas et al., 2006; Torres-Sanchez et al., 2007) indicate that exposure during prenatal critical windows may be more important for producing certain later-onset diseases. Additionally, CFS has now become a disease of pediatric concern. It is not clear if the increased diagnosis of the disease in children reflects: (1) an actual increase in incidence, (2) recent recognition by the medical field that children can and do have CFS or (3) the application of an improved set of diagnostic criteria among pediatricians. Nevertheless, given the recognition of CFS among the pediatric population, an enhanced search for early-life risk factors is needed.

In general, safety screening of drugs and chemicals has proven effective in identifying those immunotoxic agents capable of producing profound and widespread immunosuppression across age groups. However, the same system of screening used for the primary purpose of detecting profound immunosuppression was not designed to optimize detection of xenobiotics

producing far more subtle effects on the prenatal and neonatal immune system (including inappropriate immune activation, functional bias and misdirected inflammation). Yet, these types of adverse immune effects are important in risk of chronic disease (e.g. allergy, asthma, autoimmunity, etc.). Therefore, improved surveillance for toxicants adversely affecting the immune system in early life may be helpful in avoiding problematic exposures and reducing the risk of diseases like CFS.

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