Childhood stressors in the development of fatigue syndromes: a review of the past 20 years of research

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Background. Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are both highly prevalent conditions associated with extreme disability and with the development of co-morbid psychiatric disorders, such as depression and anxiety. Childhood stressors have been shown to induce persistent changes in the function of biological systems potentially relevant to the pathogenesis of both CFS and FM, such as the inflammatory system and the hypothalamic-pituitary-adrenal (HPA) axis. In this review, we examined whether multiple forms of childhood stressors are contributing factors to the development of these disorders, and of the associated psychiatric symptoms.

Method. Using PubMed, we identified 31 papers relevant to this narrative review. We included cohort studies and case-control studies, without any exclusion in terms of age and gender. No study characteristics or publication date restrictions were imposed.

Results. Most studies across the literature consistently show that there is a strong association between experiences of childhood stressors and the presence of CFS and FM, with rates of CFS/FM being two- to three-fold higher in exposed than in unexposed subjects. We also found evidence for an increased risk for the development of additional symptoms, such as depression, anxiety and pain, in individuals with CFS and FM with a previous history of childhood stressors, compared with individuals with CFS/FM and no such history.

Conclusions. Our review confirms that exposure to childhood stressors is associated with the subsequent development of fatigue syndromes such as CFS and FM, and related symptoms. Further studies are needed to identify the mechanisms underlying these associations.

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Key words: Anxiety, childhood abuse, childhood maltreatment, chronic fatigue syndrome, chronic pain, depression, fibromyalgia, stress.

Introduction

Chronic fatigue syndrome (CFS) is a debilitating and complex disorder, relatively common in adults and associated with a myriad of symptoms (Kawatani et al. 2011). This condition, also known as myalgic encephalomyelitis (ME), is characterized by persistent severe fatigue, unrelated to exertion and not relieved by rest, that lasts at least 6 months and is associated with muscle/joint pain, significant impairment of short-term memory, poor concentration and disturbed sleep (Reeves et al. 2003; Sanders & Korf, 2008; CDC, 2012a). Overall, evidence suggests a population prevalence of at least 0.2–0.4% (NICE, 2007). Individuals with a diagnosis of CFS generally experience physical impairments and difficulties in cognitive and psychological functioning (Brooks et al. 2011), which contribute to considerable personal suffering and a decreased quality of life (Solomon et al. 2003). Fibromyalgia (FM) is also a common condition that, like CFS, is concomitant with a myriad of symptoms, including chronic widespread pain, muscular stiffness, debilitating fatigue, cognitive and mood dysfunction, and sleep disturbance (CDC, 2012b; Low & Schweinhardt, 2012; Sommer et al. 2012). Despite the high incidence of these conditions, a vast proportion of patients presenting with chronic fatigue, pain and cognitive dysfunctions do not show specific organic abnormalities (Kroenke & Mangelsdorff, 1989; Cho et al. 2006; Henningsson et al. 2007). Studies have assessed the involvement of psychological, social and biological factors (Wessely, 1998; Lyall et al. 2003; Caseras et al. 2006, 2008).

Both CFS and FM are known to be associated with other co-morbid psychiatric disorders (Wolfe, 1997; Van Houdenhove et al. 2005). Indeed, the prevalence...
of both depression and anxiety is high in CFS and FM patients (Wessely & Powell, 1989; McBeth & Silman, 2001; Chou, 2013), and a recent study in a sample of 640 CFS patients found that 14% of patients had an anxiety disorder, 14% had a depressive disorder and 18% had both depression and anxiety disorders (Cella et al. 2013). A previous study in FM found that 57% of patients reported concurrent depression (Okifuji et al. 2000) and another study reported that a quarter had a current depressive episode and two-thirds a prior depressive episode (Epstein et al. 1999).

One risk factor suggested as being relevant to the onset of these disorders is the occurrence of childhood stressors. Childhood stressors, especially maltreatment and abuse, are highly prevalent in the general population: for example, a 2009 meta-analysis, examining 65 studies from 22 countries, reported the global prevalence of childhood sexual abuse (CSA) as 19.7% for females and 7.9% for males (Pereda et al. 2009). In addition, a UK survey of 2869 young adults found that maltreatment (both intra- and extra-familial) was experienced by 16% of the sample, with 11% of respondents reporting experiences of more severe forms of sexual abuse (May-Chahal & Cawson, 2005). Several review studies have shown that individuals who suffer childhood abuse are more likely to be depressed, to experience other types of psychiatric disorders, and to have more physical symptoms (Arnouw, 2004; Maniglio, 2009). In fact there is now a wealth of evidence confirming childhood abuse as a vulnerability factor for adulthood depression (Chen et al. 2010; Danese & McEwen, 2012) and anxiety (Sareen et al. 2013), and also for somatoform disorders (Lampe et al. 2003). With specific relevance to patients with fatigue syndromes, CFS patients have a high prevalence of stressful life events (Johnson et al. 1999), and a history of childhood abuse in FM patients has been associated with more severe physical symptoms and greater functional disability (Walen et al. 2001). Indeed, there is some evidence to suggest that a history of childhood abuse may play an important role in the development and severity of both CFS (Johnson et al. 2010) and FM (Van Houdenhove et al. 2005). A review by Häuser et al. (2011), assessing emotional, physical and sexual abuse during childhood in FM patients, found a significant correlation between all three types of abuse and FM. This association is particularly relevant from a mechanistic point of view because childhood abuse has been shown to induce changes in the function of biological systems, such as the inflammatory system and the hypothalamic–pituitary–adrenal (HPA) axis (Danese & McEwen, 2012), which have been found to be abnormal in patients with CFS (Fuute et al. 2008).

The aim of this review was to summarize the existing literature about the association between multiple forms of childhood abuse and CFS or FM. As mentioned, there is one existing review on the association between emotional, physical and sexual abuse during childhood in FM patients (Häuser et al. 2011). However, in this review we have also included two other types of childhood abuse (emotional and physical neglect), and have reviewed studies in both CFS and FM patients. Moreover, we looked at the clinical symptoms associated with the occurrence of childhood abuse in these patients, including depression, anxiety and pain.

Method

We performed a search of the literature using PubMed and considering cohort studies and case-control studies without any exclusion in terms of age and gender. Keywords included: ‘childhood abuse’ or ‘childhood trauma’; ‘chronic fatigue syndrome’ or ‘fibromyalgia’ or ‘myalgic encephalomyelitis’ or ‘chronic pain’. No study characteristics or publication date restrictions were imposed. Papers concerning animal models were excluded. The search was limited to English-language studies. We identified a total of 31 papers, three of which were identified from references.

Results

We identified seven papers regarding CFS, 21 papers regarding FM, and three papers that considered both CFS and FM.

Childhood stressors and CFS

Childhood sexual and physical abuse

Ten studies examined the association between childhood sexual and/or physical abuse, and CFS (Table 1). Among these, four were case-control studies. The first two studies, conducted by Taylor & Jason (2001) and Heim et al. (2006), reported a higher incidence of childhood sexual (range 16–28% v. 2–10%) and physical abuse (range 28–29% v. 5–9%) in CFS patients than in controls. More recently, these results were replicated in studies by Heim et al. (2009) and Heins et al. (2011), where CFS patients were again found to be more likely to report a previous history of childhood sexual (range 10–33% v. 4–11%) and physical abuse (range 6–33% v. 1–10%) when compared with control subjects.

Some studies investigated CFS-only populations or used non-healthy comparison samples with medical conditions, and reported similarly high rates of childhood sexual and physical abuse. Tietjen et al. (2010)
Table 1. Studies examining the association between childhood stressors and chronic fatigue syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Sample</th>
<th>Clinical measurements</th>
<th>Sexual and/or physical abuse</th>
<th>Emotional abuse</th>
<th>Emotional and/or physical neglect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al. (2011)</td>
<td>Longitudinal cohort</td>
<td>127 CFS, 241 CFS-like illness</td>
<td>Self-reported diagnoses of CFS, GHQ-12, Malaise Inventory, Self-reported childhood sexual and physical abuse</td>
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<tr>
<td>Heim et al. (2006)</td>
<td>Case-control</td>
<td>43 CFS, 60 controls</td>
<td>SF-36, MFI, CDC Symptom Inventory, CTQ</td>
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<tr>
<td>Heim et al. (2009)</td>
<td>Case-control</td>
<td>113 CFS, 124 controls</td>
<td>SF-36, MFI, CDC Symptom Inventory, CTQ</td>
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<tr>
<td>Heins et al. (2011)</td>
<td>Case-control</td>
<td>216 CFS, 227 controls</td>
<td>CTQ-SF, CIS, SIP, SF-36</td>
<td>↑</td>
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<tr>
<td>Johnson et al. (2010)</td>
<td>Longitudinal cohort</td>
<td>93 CFS</td>
<td>Wesely and Powell’s attribution scale, CTQ-SF (Wessely &amp; Powell, 1989)</td>
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<tr>
<td>Kempke et al. (2013)</td>
<td>Cross-sectional</td>
<td>90 CFS</td>
<td>CDC Symptom Inventory, CTQ</td>
<td>↑</td>
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<tr>
<td>Post et al. (2013)</td>
<td>Longitudinal cohort</td>
<td>968 patients with bipolar disorder</td>
<td>tCAS</td>
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<tr>
<td>Taylor &amp; Jason (2001)</td>
<td>Case-control</td>
<td>32 CFS, 47 controls</td>
<td>The CFS Screening Questionnaire, SPAQ</td>
<td>↑</td>
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<tr>
<td>Tietjen et al. (2010)</td>
<td>Cross-sectional</td>
<td>1348 migraine patients</td>
<td>Self-reported physician-diagnosed history of CFS, CDC Symptom Inventory, CTQ</td>
<td>↑</td>
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<td>↑</td>
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<tr>
<td>Van Houdenhove et al. (2001)</td>
<td>Cross-sectional</td>
<td>95 CFS/FM, 52 RA/MS, 95 controls</td>
<td>CDC Symptom Inventory, ACR criteria, Questionnaire on Burdening Experience</td>
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CFS, Chronic fatigue syndrome; GHQ-12, 12-item General Health Questionnaire; SF-36, Medical Outcomes Study Short Form 36-item Health Survey; MFI, Multidimensional Fatigue Inventory; CDC, Centers for Disease Control and Prevention; CTQ, Childhood Trauma Questionnaire; CTQ-SF, Childhood Trauma Questionnaire Short Form; CIS, Checklist Individual Strength; SIP, Sickness Impact Profile; tCAS, total childhood adversity score; SPAQ, Sexual and Physical Abuse Questionnaire; ACR, American College of Rheumatology; FM, fibromyalgia; RA, rheumatoid arthritis; MS, multiple sclerosis; ↑, high prevalence of childhood abuse; ↓, low prevalence of childhood abuse.
showed that a large percentage of patients with CFS reported a history of childhood sexual or physical abuse (35% and 26.5% respectively). These results are supported by a study investigating the prevalence of childhood sexual and physical abuse in CFS patients compared with patients with CFS-like illness; Clark et al. (2011) demonstrated that childhood sexual and physical abuse were both associated with the development of CFS. Other studies have also found a high prevalence of a previous history of childhood sexual (17.8%) (Kempke et al. 2013) and physical abuse (range 15–25%) in CFS patients (Johnson et al. 2010; Kempke et al. 2013). Finally, a study investigating a sample of 58 CFS patients found a significant association between a previous history of childhood physical abuse and diagnosis of CFS (Post et al. 2013).

To our knowledge only one study has reported conflicting evidence. In a sample of 95 patients suffering from CFS or FM, 52 with reumatoid arthritis (RA) or multiple sclerosis (MS), and 95 healthy controls, Van Houdenhove et al. (2001) demonstrated that CFS or FM patients had a lower prevalence of childhood victimization, including childhood sexual, physical and emotional abuse, and physical and emotional neglect, when compared with RA/MS patients and healthy controls; however, the results were not significant (14% v. 17% v. 20%).

Childhood emotional abuse

Among the above-mentioned papers, six assessed the association between childhood emotional abuse and CFS (Table 1). Two case-control studies reported that subjects with CFS had a higher prevalence of childhood emotional abuse when compared with healthy controls (range 13–42% v. 4–20%) (Heim et al. 2006, 2009; Heins et al. 2011). Some studies have investigated CFS-only populations, without including a control group. Tietjen et al. (2010) showed that 53% of CFS patients experienced childhood emotional abuse. Similarly, two descriptive studies demonstrated a high prevalence of previous episodes of childhood emotional abuse in patients with a diagnosis of CFS (range 24–38%) (Johnson et al. 2010; Kempke et al. 2013).

Childhood emotional and physical neglect

Six of the above-mentioned papers assessed the association between childhood emotional and/or physical neglect, and CFS (Table 1). Three case-control studies showed that subjects with CFS have significantly higher rates of both childhood emotional (range 24–60% v. 8–28%) and physical neglect (range 13–25% v. 3–7%) when compared with healthy controls (Heim et al. 2006, 2009; Heins et al. 2011). Other studies have also investigated this association. Tietjen et al. (2010) demonstrated that a large proportion of patients with CFS reported a history of childhood emotional (45.6%) and physical neglect (32%). Two more studies reported a high prevalence of childhood emotional (range 31–37%) (Johnson et al. 2010; Kempke et al. 2013) and physical neglect (14%) in patients with a diagnosis of CFS (Johnson et al. 2010).

Childhood stressors and FM

Childhood sexual and physical abuse

Twenty-four studies have examined the association between childhood sexual and/or physical abuse, and FM (Table 2). Among these, six were case-control studies. Three studies reported a higher incidence of childhood sexual abuse (range 37% v. 8–22%) and physical abuse (range 34% v. 4–12%) in FM patients than in controls (Boisset-Pioro et al. 1995; Ruiz-Perez et al. 2009; Smith et al. 2010). Anderberg et al. (2000) also demonstrated that FM patients had a higher prevalence of childhood sexual (7.5% v. 5%) and physical or psychological abuse (27.5% v. 13%) than patients without a history of abuse. In two other case-control studies, FM patients were more likely to report a previous history of childhood sexual (10.5% v. 0) (Imbierowicz & Egle, 2003) and physical abuse (42% v. 34%) (Ciccone et al. 2005) when compared with controls.

Ten studies have investigated FM-only populations, without including a control group, and reported similarly high rates of childhood sexual and physical abuse. Malleson et al. (1992) showed that, in a sample of 81 children with diffuse idiopathic pain, 35 patients fulfilled criteria for FM diagnosis and 7% of patients also had a previous history of CSA. However, the authors did not specify whether patients reporting CSA were also diagnosed with FM. In addition, Goldberg et al. (1999) reported that 65% of FM patients had a previous history of CSA and 47% experienced childhood physical abuse. Four more studies reported a high prevalence of childhood sexual (range 11–33%) and physical abuse (range 11–55%) in FM patients (Bell et al. 2004; Weissbecker et al. 2006; Pae et al. 2009; Kosseva et al. 2010). Similarly, in a sample of 88 FM patients, 8% were reported to have a previous history of sexual abuse and 16% experienced severe physical abuse, in childhood or adulthood (Häuser, 2005). Accordingly, in a sample of 26 FM patients, five patients experienced episodes of childhood sexual or physical abuse (McLean et al. 2006). However, the authors did not report the specific percentage for...
each type of abuse separately. Tietjen et al. (2010) demonstrated that a large percentage of patients with FM had a history of childhood sexual (39%) and physical abuse (27%). More recently, Loevinger et al. (2012) found that 19 out of 107 FM patients had a high total mean score (of 77.2) on the childhood trauma questionnaire (CTQ; Bernstein & Fink, 1998), but the specific results for the childhood sexual and physical abuse subscale were not reported.

These results are supported by three studies investigating the prevalence of CSA in FM patients compared with patients with RA or osteoarthritis (OA). In the first study, Walker et al. (1997) found a higher mean score on the childhood sexual (15.0 v. 10.4) and physical abuse (15.3 v. 10.9) subscale of the CTQ in FM patients when compared with RA patients (Walker et al. 1997). Moreover, FM patients were more likely to report a history of sexual (51% v. 32%) and physical abuse (39% v. 16%) during childhood or adulthood, and also increased duration of sexual abuse when compared to RA patients (Carpenter et al. 1998). More recently, Nicolson et al. (2010) demonstrated that FM patients had a higher mean score on the CSA subscale of the CTQ when compared with OA patients (8.9 v. 6.7). However, when considering any experience of childhood physical abuse, Nicolson et al. (2010) found was no difference between the two groups (3.9 v. 3.9).

Several studies have investigated female-only populations and found similar results. Finestone et al. (2000) showed that women who had experienced CSA had a greater risk of FM diagnoses than non-abused control patients (23% v. 8%). In a sample of 62 adolescent female in-patients from a psychiatric unit, CSA was assessed in patients who also met criteria for juvenile primary fibromyalgia syndrome (JPFS; Lommel et al. 2009). The authors found a higher prevalence of CSA in JPFS patients than in patients without JPFS (416% v. 286%). Sigurardottir & Halldorsdottir (2013) investigated a sample of seven women who had experienced CSA and reported that five out of seven women also had FM. Finally, a study investigating a sample of 29 FM patients did not find any association between a previous history of childhood physical or sexual abuse and diagnosis of FM (Post et al. 2013). However, the study did report a significant relationship between the total childhood adversity score (ICAS), including childhood sexual and physical abuse, and the overall number of co-morbidities, including irritable bowel syndrome and diabetes.

To our knowledge only one study has reported conflicting evidence. The case-control study of Ciccone et al. (2005) provided no evidence for a significant increase in CSA in the FM group when compared with controls (26.9% v. 30.2%).

Childhood emotional abuse

Among the papers discussed, eight assessed the relationship between childhood emotional abuse and FM (Table 2). Three studies assessed a previous history of emotional abuse using the CTQ. Specifically, Walker et al. (1997) report a higher mean CTQ score on the childhood emotional abuse subscale in FM patients when compared with RA patients (15.3 v. 11) (Walker et al. 1997). A later study by Nicolson et al. (2010) demonstrated that FM patients had a higher mean score when compared with OA patients (11.4 v. 9.0). More recently, the descriptive study by Loevinger et al. (2012) found that 19 out of 107 FM patients had a considerably high total mean score on the CTQ (77.2); however, the authors did not report the specific result for the childhood emotional abuse subscale.

In line with previous reports, other studies have investigated this association and found similar outcomes. Smith et al. (2010) showed that FM patients had a higher prevalence of childhood emotional abuse (58.5% v. 18%) when compared with controls, and Kosseva et al. (2010) found that 16% of FM patients reported experiencing severe childhood emotional abuse. Lastly, Tietjen et al. (2010) demonstrated that a large percentage of patients with FM had a history of childhood emotional abuse (54%).

By contrast, the descriptive study by Weissbecker et al. (2006) found a low mean CTQ score for FM patients (10.6) when considering childhood emotional abuse. However, their results were still higher than scores reported for a female normative Health Maintenance Organization (HMO) sample (Bernstein & Fink, 1998). Lastly, Ruiz-Perez et al. (2009) report a similar prevalence of childhood emotional abuse in FM patients when compared with controls without a diagnosis of FM (15.5% v. 17%).

Childhood emotional and physical neglect

Eight papers also assessed the association between childhood emotional and/or physical neglect, and FM (Table 2). Three papers used the CTQ to assess these specific forms of abuse. Walker et al. (1997) found a higher mean score on the childhood emotional (49.2 v. 34.3) and physical (5.0 v. 3.7) neglect subscales in FM patients than in RA patients. In addition, Nicolson et al. (2010) found that FM patients had a higher mean CTQ score on the childhood emotional neglect subscale when compared with OA patients (10.7 v. 9.5). However, when looking at the childhood physical neglect subscale, the authors did not find any difference between the two groups (7.1 v. 7.1) (Nicolson et al. 2010). Lastly, as mentioned, Loevinger et al. (2012) found that 19 out of 107 FM patients had
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Sample</th>
<th>Clinical measurements</th>
<th>Sexual and/or physical abuse</th>
<th>Emotional abuse</th>
<th>Emotional and/or physical neglect</th>
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</thead>
<tbody>
<tr>
<td>Anderberg et al. (2000)</td>
<td>Case-control</td>
<td>40 FM, 38 controls</td>
<td>All FM patients fulfilled ACR criteria, Self-made questionnaire on childhood abuse</td>
<td>↑</td>
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<td>Bell et al. (2004)</td>
<td>Longitudinal cohort</td>
<td>53 FM</td>
<td>Physician diagnosis of FM, CECA.Q</td>
<td>↑</td>
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<td>Boisset-Pioro et al. (1995)</td>
<td>Case-control</td>
<td>83 FM, 161 controls</td>
<td>Questionnaire (short version of interviews on abuse of the NPSC)</td>
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<td>Carpenter et al. (1998)</td>
<td>Cross-sectional</td>
<td>205 FM, 84 RA</td>
<td>Self-made questionnaire on childhood abuse</td>
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<tr>
<td>Ciccone et al. (2005)</td>
<td>Case-control</td>
<td>52 FM, 53 controls</td>
<td>Sexual and Physical Abuse Interview</td>
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<tr>
<td>Finestone et al. (2000)</td>
<td>Cross-sectional</td>
<td>26 women with history of CSA, 54 controls</td>
<td>MPI, CSA questionnaire</td>
<td>↑</td>
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<tr>
<td>Goldberg et al. (1999)</td>
<td>Cohort</td>
<td>91 patients with chronic pain</td>
<td>CHQ, Childhood Traumatic Events Scale, McGill Melzack Pain Questionnaire, PDI</td>
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<tr>
<td>Häuser et al. (2005)</td>
<td>Cohort</td>
<td>88 FM</td>
<td>All FM patients fulfilled ACR criteria, CTQ</td>
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<tr>
<td>Imbierowicz &amp; Egle (2003)</td>
<td>Case-control</td>
<td>38 FM, 71 somatoform pain disorders, 44 controls</td>
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<tr>
<td>Kosseva et al. (2010)</td>
<td>Cohort</td>
<td>293 FM</td>
<td>CTQ</td>
<td>↑</td>
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<tr>
<td>Loevinger et al. (2012)</td>
<td>Cross-sectional</td>
<td>107 FM</td>
<td>All FM patients fulfilled ACR criteria, CTQ</td>
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<td>Lommel et al. (2009)</td>
<td>Cohort</td>
<td>62 adolescent females assessed for JPS</td>
<td>CSI, FIQ-C, YSR, PSQ</td>
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<td>Malleson et al. (1992)</td>
<td>Longitudinal cohort</td>
<td>81 RA</td>
<td>Yunus and Masi criteria for JPS</td>
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<td>McLean et al. (2006)</td>
<td>Cross-sectional</td>
<td>26 FM</td>
<td>All FM patients fulfilled ACR criteria, CIDI</td>
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<td>(sexual abuse) (= (physical abuse) (physical neglect))</td>
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<tr>
<td>Nicolson et al. (2010)</td>
<td>Longitudinal cohort</td>
<td>35 FM, 35 OA</td>
<td>CTQ-SF</td>
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<tr>
<td>Pae et al. (2009)</td>
<td>Longitudinal cohort</td>
<td>112 FM</td>
<td>Sexual and Physical Abuse Questionnaire, FIQ</td>
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<tr>
<td>Post et al. (2013)</td>
<td>Longitudinal cohort</td>
<td>968 patients with bipolar disorder</td>
<td>tCAS</td>
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<tr>
<td>Ruiz-Perez et al. (2009)</td>
<td>Case-control</td>
<td>287 FM, 287 controls</td>
<td>All FM patients fulfilled ACR criteriaSelf-made questionnaire (based on WHO Multi-Country Study on Women’s Health and Life Events)</td>
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A considerable high total mean CTQ score but they did not report the specific score on the childhood emotional and physical neglect subscales. Four other studies were able to replicate these results. Anderberg et al. (2000) demonstrated that FM patients had a higher prevalence of childhood neglect when compared with controls (17.5% vs. 8%), but the authors did not specifically assessed physical and emotional neglect. Tietjen et al. (2010) found that a large percentage of patients with FM had a history of childhood emotional (47%) and physical neglect (32%). Similarly, Bell et al. (2004) and Kosseva et al. (2010) found a high prevalence of childhood emotional (range 25–46%) and physical neglect (range 6–13%) among FM patients. By contrast, the descriptive study conducted by Weissbecker et al. (2006) found unclear evidence, as mentioned earlier, reporting a low mean CTQ score for FM patients when considering childhood emotional (12.6) and physical (10) subscales. However, when compared with controls (17.5% vs. 8%), the authors did not specifically assessed physical and emotional neglect. Tiefen et al. (2010) found a high prevalence of childhood emotional (range 25–46%) and physical neglect (range 6–13%) among FM patients.

<table>
<thead>
<tr>
<th></th>
<th>Study Type</th>
<th>Sample Description</th>
<th>CTQ Score for FM Patients</th>
<th>CTQ Score for Controls</th>
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<tbody>
<tr>
<td>Sigurdardottir &amp; Halkjordottir (2013)</td>
<td>Longitudinal cohort</td>
<td>Seven women with CSA history</td>
<td>Sexual Abuse Interview</td>
<td>Rheumatologist confirmation of diagnoses history of FM, Questionnaire (standardized self-report measures of civilian trauma)</td>
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<tr>
<td>Smith et al. (2010)</td>
<td>Case-control</td>
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<td>Self-reported physician-diagnosed history of FM, CDC Symptom Inventory, CTQ</td>
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<td>Walker et al. (1997)</td>
<td>Cohort</td>
<td>36 FM, 33 RA</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Weissbecker et al. (2006)</td>
<td>Cohort</td>
<td>85 FM</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

FM, Fibromyalgia; ACR, American College of Rheumatology; CECAQ, Childhood Experience of Care and Abuse Questionnaire; NPSC, National Population Survey of Canada; RA, rheumatoid arthritis; MPI, McGill Pain Questionnaire; CHQ, Childhood History Questionnaire; PDI, Pain Disability Index; CTQ, Childhood Trauma Questionnaire; SBI-P, Structural Biographical Interview for Pain Disorders; ACE, Adverse Childhood Experiences Questionnaire; VAS, Visual Analogue Scale; JPFS, juvenile primary fibromyalgia syndrome; CS, Children’s Somatization Inventory; FIQ-C, Fibromyalgia Impact Questionnaire for Children; YSR, Achenbach Youth Self Report; PSQ, Pain Symptom Questionnaire; CID, Composite International Diagnostic Interview; OA, osteoarthritis; CTQ-SF, Childhood Trauma Questionnaire Short Form; FIQ, Fibromyalgia Impact Questionnaire; ICAS, total childhood adversity score; WHO, World Health Organization; CSA, childhood sexual abuse; CDC, Centers for Disease Control and Prevention; CMI, Child Maltreatment Interview; ↑, high prevalence of childhood abuse; ↓, low prevalence of childhood abuse; =, no difference in prevalence of childhood abuse.
the interaction between childhood abuse and pain in patients with FM (Table 3). In the study by Walker et al. (1997), a significant association was found between childhood abuse, including sexual, physical and emotional abuse, and physical and emotional neglect, and pain symptoms, in FM patients when compared to RA patients. In a sample of seven women with a history of CSA, five were diagnosed with FM and all seven suffered chronic and widespread pain (Sigurdardottir & Halldorsdottir, 2013).

Discussion

This review presents the current literature on the relationship between multiple forms of childhood stressors and the fatigue syndromes, CFS and FM. Our results highlight a strong relationship between experiences of childhood abuse and the occurrence of CFS and FM. However, when looking at a specific type of abuse, such as CSA, and the presence of CFS/FM, only two studies have reported conflicting evidence. The first study by Van Houdenhove et al. (2001) demonstrated that CFS or FM patients had a lower prevalence of childhood victimization, including CSA, when compared with RA/MS patients and healthy controls. This inconsistent result may be attributed mainly to the administration of a specific questionnaire when assessing experiences of CSA, the Questionnaire on Burdening Experiences, which has not been validated according to international standards. Similarly, the second study, by Ciccone et al. (2005), provided no evidence for a significant increase in CSA in the FM group when compared with controls. In this case, one of the major causes of this contrasting finding may be due to the inclusion in both groups (FM patients and controls) of subjects with co-morbid depression, which might partly explain the increased rate of childhood trauma in the controls. Aside from those two studies, overall our findings confirm and extend evidence linking early life experience and CFS/FM, also providing evidence for an association between childhood abuse and other co-morbid symptoms, such as depression, anxiety and pain, in individuals with CFS and FM.

There may be several underlying mechanisms driving the association between childhood abuse and a higher prevalence of CFS and FM. We focus on two, not mutually exclusive, possible biological mechanisms linking a history of childhood stressors and the increased risk of CFS/FM: increased inflammation and abnormal HPA axis activity (Fig. 1); however, it is important to stress that the biological substrates of CFS and FM are still unclear. Moreover, we cannot exclude the possibility that psychological changes associated with a history of childhood stressors play

Table 3. Studies examining the association between childhood stressors and symptom profiles

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Sample</th>
<th>Clinical symptoms</th>
<th>Clinical measurements</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heins et al. (2011)</td>
<td>Case-control</td>
<td>216 CFS, 227 controls</td>
<td>Depression</td>
<td>BDI-PC</td>
<td>CFS patients with a history of childhood abuse had a higher prevalence of depression compared with non-abused patients (44% v. 25%)</td>
</tr>
<tr>
<td>Sigurdardottir &amp; Halldorsdottir (2013)</td>
<td>Longitudinal cohort</td>
<td>Seven women with CSA</td>
<td>Depression</td>
<td>SCL</td>
<td>Five out of seven women had FM and all had depression</td>
</tr>
<tr>
<td>Heins et al. (2011)</td>
<td>Case-control</td>
<td>216 CFS, 227 controls</td>
<td>Anxiety</td>
<td>SCL</td>
<td>CFS patients with a history of childhood abuse reported higher levels of anxiety compared with controls (21% v. 15%)</td>
</tr>
<tr>
<td>Sigurdardottir &amp; Halldorsdottir (2013)</td>
<td>Longitudinal cohort</td>
<td>Seven women with CSA</td>
<td>Pain</td>
<td>SCL</td>
<td>Five out of seven women had FM and all reported chronic pain and widespread pain</td>
</tr>
<tr>
<td>Walker et al. (1997)</td>
<td>Cohort</td>
<td>36 FM, 33 RA</td>
<td>Pain</td>
<td>SF-36</td>
<td>Childhood abuse was significantly associated with pain symptoms in FM patients when compared to RA patients</td>
</tr>
</tbody>
</table>

CFS, Chronic fatigue syndrome; BDI-PC, Beck Depression Inventory for Primary Care; FM, fibromyalgia; CSA, childhood sexual abuse; SCL, Symptom Checklist Questionnaire; RA, rheumatoid arthritis; SF-36, Medical Outcomes Study Short Form 36-item Health Survey.
a role in this increased risk of CFS/FM, including low self-esteem, greater social introversion, lower general activity levels and unhelpful perceptions and coping skills (Masuda et al. 1994; Chartier et al. 2009).

The first such mechanism is inflammation, whereby childhood stressors lead to increased inflammation and the subsequent development of CFS (Maes & Twisk, 2010). There is an increasing body of evidence supporting the activation of the immune system and of abnormal inflammatory processes in individuals with a history of childhood stressors. Specifically, we have demonstrated that adults with a history of childhood abuse and social isolation have elevated inflammation levels in adulthood, as shown by the levels of the inflammatory marker, C-reactive protein (CRP) (Danese et al. 2007, 2009; Hepgul et al. 2012).

Carpenter et al. (2010) examined plasma interleukin (IL)-6 concentrations in healthy subjects without depression or post-traumatic stress disorder (PTSD), during a standard stress challenge, the Trier Social Stress Test (TSST). Their results still showed a significant relationship between a previous history of childhood maltreatment and an increased level of plasma IL-6 concentration, when compared with individuals without such history. More recently, a study by Heath et al. (2013) reported that individuals exposed to a history of sexual or physical abuse are more likely to be diagnosed with PTSD and exhibit high CRP levels than patients without PTSD, suggesting a possible role of PTSD in explaining the association between childhood stressors and immune system activation. The inflammatory response in patients with a previous
history of childhood stressors has also been shown to be exaggerated in the presence of stressful conditions during adulthood (Pace et al. 2006). This evidence is consistent with the notion that inflammatory markers may also play a role in the pathophysiology of CFS and FM (Pariante, 2009). Levels of pro-inflammatory cytokines, such as IL-1, tumour necrosis factor (TNF)-α (Maes et al. 2012) and nuclear factor (NF)-κB (Morris & Maes, 2012), have been shown to be higher in CFS patients than in healthy controls. In addition, Raison et al. (2009) demonstrated that CRP levels are significantly higher in subjects with CFS and insufficient fatigue (ISF, a milder form of chronic fatigue) when compared with healthy control subjects. Furthermore, a dysregulation of cytokines, including IL-1, IL-6 and IL-8, has been shown to be present in FM patients and to be associated with more pain and fatigue symptoms (Wallace, 2006). Therefore, it is plausible that increased inflammation in individuals with a history of CSA may in turn cause fatigue and somatic symptoms such as those seen in CFS patients (Maes & Twisk, 2010). Indeed, this increase in inflammatory markers as a result of childhood maltreatment has also been associated with the later development of other adult psychiatric conditions, such as depression (Danese et al. 2008). For example, individuals with a history of adversities during childhood are at greater risk of both inflammatory abnormalities and mood disorders later in life, especially in the context of additional adult stressors (Heim et al. 2001). Clearly, the association between childhood abuse, inflammation and adult fatigue may not need to be ‘causal’: fatigue and inflammation may both be only associated with the third, common factor, childhood trauma (Pariante, 2009). To the best of our knowledge, no studies have investigated inflammatory markers in individuals with childhood abuse and a diagnosis of CFS or FM. Hence, future research would need to clarify whether indeed inflammation may, at least in part, mediate the relationship between childhood stressors and the development of these chronic conditions.

The HPA axis may also be involved in the association between childhood abuse and CFS/FM. Of note, most studies have found a reduced basal cortisol output in CFS, whereas FM and depression tend to be associated with an increased cortisol output. For example, patients with CFS have lower activity of the HPA axis (Strickland et al. 1998; Di Giorgio et al. 2005), including a blunted salivary cortisol response to awakening (Roberts et al. 2004), that is associated with poorer response to cognitive behavioural therapy (CBT) (Roberts et al. 2009). There are many other factors that may affect HPA axis hypoactivity in CFS patients, such as inactivity, sleep disturbance and medication (Cleare, 2004), but there is no evidence for a unique or uniform dysfunction of the HPA axis in these conditions. By contrast, studies in FM patients have shown higher cortisol levels (Catley et al. 2000; Crofford et al. 2004) and exaggerated HPA axis response to stimulation (Griep et al. 1993; Crofford et al. 1994). Of interest, HPA axis hyperactivity is one of the most consistent findings in depression; indeed, it is conceptualized not only as a consequence of depression but also as a biological marker of vulnerability, often brought about by childhood stressors, and predisposing to the development of depression (Pariante & Lightman, 2008). Moreover, childhood abuse per se is associated with abnormal HPA axis activity, although both hyper- and hypoactivity have been described. For example, some clinical studies have shown that individuals who have been sexually or physically abused during childhood exhibit hyperactivation of the HPA axis when exposed to a standardized psychosocial stress, the TSST (Heim & Nemeroff, 2002; Heim et al. 2008b). By contrast, other studies have shown that adults reporting a previous experience of childhood abuse have a hypoactivation of the HPA axis and a consequent lower production of cortisol (Bremner et al. 2003, 2007; Carpenter et al. 2007). It is possible that early and severe stress may lead to an initial heightened stress response, which reduces over time (Gunnar & Vazquez, 2001; Susman, 2006; Heim et al. 2008b). Of note, the relationship between childhood abuse and HPA axis activity was assessed in two of the papers we reviewed and they showed contrasting evidence, with one study reporting an increased (Weissbecker et al. 2006) and one a blunted cortisol awakening response (Heim et al. 2009). Of note, Heim et al. (2009) reported that only those individuals with CFS and exposure to childhood trauma exhibit decreased mean cortisol levels after awakening whereas individuals with CFS without childhood trauma experience do not differ from controls. Therefore, further studies are needed to obtain a clearer understanding of the involvement of the HPA axis.

One of the main limitations of our review is that the quality of the findings varied across the studies reviewed. Indeed, many of the studies, being case-control, were empirically weakened by the inability to examine cause and effect in the relationship between childhood abuse and CFS or FM. There was also no uniformity in the diagnostic criteria used for the assessment of childhood abuse and other clinical symptoms. Furthermore, sample sizes were often small and several studies did not include a control or a comparison group.

In conclusion, to our knowledge this is the first review to summarize the existing literature on the relationship between different forms of childhood...
abuse, and CFS and FM. Despite the limitations of the available literature, we show evidence for the involvement of childhood abuse in the aetiology of both these conditions. In addition, we highlight the link between childhood abuse and the development of other symptoms such as depression, anxiety and pain, in both CFS and FM patients. Demonstrating a causal relationship between childhood abuse and an increased risk of CFS and FM could have significant implications in terms of raising awareness, targeting more vulnerable individuals and identifying biological mechanisms underlying this putative causal relationship. Finally, it is important to note that these biological mechanisms, such as low cortisol, are potentially reversible as has been shown in a previous study of CBT (Roberts et al., 2009).

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Declaration of Interest

None.

References


