European Child & Adolescent Psychiatry (2019) 28:491–504
https://doi.org/10.1007/s00787-018-1212-2

ORIGINAL CONTRIBUTION

Blood CRP levels are elevated in children and adolescents with functional neurological symptom disorder

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Received: 21 March 2018 / Accepted: 3 August 2018 / Published online: 24 August 2018

Abstract
There is accumulating evidence that patients with functional neurological symptom disorder (FND) show activation of multiple components of the stress system—the hypothalamic–pituitary–adrenal axis, autonomic nervous system, and brain regions involved in arousal- and emotion-processing. This study aims to examine whether the immune-inflammatory component of the stress system is also activated. C-reactive protein (CRP) blood titre levels were measured in 79 children and adolescents with FND. CRP values ≥ 2 mg/L suggest low-grade inflammation. CRP values > 10 mg/L suggest a disease process. Sixty-six percent of subjects ($n = 52$) had CRP titres ≥ 2 mg/L. The upward shift in the distribution of CRP levels suggested low-grade inflammation (median CRP concentration was 4.60 mg/L, with 75th and 90th percentiles of 6.1 and 10.3 mg/L, respectively). Elevated CRP titres were not explained by sex, pubertal status, BMI, or medical factors. Confounder analyses suggested that history of maltreatment ($\chi^2 = 2.802$, $df = 1$, $p = 0.094$, $\varphi = 0.190$; $\beta = 2.823$, $p = 0.04$) and a diagnosis of anxiety ($\chi^2 = 2.731$, $df = 1$, $p = 0.098$, $\varphi = 0.187$; $\beta = 4.520$, $p = 0.061$) contributed to elevated CRP levels. Future research will need to identify the origins and locations of immune cell activation and the pathways and systems contributing to their activation and modulation. Because functional activity in neurons and glial cells—the brain's innate effector immune cells—is tightly coupled, our finding of elevated CRP titres suggests activation of the immune-inflammatory component of the brain's stress system. A more direct examination of inflammation-related molecules in the brain will help clarify the role of immune-inflammatory processes in FND.

Keywords Functional neurological symptoms · Conversion disorder · Non-epileptic seizures · Neuroinflammation · Dissociation

Introduction

Functional neurological symptom disorder (FND) involves disturbances of body function characterized by neurological sensory or motor symptoms. FND typically occurs against a background of cumulative stress and is triggered by illness, injury, emotional distress, or psychological trauma. FND commonly presents alongside comorbid anxiety, depression, functional pain, and a multitude of nonspecific somatic symptoms [1–3]. Accumulating data suggest that children and adolescents with FND show activation or dysregulation of multiple components of the stress system and that a stress system model of illness provides an overarching neurobiological framework for understanding this complex group of patients [4]. According to the stress system model, each component of the stress system—the hypothalamic–pituitary–adrenal (HPA) axis, autonomic nervous system, immune-inflammatory system, and brain systems underpinning pain, arousal, and emotional states—is part of a larger, integrated system that is designed to protect the individual from a broad range of threats. Activation within any part of the stress system by a physical or psychological stressor can activate the system as a whole [5–7]. Depending on genetic/epigenetic vulnerability on previous priming, and the time frame of activation and allostatic load, the pattern of somatic and psychological symptoms associated with activation of the stress system will vary from one individual

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to another, fluctuate in severity, and change over time [7, 8]. In children and adolescents with FND, the immune-inflammatory component of the stress system has not been previously investigated. The current study examines whether C-reactive protein (CRP)—a systemic marker of inflammation—is elevated in children and adolescents presenting with FND. See Text Box 1.

Box 1: C-reactive protein

C-reactive protein (CRP) is a sensitive systemic marker of systemic inflammation [9, 10]. It is produced by hepatocytes in the liver (and micro-vessel endothelial cells that form the blood–brain barrier) in reaction to pro-inflammatory cytokines [9, 11]. It is typically not detectable in the blood—or is detectable at very low titer levels—unless some degree of inflammation is present in the body.

Two decades ago, Maes and colleagues proposed that the immune-inflammatory system plays a role in the neurophysiology of functional somatic symptoms [12]. Since that time, a growing number of studies with both children and adults have documented elevated inflammatory markers in patients with chronic pain, fatigue, musculoskeletal complaints, and other somatization syndromes [13–19]. A recent large, prospective study of 2230 Dutch youth—the TRAILS study [20]—has shown that adolescents reporting non-neurological functional somatic symptoms (overtiredness, dizziness, headache, stomach pain, vomiting, nausea, and musculoskeletal symptoms [pain in the back, neck, shoulders, arms, or legs]) on the Somatic Complaints scale of the Youth Self-Report (YSR) have elevated levels of CRP, alongside dysregulations of the HPA axis [21].

Research on childhood adversity and on anxiety (commonly comorbid with FND in children and adolescents) and depression (less commonly comorbid) provides further evidence linking inflammation and FND. Childhood adversity, which is known to contribute to a pro-inflammatory state across development [22, 23], is associated with FND [24] and with chronic pain and fatigue as well as other somatization syndromes [25–28]. Patients with anxiety and pain catastrophizing have been shown to have peripheral blood elevations in IL-6 [29]. In addition, peripheral blood elevations in cytokines (IL-6 and tumour necrosis factor α) and CRP have been shown (in adult patients with depression) to be among the most reliable markers of increased inflammation [30, 31]. In depression, postmortem findings of decreased glial cell numbers in the prefrontal cortex and amygdala suggest that, alongside changes in neural networks, stress-induced activation of glial cells, followed by inflammation-related oxidative-stress loss of glial cells, may play a key role in the disease process [32].

More recently, emerging evidence from post-traumatic stress disorder (PTSD) research suggests that alongside functional and structural changes in the brain, the molecular consequences of PTSD lead to elevated systemic levels of oxidative stress and inflammation [33]. Like PTSD, FND is a stress-related disorder [4, 34] characterized by both functional and structural changes in the brain (see below) and accompanied by activation or dysregulation of the HPA axis and autonomic nervous system [35]. Group-level analyses looking at brain function suggest that arousal/emotion-processing regions—which are overactive and overly dominant in patients with FND—overconnect with motor regions, thereby disrupting motor function and causing functional neurological symptoms (see Blakemore for review) [36]. Group-level analyses looking at brain structure suggest experience-dependent changes: increases in grey matter in motor- and emotion-processing regions in children and adolescents [37] and increases or decreases in grey matter in motor- and emotion-processing regions are seen in adult patients [34, 38–43]. Finally, because the brain's innate immune effector cells (glial cells)—which confer immunological memory for past stress and which play an important role in the brain's stress response—are implicated in both adaptive and maladaptive responses to stress [44–47], it is hypothesized that they also play a key role in the experience-dependent plasticity changes seen in patients with FND [4, 48, 49].

Taken together, contemporary neurophysiological studies suggest that at a group level of analysis, patients with FND show activation, dysregulation or experience-dependent plasticity in multiple components of the stress system. Because the immune-inflammatory system is an important component of the stress system and because the immune-inflammatory system is typically activated in stress-related disorders [6, 8, 33], we hypothesized that children and adolescents presenting to our tertiary care hospital with FND would show elevated serum levels of CRP.

Materials and methods

Participants

Participants were 79 Australian children and adolescents with FND (57 girls; 22 boys) aged 9–18 years (mean 13.32, SD 2.29, median 13.5 years) who had been recruited into studies within our FND research program between August 2006 and March 2016, and who had had their CRP screen done via our paediatric tertiary care hospital laboratory. The research program was approved by the Sydney Children's Hospital Network Ethics Committee and Sydney West Area Health Service Human Research Ethics Committee. Participants and their legal guardians provided written informed consent.

Procedure

Participants were diagnosed according to modified DSM-IV-TR criteria [50] by both a paediatrician (typically a paediatric neurologist) and a child psychiatrist, whilst DSM-5 criteria were being developed. Consistent with DSM-5 criteria, we did not adhere to the DSM-IV-TR "psychological stressor criterion", because our previous research with children/adolescents had highlighted that the psychological stressor criterion was too narrow [51, 52]. Instead, we documented, if present, any antecedent stressors—both psychological and physical. Again, in keeping with DSM-5 criteria, all participants had documented positive symptoms on neurological examination, plus a worsening of symptoms with attention and a decrease of symptoms when distracted by schoolwork and other activities during family assessment, individual assessment, and the inpatient admission.

All 79 participants with FND underwent routine blood testing through our hospital laboratory as part of their medical workups. The blood testing panel included a CRP titre, white cell blood count (WCC) (a marker of infection), and erythrocyte sedimentation rate (ESR).

Serum CRP was measured by a commercial reflectance spectrometry enzyme-linked immunoassay (Ortho-Clinical Diagnostics, Rochester NY), which utilizes a monoclonal mouse anti-CRP antibody conjugated to horseradish peroxidase. The sensitivity of the assay (Limit of Blank) is 2.03 mg/L, equivalent to the concentration above which CRP may reliably be ascertained to be present in the sample. The assay has a coefficient of variation of 12% at a concentration of 7.3 mg/L. A CRP reference interval of ≥ 10 mg/L is reported by the laboratory as indicating inflammation or infection.

The WCC counts were performed using a Beckman Coulter UniCel DxH 800 cell counter. ESR was measured using a modified Westergren micro-method.

Calculation

Following the lead of Jonker et al. in the TRAILS study [20]—a large, prospective study of 2230 Dutch youth—we used CRP titre values of ≥ 2 mg/L to indicate an elevated CRP titre. In contrast to the TRAILS study, however, we did not exclude CRP values > 10 mg/L, because physical stressors (viral illness, injuries, medical procedures, and vaccinations) trigger FND in a significant proportion of cases [4, 53], and this subgroup of patients with FND could theoretically have CRP titres of > 10 mg/L. In comparison to the CRP assay used in the TRAILS study, the CRP assay used by our hospital had a measuring limit of 2 mg/L with lower concentrations being reported as "< 2 mg/L".

For comparative reference ranges, we used published data from the TRAILS study, with its 2230 16-year-old adolescents [20] and a cohort of 468 healthy young adult volunteer blood donors [54]. Shine and colleagues had previously shown that in healthy young adults the median concentration of CRP was 0.8 mg/L, the 90th percentile was 3.0 mg/L, and the 99th percentile was 10 mg/L, indicating that values > 10 mg/L were strongly suggestive of a pathological process [54]. The TRAILS study showed a similar pattern of findings: the median concentration of CRP was 0.4 mg/L, the 25th percentile was 0.2 mg/L, the 75th percentile was 1.0 mg/L, and the 90th percentile was 3.13 mg/L [20]. In our hospital, the clinical cutoff of > 10 mg/L is used by clinicians in day-to-day clinical practice to signal potential systemic inflammation. One outlier in our study—with a CRP of > 50 mg/L—was excluded from all subsequent analyses.

Normal ranges used by clinicians in the hospital were used to assess whether WWC (4.5–13.5 10^9/L) and ESR (ESR of 0–20 mm/h) were elevated.

Body mass index (BMI) percentiles from the Centers for Disease Control and Prevention (CDC) [55] were used to examine the potential contribution of excessive body mass to elevated CRP titres [56]. BMI percentiles are more accurate than BMI when looking at children and adolescents across developmental stages. In the current study, patients fell into three BMI percentiles: healthy (5 to < 85), overweight (85 to < 95), and obese (≥ 95).

CRP levels less that 2 mg were not reported. Tobit regression left censored at 2 was used to test for associations between CRP and potential confounders.

The potential contribution of confounding factors was examined in two different ways. First, we subdivided patients into two groups—those with normative CRP titres (< 2 mg/L) and those with elevated CRP titres (≥ 2 mg/L)—and we used Pearson's Chi-squared test to examine the potential contribution of confounding factors. (In using this cutoff of 2 mg/L, we followed the TRAILS study, which used that level because previous studies had found CRP titres ≥ 2 mg/L to be a risk factor for mood disorders.) Second, because CRP levels less that 2 mg/L were not reported, we also used Tobit regression left censored at 2 mg/L to test for associations between CRP and potential confounders. Confounders examined included sex; female, postpubertal status; acute vs. chronic (≥ 6 months) presentation; physical stressor (see description in "Patient characteristics"); viral infection antecedent to the FD; other comorbid medical illnesses (see Table 1 in "Patient characteristics"); clinical pain; clinical fatigue; and BMI percentile [patients within healthy BMI percentiles (5 to < 85) vs. those within overweight/obese percentiles (≥ 85)]. We also examined between-group differences with regard to comorbid mental health conditions that commonly co-occur with FND: diagnosis of clinical anxiety; diagnosis of clinical depression; and maltreatment history (see Table 2 in "Patient

Table 1 Comorbid medical and mental health diagnoses in the 79 children and adolescents with FND

Medical condition	Number*	Percentage (%)
Comorbid neurological condition		
Epilepsy	6	8
Congenital conditions with neurological manifestations (neurofibromatosis Type 1 with hydrocephalus, epilepsy, and ocular gliomas; chromosome deletion 8 with spontaneous intraventricular bleeds, hydrocephalus, and ventriculo-peritoneal shunting procedures)	2	3
Left cerebral atrophy of unknown cause (unchanging over time)	1	1
Hereditary angio-oedema	1	1
Migraine	1	1
Benign cranial hypertension	1	1
Foot drop	1	1
Past history of a neurological insult to the central nervous system		
Viral meningitis	1	1
Transverse myelitis	1	1
Other comorbid medical conditions		
Asthma	5	6
Hypermobility	5	6
History of vasovagal episodes	2	3
Postural orthostatic tachycardia syndrome (POTS)	2	3
Diabetes	1	1
Fracture	3	4
Internal injuries and fractures from a motor vehicle accident	1	1
Fasciitis in the leg	1	1
Diabetes	1	1
Keratoconus	1	1
Abdominal infection diagnosed on laparoscopy (18 months before)	1	1
Appendicitis (operated on 2 months before)	1	1
Glomerulonephritis (12 months before)	1	1
Cancer of the kidney (treated)	1	1
Congenital heart disease (operated on in early childhood)	1	1
Osgood–Schlatter's disease	1	1
Brown syndrome (superior oblique tendon sheath syndrome)	1	1
Comorbid mental health diagnoses and symptoms		
Condition		
Anxiety	37	47
Depression	11	13
Mixed anxiety/depression	8	10
Behavioural disorder	5	6
Learning disorder	2	3
Eating disorder	1	1
Enuresis	1	1
Dissociative symptoms (memory loss, loss of recognition of parents, etc.)	8	10

*In total 37 (47%) patients had one or more comorbid medical conditions and sixty (76%) patients had one or more comorbid mental health conditions

characteristics"). Finally, we also examined between-group differences in participants whose FND presentation included psychogenic non-epileptic seizures (PNES) and those that did not, because previous data from our research program had shown that in children and adolescents the presence of PNES marked a more severe FND illness profile [57, 58].

Results

Missing data

All patients had CRP data, 78 (99%) had WCC data, and 61 (77%) had ESR data.

Table 2 Summary of antecedent life events (physical and psychological stressors) reported by families at assessment during the structured interview

	Number	Percentage (%)
Adverse life events reported by families		
Maltreatment history and child protection service involvement (either past and current)		
Domestic violence	15	19
Physical abuse	9	11.4
Sexual abuse	8	10
Neglect	7	9
Emotional abuse by a father	4	5
Emotional abuse by a mother	1	1
Other stressful life events		
Family conflict	48	61
Antecedent illness event experienced by the child	41	52
Loss by separation	39	49
Maternal mental illness	33	42
Bullying	32	41
Loss by death	26	33
Paternal mental illness	23	29
Multiple moves	16	20
Paternal physical illness	15	19
Maternal physical illness	12	15
Stress from sibling/cousin/family member illness	8	10
Custody battle	6	8
Academic (learning) stress	6	8
Grandparent illness	5	6
Financial stress	5	6
Family reconfiguration: new siblings move in/birth of baby	5	6
Migration	5	6
Performance (sporting or academic) pressure	4	5
Father/grandfather attempted suicide	2	3
Multiple previous hospitalizations/injuries	2	3
Change of school	2	3
Conflict or lack of connection with a particular family member	2	3
Sibling was sexually assaulted	2	3
Murder of a father	1	1
Murder of a friend	1	1
Father lost job	1	1
Heard missile explode over phone to soldier father	1	1
Death of a pet who had provided the child with comfort	1	1
Father having affairs	1	1
Left without a caregiver in context of illness	1	1
House fire	1	1
Sibling in jail	1	1
Adoption (potential breakdown)	1	1
Explicit accounts about sexual intercourse from a grandparent and threats that the child's parents would separate	1	1

Patient characteristics

The sample was characterized by the presence of one or more FND symptoms (mean 2.56, median 2, range 1–8)—sensory symptoms ($n=37$, 47%), motor symptoms ($n=51$, 65%), psychogenic non-epileptic seizures (PNES) ($n=48$, 61%)—that were sufficiently disabling to require hospital treatment in 96% (76/79) of cases (see Fig. 1). The

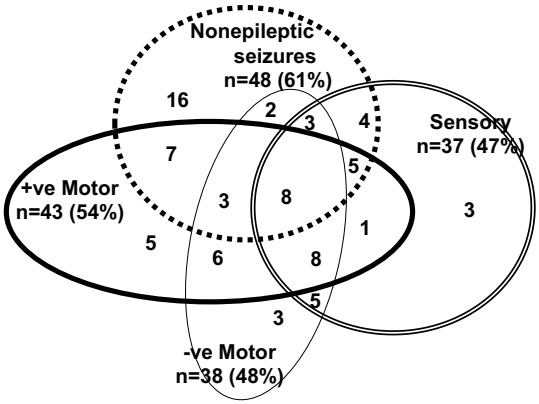

Fig. 1 Different subtypes of functional neurological symptoms and the high rate of comorbidity between functional neurological symptoms in the study sample including PNES with positive motor symptoms (tremor, dystonia, or gait abnormalities); PNES with negative motor symptoms (limb paresis or partial loss of motor function); PNES with complex combinations of motor and sensory symptoms; and negative motor symptoms alternating with positive motor symptoms

majority of patients ($n=64$, 81%) had acute presentations with FND (<6 months, range of 1 day to 5 months at presentation, mean 1.2 months, median 1.1 month), and the remainder presented to our service in the context of chronic FND presentations (≥6 months, range of 6 months to 3 years at presentation, mean 15 months, median 12 months).

In addition, 50 patients (63%) suffered from comorbid medically unexplained pain, and 55 (70%) from comorbid nonspecific somatic symptoms: nausea ($n=25$, 32%), dizziness ($n=37$, 47%), breathlessness ($n=30$, 38%), and fatigue ($n=30$, 38%). Thirty-seven (47%) children and adolescents had a comorbid medical condition (see Table 1). Sixty (76%) patients also met criteria, and were subsequently treated, for one or more comorbid DSM-IV-TR diagnoses, with comorbid anxiety ($n=37$, 47%), depression ($n=11$, 13%), and mixed anxiety/depression ($n=8$, 10%) being the most common (see Table 1). Seven (9%) of the patients with a diagnosis of an anxiety disorder(s) met criteria for PTSD.

All families reported antecedent stressors (range 1–11, mean=5, median 5) (see Table 2). Family conflict ($n=48$, 61%) and illness events ($n=41$, 52%) were the most common antecedent stressors (see Table 2). Illness events (physical stressors)—sometimes in the same child—included injury ($n=18$) secondary to a fall ($n=15$) or to a fall secondary to physical assault from bully peers ($n=3$); viral illness ($n=14$); surgery ($n=2$) (shunt insertion and appendectomy); recent vaccination ($n=1$); a spider bite ($n=1$); exhaustion and dehydration following a sporting event ($n=1$); vasovagal faint ($n=1$) and other medical illnesses ($n=6$) [flare-up of hereditary angio-oedema, transverse myelitis, fasciitis in the leg, foot drop, diagnosis of keratoconus (with vision loss), and injuries from a motor vehicle accident]. One-third of the children and adolescents ($n=27$, 34%) had experienced one or more forms of maltreatment (see Table 2). In all these cases, there was a past or current history of contact with the Child Protection Service.

CRP titres

Two-thirds of children and adolescents with FND ($n=52$, 66%) had elevated CRP titres (≥2 mg/L), and one-third ($n=27$, 34%) had normative titres (<2 mg/L) (see Table 3). The CRP distribution for our cohort, compared to previous studies by Jonker et al. [20] and Shine et al. [54], is shown in Table 4 and Fig. 2.

Other blood markers

Two patients (2.60%) had WCC counts just above the upper cutoff (13.7 and 14.0 10^9/L), and 8 (13%) had an elevated ESR.

Examination of confounding factors and comorbid mental health conditions

The Chi-square comparison of confounding factors and comorbid mental health conditions between patients with a normative CRP (<2 mg) and an elevated CRP (>2 mg) is documented in Table 5. The Tobit regression analysis is

Table 3 Distribution of CRP titres in the 79 children and adolescents with FND

CRP titre range mg/L	Number of participants	Percentage (%)
<2	27	34.2
2–5	13	16.5
5.1–10	30	38.0
10.1–50	8	10.1
>50	1	1.3
Total	79	100

Table 4 Comparison of CRP distribution between the current study and previous studies

CRP distribution	25th percentile mg/L	50th percentile (median) mg/L	75th percentile mg/L	90th percentile mg/L
Current study	<2*	4.6	6.1	10.3
Jonker et al. [20]	0.2	0.4	1.0	3.1
Shine et al. [54]		0.8		3.0

*The CRP assay used in the present study enabled reporting down to 2 mg/L

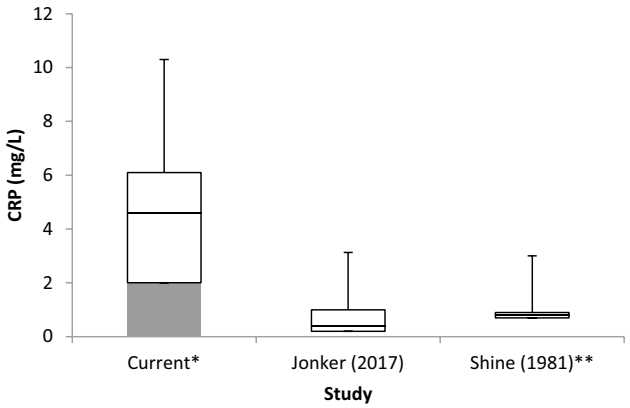

Fig. 2 Comparison of CRP distribution with previous studies. Box indicates the 25th, median and 75th centiles. Upper whiskers indicate the 90th centile. Asterisk: the 25th centile of CRP in the present study was < 2 mg/L. Double asterisk: the 25th and 75th percentile values from Shine et al. [54] are unavailable

presented in Table 6. Patients with elevated CRP titres were more likely to report history of maltreatment and to suffer from comorbid clinical anxiety (trend level finding) (see Table 7). Although the Chi-square analysis suggested that patients with PNES were more likely to have elevated CRP levels (trend level finding), this finding was not borne out in the regression analysis. Unexpectedly, the small group patients with comorbid clinical depression were less likely to have elevated CRP titres. All other analyses were not significant.

Discussion

This study examined CRP titres—a systemic measure of inflammation—in 79 children and adolescents with functional neurological symptoms to ascertain whether the immune-inflammatory component of the stress system is activated in FND. Two-thirds of patients had elevated CRP titres (≥ 2 mg/L), falling mostly in the low-grade inflammation (2–10 mg/L) range. The distribution of CRP titres, as indicated by the median percentiles (see Fig. 1), was demonstrably higher than reference ranges previously reported in a Dutch population sample of 16-year-old adolescents and a United Kingdom sample of healthy young adult blood donors [20, 54]. Children and adolescents with FND who had elevated CRP titres (≥ 2 mg/L) were more likely to report a history of maltreatment or to have a clinical diagnosis of anxiety. Other confounding factors—BMI, presence or absence of pain, presence or absence of fatigue, type of antecedent stressors (physical or psychological), and presence of comorbid medical conditions—did not explain increases in CRP titres. Our finding of elevated CRP titres in child and adolescent patients with FND suggests that the immune-inflammatory component of the stress system is activated in a significant proportion of patients with FND and that history of maltreatment and anxiety function as contributory factors. Our findings cohere with those of Jonker et al. who found an association between CRP titres and functional somatic

Table 5 Chi-square analyses examining confounders in patients with normative CRP titres vs. patients with elevated CRP titres

Confounding factor/comorbid mental health diagnosis	% within CRP < 2 mg/L Subgroup ($n = 27$)	% within CRP ≥ 2 mg/L Subgroup ($n = 51$)	Chi square	*df*	*p* value	Phi effect size
Sex (female)	70.4	74.5	0.154	1	0.695	–
♀ postpubertal status	51.9	47.1	0.162	1	0.687	–
BMI percentile (overweight/obese range)	29.6	31.4	0.025	1	0.874	–
Acute presentation [vs. chronic (≥ 6 months)]	77.8	82.4	0.238	1	0.626	–
Any physical (illness) trigger	55.6	49.0	0.302	1	0.583	–
Viral infection physical trigger	25.9	13.7	1.784	1	0.182	–
Comorbid medical illness*	48.1	45.1	0.066	1	0.797	–
Clinical pain	63.0	62.7	0.0	1	0.985	–
Clinical fatigue	40.7	37.3	.091	1	0.763	–
Clinical anxiety (no depression)	33.3	52.0	2.731	1	0.098	0.187
Clinical depression (no anxiety)**	29.6	5.9	8.814	1	0.003	– 0.352
Maltreatment history	22.2	41.2	2.802	1	0.094	0.190
PNES	48.1	68.1	3.128	1	0.077	0.200

*The variable comorbid medical illnesses included all conditions listed in Table 1

**Children with mixed anxiety–depression were excluded from this analysis

***The variable maltreatment history included all maltreatment conditions listed in Table 2

Table 6 Tobit regression analysis examining confounders with CRP levels censored at 2 mg/L

Confounding factor/comorbid mental health diagnosis	Coefficient (SE)	*p* value
Sex (female)	3.15 (2.84)	0.267
♀ postpubertal status	− 0.80 (2.40)	0.738
BMI percentile (overweight/obese range)	− 0.36 (1.59)	0.820
Acute presentation [vs. chronic (≥ 6 months)]	− 3.57 (3.11)	0.250
Any physical (illness) trigger	− 2.18 (2.39)	0.360
Viral infection physical trigger	− 4.00 (4.03)	0.321
Comorbid medical illness*	0.52 (2.72)	0.849
Clinical pain	− 2.62 (2.39)	0.285
Clinical fatigue	1.88 (2.39)	0.432
Clinical anxiety	4.52 (2.42)	0.061
Clinical depression	− 5.66 (2.64)	0.032
Maltreatment events	2.82 (1.36)	0.038
PNES	3.00 (2.40)	0.210

Table 7 Anxiety diagnoses in the 45/79 children that received treatment for a comorbid anxiety disorder

Anxiety diagnosis (DSM-IV-TR)	Number of children ($n = 79$)*
Generalized anxiety disorder	13
Panic disorder (without agoraphobia)	8
Post-traumatic stress disorder	7
Specific phobia	2
Separation anxiety	2
Anxiety NOS	18

*Some children met criteria for more than one anxiety diagnoses

symptom scores in their sample of 2230 Dutch adolescents reporting non-neurological functional somatic symptoms on self-report [20]. Our findings also cohere with the broader literature that points to a relationship between childhood adversity, chronic anxiety, and elevated markers of inflammation [22, 23, 29, 33].

CRP is a nonspecific marker of inflammation, and our findings of elevated CRP titres in our patients with FND provide no information about the origin and location of immune cell activation and signalling. That said, our data suggest that in children and adolescents with FND, physical factors (antecedent falls, injuries and viral illnesses, and comorbid medical conditions) did not explain elevated CRP titres, whereas mental health factors (a history of maltreatment and comorbid anxiety) contributed to elevated CRP titres. Because maltreatment and anxiety are in and of themselves associated with HPA axis/autonomic dysfunction [59–62] and functional/plasticity-related changes in the brain [33, 62, 63], they may function as markers of more severe stress-system dysregulation and a more severe illness profile.

The brain–body pathways that link psychological stress to ill health are a current area of research. In the current study, one possible brain–body pathway mediating elevated CRP titres in our sample involves the sympathetic and parasympathetic modulation of peripheral immune responses [64, 65]. In this scenario, up-regulation of the sympathetic system and down-regulation of the parasympathetic system would cause a systemic shift-of-balance towards an inflammatory body state. Activation and dysregulation of the autonomic system is well documented in children and adults patients with FND [35, 57, 58, 66, 67]. The severe paroxysmal nature of autonomic activation in patients with PNES may make this subgroup of patients particularly vulnerable to autonomic immune modulation [66].

A second possible explanation, not mutually exclusive, involves the stimulatory effects of glucocorticoids on the brain's innate immune effector cells—glial cells—in the central nervous system [6]. Glial cells are prime targets of glucocorticoids [6], and glucocorticoids modify glial cell function via a complex range of genomic and non-genomic mechanisms. In a parallel process, glial cells are activated by catecholamine release in the brain [68], a phenomenon that also occurs in the context of stress [69]. Under certain circumstances, including priming of glial cells by past stress, glucocorticoids can stimulate—rather than inhibit—the brain's immune response [6]. In turn, activation of immune-inflammatory processes in the brain may be reflected in peripheral biomarkers because neurons and the immune-inflammatory system, as well as the brain and peripheral immune-inflammatory systems, are constantly engaged in crosstalk [70] (see Text Box 2). Child maltreatment and anxiety may be important contributory factors in the priming process because they are both associated with relational stress and family dysfunction [62, 71]; these recurrent stressful experiences may prime glial cells and may create the necessary conditions under which glucocorticoids will stimulate a pro-inflammatory brain response. Activation of the HPA

axis has been documented in adults with FND [35, 72], and it is presumably also a feature of childhood presentations.

Box 2

The crosstalk between the brain and peripheral immune-inflammatory systems involves many different mechanisms and enables ongoing communication between the neurons and immune-inflammatory cells residing in the body, on the one hand, and the neurons and immune-inflammatory cells residing the brain, on the other. Peripheral immune-inflammatory cells communicate with the brain via vagal and sympathetic afferents, by the transport of cytokines (and other mediators) at the blood–brain barrier, or by the transport of cytokines (and other mediators) via circumventricular organs (areas in the brain that lack a blood–brain barrier and that act as a transport route between the blood and the brain) [46, 73]. The brain communicates with peripheral immune cells via activation of the HPA axis (pro- or anti-inflammatory modulation of the glucocorticoid receptor on immune cells to inhibit or enhance the immune response [6], via vagal and sympathetic efferents) [65, 74], by the activation of central arousal (noradrenergic) systems that activate immune cells directly in the CNS [45], and by the export of immune cells from the brain to the body via elimination gateways for cerebrospinal and interstitial fluid [75]. In this way, activation of brain glial cells by stress—physical, psychological, or both—will be registered by the peripheral immune-inflammatory system and will result in elevated levels of CRP.

A third possible explanation, not mutually exclusive, involves experience-dependent gliogenesis in response to stress. As previously noted, imaging studies show that patients with FND show increases in grey matter volume in a number of cortical regions involved in motor and emotion processing (see review of studies in Kozlowska et al. 2017). Glial cells are both primed by past stress and undergo gliogenesis in response to learning [76, 77]. In this context, it is possible that aberrant functional and experience-dependent structural neural changes that underpin FND may involve aberrant glial cell activation and proliferation. Importantly, over time this pattern of experience-dependent changes may be followed by "wear and tear" [78]—cell death and tissue atrophy—as a later stage in the illness process [33]. Stephenson and Baguley (2018) provide a current review of glial-based plasticity mechanisms, and they hypothesize that such glial-based mechanisms explain many of the clinical features of FND [79].

A fourth possible explanation, also not mutually exclusive, is that patients with FND show elevated CRP titres because of the aberrant changes in the gut microbiota—the community of bacteria and other organisms living in the gut. Emerging findings suggest that gut microbiota appear to be involved in brain development, modulation of the immune system, mental well-being, and stress-related disorders [80–82]. In this context, even though gut symptoms were not a key feature of the current study cohort—25 (32%) reported nausea and 10 (13%) had comorbid pain abdominal pain as part of their comorbid pain presentations; the role of the gut microbiota as a possible modulator of the systemic or brain immune systems (and a contributor to elevated CRP levels) is important to keep in mind.

The study had some unexpected findings. First, we were surprised that the confounder analyses identified maltreatment history as a probable confounding factor because the children without a maltreatment history had also been exposed to cumulative adverse life events (see Table 2). These findings suggest that maltreatment—which typically involves a more pervasive pattern of dysfunction from a young age—has a more deleterious effect on the stress system than other types of adverse life events, which often can occur in the context of a better-functioning family system. Importantly, an emerging body of work is looking at epigenetic processes in maltreatment syndromes and at the effect of such processes on gliogenesis [83–85]. Elevated CRP is a possible marker of maltreatment- and stress-associated increases in gliogenesis.

Second, the presence of comorbid pain (present in 50/79 patients (63%))—which is known to be maintained (in part) by activation of peripheral macrophages [86]—did not seem to contribute to elevated CRP titres. Although contemporary diagnostic systems [87] separate pain and FND into separate disorders, an important feature of our cohort was that the chronic pain suffered by our patients emerged alongside their functional neurological symptoms and was an integral part of their FND presentations. Conceptually, chronic pain and functional neurological symptoms can both be understood as resulting from the aberrant activation of emotion-processing regions, which disrupts voluntary motor function [88] and also maintains pain [89].

Third, we unexpectedly found that the small group of patients (10/79, 13%) with depression were less likely to have elevated CRP titres than patients without depression. In contrast to adult patients with chronic depression, from whom much of the data about depression and inflammation are drawn, depression in child and adolescent patients with FND is usually relatively reactive and not long-standing, and our findings may be reflective of these differences.

Fourth, in the subgroup of children with elevated CRP—two-thirds of the sample—the CRP titres were significantly higher than those reported in adolescents with functional somatic symptoms in the TRAILS study [20] (see Fig. 2). Notably, the clinical presentations of the children and adolescents in our study were much more complex. Like the children and adolescents in the TRAILS study, those in our study experienced variety of functional somatic symptoms (63% with comorbid pain and 70% with nonspecific somatic symptoms (nausea, dizziness, breathlessness, and fatigue)). Our participants, however—in virtue of satisfying the criteria for FND—also presented with functional neurological symptoms. They were, therefore, likely to activate several aberrant brain processes in

parallel, each of which is likely to involve activation of the brain–body immune-inflammatory system leading to an overall increase in CRP titres [16, 79, 86, 90].

This study has a number of limitations. First, the laboratory assay used to measure CRP in our cohort had a coefficient of variation (CV) of 12% at 7.3 mg/L, with a limit of blank of 2.1 mg/L. Consequently, CRP titres less than 2 mg/L are not able to be reliably quantified; the increased assay imprecision at very low CRP concentrations results in a corresponding increase in the measurement uncertainty. In future studies, the use of CRP assays with lower limits of detection will be able to better measure subtle changes in systemic inflammation (lower CRP levels) [91].

Second, the current study lacked age- and sex-matched healthy controls from the Australian population; clinical norms established in previous studies were used to evaluate our findings. We note, however, that the population norms provided for 16-year-old Dutch adolescents from the TRAILS study [20] came from a very large population cohort ($n = 2230$) and mapped almost perfectly with the norms previously established by Shine et al. in their UK cohort of 468 healthy young adult volunteer blood donors [54]. It seems unlikely that clinical norms for healthy Australian children and adolescents would be significantly different to the above-described findings.

Third, our data about anxiety, depression, pain, and fatigue were categorical. Use of self-report measures and Likert scales to obtain continuous measures that provided information about the severity of anxiety, depression, pain, and fatigue would potentially be useful. Unfortunately, many self-report measures validated for children and adolescents with mental health disorders have little utility in patients with FND because they fail to identify comorbid anxiety or depression [92]. Research to identify or develop valid and reliable self-report measures in this population is much needed. In the meantime, clinical assessment using diagnostic criteria remains the current best practice [92].

Fourth, we had no way of quantifying maltreatment and other life adversities that our patients had experienced during their lifetimes. More sophisticated measures that quantify the severity or pervasiveness of past maltreatment events (and other adverse life events) in more complex ways—such as the life events and difficulties schedule (LEDS) [93] or formal assessments of attachment [52]—would potentially be helpful.

Fifth, we did not measure genetic variation in relevant genes such as CRP. Miller et al. [33] highlight that the genetic contribution to blood CRP levels are significant, with heritability estimated between 25 and 40% and with individual CRP polymorphisms being associated with up to 64% differences in blood CRP levels [33]. In this context, genetic variations in CRP are potentially a risk factor for FND.

Sixth, in a future study it would be useful to track CRP levels from the time of onset of FND symptoms to recovery—or, over time, in patients that become chronic—to see whether CRP levels normalize or not.

Conclusions

The current study found that two-thirds of child and adolescent patients with FND had elevated CRP titres. A history of maltreatment and a clinical diagnosis of anxiety appeared to contribute to elevated CRP titres (≥ 2 mg/L). Our findings cohere with those of Jonker et al. [20], who found an association between CRP titres and functional somatic symptom score in adolescents with non-neurological functional somatic symptoms. This finding suggests that activation of the immune-inflammatory component of the stress system may be an important part of the neurobiology of FND. Emerging methodologies and future research will enable researchers to examine the origins and locations of immune cell activation and signalling, and the many different factors that may contribute to the modulation of the immune-inflammatory system in patients with FND.

Acknowledgements We thank Matthew Frank for his reading of the manuscript as a critical reviewer and Jenny Peat for her help with statistical analyses.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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