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Pain and pressure pain thresholds in adolescents with chronic fatigue syndrome and healthy controls: a cross-sectional study

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ABSTRACT

Objectives: Although pain is a significant symptom in chronic fatigue syndrome (CFS), pain is poorly understood in adolescents with CFS. The aim of this study was to explore pain distribution and prevalence, pain intensity and its functional interference in everyday life, as well as pressure pain thresholds (PPT) in adolescents with CFS and compare this with a control group of healthy adolescents (HC).

Methods: This is a case–control, cross-sectional study on pain including 120 adolescents with CFS and 39 HCs, aged 12–18 years. We measured pain frequency, pain severity and pain interference using self-reporting questionnaires. PPT was measured using pressure algometry. Data were collected from March 2010 until October 2012 as part of the Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial.

Results: Adolescents with CFS had significantly lower PPTs compared with HCs (p<0.001). The Pain Severity Score and the Pain Interference Score were significantly higher in adolescents with CFS compared with HCs (p<0.001). Almost all adolescents with CFS experienced headache, abdominal pain and/or pain in muscles and joints. Moreover, in all sites, the pain intensity levels were significantly higher than in HCs (p<0.001).

Conclusions: We found a higher prevalence of severe pain among adolescents with CFS and lowered pain thresholds compared with HCs. The mechanisms, however, are still obscure. Large longitudinal population surveys are warranted measuring pain thresholds prior to the onset of CFS.

Trial registration number: Clinical Trials, NCT01040429; The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial (NorCAPITAL) http://www.clinicaltrials.gov.

Strengths and limitationsof this study

- This is one of the first large studies to test and to discuss pressure-provoked pain in adolescents with chronic fatigue syndrome (CFS) and healthy adolescents.
- The relatively large sample of patients together with few missing data strengthens the study and makes it possible to generalise the findings. On the other hand, the study only included patients who were able to attend our research clinic; and the results cannot be extrapolated to the most seriously affected CFS adolescents.
- The study could have benefitted from a larger sample of healthy controls.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a well-known condition among adolescents, with an estimated prevalence from 0.1% to 1.0%.[1 2] However, despite growing research, it is still a poorly understood disorder and there is no general agreement for a reference standard for diagnosis. According to US Centers for Disease Control (CDC-1994), a CFS diagnosis requires three criteria: (1) severe chronic fatigue for 6 or more consecutive months, (2) fatigue that significantly interferes with daily activities and (3) at least four of eight accompanying symptoms. Five of these eight symptoms are regarding pain.[3] For some patients, the ongoing pain is even more disabling than fatigue[4] and is associated with poor physical function.[5] Although the CDC-1994 criteria for CFS are frequently used, the requirement regarding the number of accompanying symptoms has been questioned.[6–8] A recent review found no evidence that any case definitions (diagnostic criteria) for CFS identified patients with specific disease aetiology.[9] For children and adolescents, there are specific recommendations with a broad case definition, requiring 3 months of unexplained disabling, chronic/relapsing fatigue of new onset.[10 11] Although some definitions emphasise pain as an important component,[3 12] this symptom is

often ignored by clinicians and researchers[13] and little progress has been made in understanding the pain component in patients with CFS.[14] Patients with CFS report increased sensitivity to stimuli such as light and sound,[15] and some researchers have hypothesised that the pain is caused by increased sensitivity of the nervous system,[16–18] defined as an "increased responsiveness to normal or sub-threshold input."[19] Based on the theory of the cognitive activation theory of stress, the sustained arousal theory was suggested as a mechanism for the development of CFS, resulting in several bodily symptoms, including pain.[20] Hypersensitivity, measured by means of pressure has been investigated in the adult CFS population, but only with a small number of patients.[18] To the best of our knowledge, hypersensitivity measured by pressure has been insufficiently studied in adolescents with CFS using a control group of healthy adolescents. One exception is a study by van de Putte *et al*,[21] finding that there is considerably lowered pressure pain threshold (PPT) in adolescents with CFS compared with a group of healthy controls (HCs), but the authors did not discuss the lowered PPT in adolescents with CFS other than stating the difference. So far, the pain research on adolescents with CFS has focused on the cluster of symptoms characterising CFS.[1 8 22 23] One way to detect if there is an increased sensitivity is to compare pressure PPT in symptomatic and asymptomatic areas in patients with CFS to HCs.[13] The definition of pain as described by The International Association for the Study of Pain (IASP) emphasises that pain is a complex concept.[24] Thus, there is a need for a broad approach to understanding pain in patients with CFS.

The aim of this study was to evaluate pain in adolescents with CFS compared with healthy adolescents and, more specifically, to explore: (1) the prevalence and location of pain symptoms, (2) pain severity and its functional interference on everyday life and (3) baseline PPTs.

MATERIALS AND METHODS

Design

This is a case–control, cross-sectional study, which compares pain (frequency, severity and interference) and PPTs in adolescents with CFS to a comparable group of healthy adolescents. The study is part of the NorCAPITAL project (The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial; Clinical Trials ID: NCT01040429), which explores possible mechanisms of CFS, the effect of low-dose clonidine treatment and patients' experiences in adolescents with CFS.[15]

Participants

Patients with CFS

One hundred and twenty adolescents with CFS and 39 adolescents without any known health problem were recruited between March 2010 and March 2012. All paediatric departments in Norwegian hospitals (n=20), as well as primary care paediatricians and general practitioners, were invited to refer adolescents with CFS (table 1). The

Table 1 Criteria for inclusion and exclusion

	Patients with CFS	Healthy control participants
Inclusion criteria	Persisting or constantly relapsing fatigue lasting 3 months or more Functional disability resulting from fatigue to a degree that prevents normal school attendance Age ≥12 and <18 years	Age ≥12 and <18 years
Exclusion criteria	Another current process or chronic disease or demanding life event that might explain the fatigue Permanent use of drugs (including hormones) possibly interfering with measurements Permanently bed-ridden Positive pregnancy test Pheochromocytoma Evidence of reduced cerebral and/or peripheral circulation due to vessel disease Polyneuropathy Renal insufficiency Known hypersensitivity towards clonidine or inert substances (lactose, saccharose) in capsula Abnormal ECG (apart from ectopic beats) Supine heart rate <50 bpm Supine systolic blood pressure <85 mm Hg Upright systolic blood pressure fall >30 mm Hg	Another chronic disease Permanent use of drugs (including hormones)

The criteria are designed for the randomised control trial in the NorCAPITAL project (The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial; Clinical Trials ID: NCT01040429), which explores possible mechanisms of CFS, the effect of low-dose clonidine treatment and patients' experiences in adolescents with CFS (9).
CFS, chronic fatigue syndrome.

referring units were required to confirm that the patients did not have any medical or psychiatric disorder that might explain the fatigue. In agreement with clinical guidelines,[10 11] a 'broad' case definition with 3 months of unexplained, disabling fatigue of new onset was required. We did not require any other accompanying symptom criteria to be present. However, we required that the patient (A) was unable to follow normal school routines due to fatigue; (B) was not permanently bedridden; (C) did not use pharmaceuticals (including hormone contraceptives) regularly. Those who fulfilled the prespecified criteria for inclusion (table 1) were included in the NorCAPITAL study. Most participants (75%) satisfied the Fukuda criteria from the International Chronic Fatigue Syndrome Study Group.[3] There are disagreements on the numbers of accompanying symptoms that have to be present for the diagnosis of CFS. At present, there is no evidence for an obvious cut-off for the number of symptoms.[11]

A control group of healthy adolescents

To recruit a control group of healthy adolescents, information of the study was sent to local schools. Those who replied were given extended information. No regular use of pharmaceuticals was allowed. A group of 39 adolescents, reporting themselves as healthy and normally active and matched on gender and age, was enrolled.[15]

Measures

Brief Pain Inventory

To assess pain, the Brief Pain Inventory (BPI) was used.[25] BPI assesses the intensities of pain and to what extent pain interferes with different aspects of life.[26] The Norwegian version of BPI has been validated in cancer pain patients.[27] The questionnaire has also been validated in several chronic non-malign and musculoskeletal disorders[28 29] and in youths with neuromuscular diseases.[30] The numeric rating scale has been shown appropriate for use with children from 5 years of age.[31] Modified versions of the BPI interference score has been used in previous studies with participants aged between 8 and 20.[32 33]

In order to reduce the total burden of questions, we removed the question about pain interference with sleep, and to make it more age-relevant, we asked how pain affected school and homework instead of asking how pain affected work. 'Total Pain Severity Score' was expressed as the mean of the four pain intensity items while 'Total Pain Interference Score' was obtained by calculating the mean of the seven interference items.[28] By removing the question about sleep we ended up with six interference scores that were averaged. Internal consistency of the modified questionnaire was assessed with Cronbach's α computed separately for cases and controls. The values were 0.89 and 0.87 for cases and controls, respectively.

Each item from BPI was read aloud by one of the researchers and answered by the participant. In the body diagram of BPI, patients were asked to indicate the location of their pain by shading the areas corresponding to painful areas of their own body.

CFS questionnaire

A comprehensive CFS questionnaire was constructed and used in the NorCAPITAL study,[15] and in the present study, we focused on four questions from this inventory related to pain: headache, pain in muscles, pain in joint (s) and pain in the abdomen. Frequency of pain was measured on a five-point Likert scale. Single item questions about pain have shown to be reliable in measuring pain in children and adolescents.[34] In contrast to the BPI, which was filled in at the hospital, the CFS inventory was filled in by the participants at home and returned in prestamped envelopes within a few weeks. All measures were performed at baseline, 8 weeks after inclusion and 30 weeks after inclusion. Only the baseline data are presented here.

Pressure pain threshold

PPT is a reliable variable to test for hyperalgaesia in superficial structures such as skin, nails and underlying muscles.[35] The pain threshold is defined by IASP (1986) as "the minimum intensity of a stimulus that is perceived as painful."[19] Pressure provoked pain thresholds were mapped using a commercially available force transducer with a rubber tip of 0.5 cm^2 (Algometer, JTECH, medical, Salt Lake City, Utah, USA). Values are presented in Newton (N). The intensity was increased until the PPT was reached. For each person we assessed all sites in the same order. We intended to measure PPTs at places where people commonly have pain (trapezius and supraspinatus), as well as at places that rarely hurt (fingernails) and selected three predefined sites: (1) the fingernail of the third finger, (2) skin superficial to the trapezius (ascending part) and (3) supraspinatus muscles bilaterally. Reduced thresholds on symptomatic as well as asymptomatic/remote places may indicate a general sensitisation.[18] To ensure reliability, the pressure stimuli were applied twice to each spot and then averaged, a procedure that is commonly used in other studies to ensure reliability.[36] The participants were instructed to indicate pain threshold by saying 'stop'. In between the two measurements, they filled in the BPI assessment form, which took about 10 min to complete. The researcher was not blinded regarding patients with CFS and HCs.

Ethical considerations

Participation in the project required informed consent by the adolescent and by their parents/next-of-kin, after written and oral information about the study.

Statistical analyses

Continuous variables are presented with medians and ranges while categorical variables are described as counts and percentages. Pain intensity and pain interference were measured on ordinal scales, and group

Table 2 Frequency of pain episodes in different locations among patients with CFS and healthy controls

	Patients with CFS, n=120 (%)				Healthy controls, n=39 (%)			
Frequency	Head	Abdomen	Joints	Muscles	Head	Abdomen	Joints	Muscles
0–1 times/month	9 (8)	30 (25)	36 (30)	21 (18)	18 (46)	20 (51)	35 (90)	26 (67)
2–3 times/month	28 (23)	30 (25)	19 (16)	20 (17)	14 (36)	15 (39)	2 (5)	7 (18)
1–2 times/week	28 (23)	21 (18)	24 (20)	24 (20)	4 (10)	1 (3)	0	2 (5)
3–5 times/week	20 (17)	21 (18)	15 (13)	17 (14)	0	1 (3)	0	1 (3)
~Every day	32 (27)	15 (13)	23 (20)	34 (28)	1 (3)	0	0	1 (3)
Missing (%)	2.5	2.5	2.5	3.3	5.1	5.1	5.1	5.1

Group comparisons for different pain sites (head, abdomen, joints and muscles); p<0.001 for all four sites.
CFS, chronic fatigue syndrome.

differences were therefore analysed by a non-parametric test (Mann-Whitney-Wilcoxon test). For frequency differences between the groups, the χ^2 test was applied. An average of two pain pressure threshold measurements were calculated for three body parts on each body side. As the values were normally distributed in both groups, they were compared using two independent samples t tests.

To assess internal consistency of the instruments, Cronbach's α was computed separately for cases and controls. α>0.7 was considered acceptable.[37] All tests were two sided and, due to multiple testing, only p values <0.01 were considered statistically significant. All analyses were performed using SPSS, IBM Statistics V.20.

RESULTS

In the whole sample (including the CFS and the control group), about 25% were males and 75% females. Mean age was 15.4 years (SD 1.6) for patients and 15.2 (SD 1.6) for HCs. There were almost no missing data in any of the data sets (details are given in tables 2 and 3). There were no statistically significant differences between cases and controls concerning possible confounders (age, body mass index and gender distribution), and there was no difference between patients and controls regarding socioeconomic status (table 4).

Pain prevalence and distribution

The frequency data from the CFS Symptom Inventory showed that adolescents with CFS were, on a weekly basis, seriously influenced by pain (table 2). Summing up the categories 3, 4 and 5 in table 2 (1–2 times/week, 3–5 times/week and approximately every day), almost all adolescents with CFS versus one-third of the HCs reported pain during the previous week, and the group difference was highly significant. Headache was most common (67% reported weekly attacks), followed by muscle pain (62%), pain in joints (53%) and abdominal pain (49%). Headache was also the most reported pain in HCs (13%), followed by pain in muscles (11%) and abdominal pain (6%). No HCs reported pain in joints as a problem on a weekly basis. Studying the body map, almost 30% of the patients with CFS marked more than four sites as painful while none of the HCs did (table 5).

Pain severity and functional interference

Patients with CFS demonstrated higher Pain Severity Scores (p<0.001) and Pain Interference Scores

Table 3 Pain Intensity, Severity and Interference scores among patients with CFS and healthy controls

	Patients with CFS		Healthy controls		
	n	Median (range)	n	Median (range)	p Value*
Pain worst	117	6 (0–10)	39	3 (0–10)	
Pain least	118	1 (0–7)	39	0 (0–7)	
Pain average	118	5 (0–9)	39	3 (0–6)	
Pain now	118	2 (0–8)	39	0 (0–7)	
Total Pain Severity Score	117	14.5 (0–31)	39	6 (0–23)	<0.001
Interference in					
General activity	118	4 (0–10)	39	1 (0–8)	
Mood	118	3 (0–9)	39	1 (0–8)	
Walking	118	2 (0–10)	39	0 (0–7)	
School	118	4 (0–10)	39	0 (0–8)	
Relation to others	118	2 (0–9)	39	0 (0–8)	
Enjoyment of life	118	2 (0–9)	39	0 (0–10)	
Total Pain Interference Score	118	17 (0–49)	39	4 (0–36)	<0.001

*Statistical group comparisons; Mann-Whitney-Wilcoxon test.
CFS, chronic fatigue syndrome.

Table 4 Demographic data and adherence to specific CFS criteria (Fukuda, 1994)

	Patients with CFS n=120	Controls n=39
Male, n (%)	34 (28)	11 (28.2)
Female, n (%)	86 (72)	28 (71.8)
Age (years), mean (SD)	15.4 (1.6)	15.2 (1.6)
Disease duration (months), Mean (range)	21.4 (4–104)	NA
Fukuda criteria, n (%)	88 (75)	NA
Lives with both parents, n (%)	85 (73)	26 (70)
Parents' highest education, n (%)		
Primary school	5 (4.3)	0 (0)
Secondary school	30 (26)	8 (23)
Lower university	34 (29)	9 (23)
Higher university	48 (41)	19 (54)

n, number of individuals; CFS, chronic fatigue syndrome.

(p<0.001) than HCs. Among the patients with CFS, pain interfered most with attendance at school and general activity (table 3). Ability to enjoy life, however, was one of the life domains that was least affected by pain, among patients with CFS and also among HCs; but it is important to notice that 8.4% of the adolescents with CFS scored above seven on this item. Three HCs scored high (≥8) on pain severity while four on pain interference, reflecting the large variation in the normal population.

Pressure pain thresholds

At all measure points, PPTs were significantly lower (all p<0.001) among patients with CFS than HCs. For the trapezius muscle, the mean values were 15.4, 95% CI (14.1 to 16.8) and 24.5, 95% CI (21.0 to 28.0) for cases and controls, respectively. On fingernails 18.5, 95% CI (16.9 to 20.0) for cases and 30.8, 95% CI (26.5 to 35.4) for controls. Concerning supraspinatus muscle the mean values were 17.1, 95% CI (15.6 to 18.6) for cases and 27.7, 95% CI (23.3 to 31.6) for controls. The values show that PPT was as much as 50% lower in patients with CFS than in HCs, at locations that usually are painful (muscles) as well as in areas that usually are not reported painful (finger nails). There were no missing data for HCs and for patients with CFS data were missing for one individual.

Table 5 Number of body sites mapped as painful among patients with CFS and healthy controls

	Patients with CFS n=117	Healthy controls n=39
0 locations, n (%)	8 (7)	7 (18)
1 location, n (%)	13 (11)	13 (33)
2 locations, n (%)	19 (16)	10 (10)
3 locations, n (%)	30 (26)	5 (5)
4 locations, n (%)	13 (11)	4 (10)
5 locations, n (%)	17 (15)	0 (0)
6 locations, n (%)	6 (5)	0 (0)
7 locations, n (%)	11 (9)	0 (0)

The located areas shaded are head, neck/shoulder, chest, back, abdomen, upper limb, lower limb. Only the counted number of locations are presented in the table.
n, number of individuals; CFS, chronic fatigue syndrome.

DISCUSSION

This study shows that adolescents with CFS have significantly lower pain thresholds than a comparable control group of healthy adolescents. The study also demonstrates that adolescents with CFS are severely troubled by pain and that pain has great functional consequences. A more unexpected finding is the lower pain interference on joy of life for the patients.

Hypersensitivity

The significantly lower PPTs among adolescents with CFS compared with HCs in symptomatic and asymptomatic places could indicate a more general sensitisation of the nervous system.[38] Lowered PPT in asymptomatic areas, indicating general sensitisation, has also been found in patients with Ehlers-Danlos syndrome.[36] General hypersensitivity has been suggested as a reason for pain among patients with CFS, as it has for chronic widespread pain[16] and fibromyalgia.[39] Our own research group found significantly higher sensitivity scores among adolescents with CFS and hypothesises that the hypersensitivity could be an effect of sustained arousal.[15] Other researchers have highlighted altered pain inhibition as a potential factor in patients with generalised pain.[40] Patients with CFS have also reported being more sensitive to other sensory stimulations such as light and sound.[15 41] Thus, it might be the case that adolescents with CFS are more sensitive to several types of sensory stimuli. On the other hand, it should be borne in mind that lowered PPT only reflects increased sensitivity to mechanical stimuli, and does not predict the response to, for instance, thermal stimuli.

Researchers have suggested that patients with CFS are genetically more prone to develop the disease,[20] in line with epidemiological data on chronic pain.[42] The factors and processes for pain among patients with CFS remain unclear, but in other populations, pain beliefs, emotions, understanding of pain and psychosocial factors have been found to influence the perception of pain.[43] In patients with fibromyalgia, Turk[43] showed that fear of movement maintains the pain experience and increases the disability. The model on pain-related fear and avoidance suggests this as essential for perpetuation of pain,[44] and among adults with CFS, Nijs *et al*[45] demonstrate a clear association between pain catastrophising, pain severity and activity limitation/participation. There is no obvious reason to believe that this is not the case for adolescents with CFS. Negative thoughts may also develop when patients do not understand the aetiology

of pain.[36] A qualitative study suggests that multiple perspectives, including individual differences, developmental and relational focus, should be taken into account when treating and studying young persons with CFS.[46] Cognitive behaviour therapy for CFS has shown to be effective in improving fatigue and pain in adults and adolescents.[4] A multidimensional perspective of CFS, opposing the dichotomy between bodily and mental processes and acknowledging the impact of cognitive processes on physiological responses, is supported by previous studies[47 48] and is in line with the sustained arousal theory.[20]

More knowledge about pain and the relation to increased sensitivity before and throughout the process of the illness might provide a better understanding of CFS. Except for one study (published as editorial letter 2013) showing improvement in pain and pain threshold after successful cognitive behaviour therapy,[49] we are not aware of other published studies focusing on this aspect in adolescents with CFS.

Frequency of pain

In the present study, almost three-quarters of the adolescents with CFS suffered from weekly pain, and pain on a daily basis was a problem for half of the patients. HCs also reported pain on a weekly basis, but the rates were much lower. Pain is indeed a common problem among teenagers in general[50–53]; in a large Norwegian health survey, 10% of healthy adolescents reported pain on a daily basis and 19% were troubled by musculoskeletal or abdominal pain.[52] In our study, nearly half of the adolescents with CFS reported abdominal pain every week. Such a high proportion of recurrent abdominal pain has also been reported in a study on CFS adolescents from the UK.[54] These authors demonstrated in another study the same somatic symptoms among HCs and adolescents with CFS, although with a lower degree of severity in HCs[55]; headache and sore muscles were among the top 10 bodily complaints. Our study confirms these findings. Adolescents with CFS report pain in the same places as the HCs do, although the pain frequency is higher. In both groups, headache is the most common pain followed by abdominal pain.

The largest group difference in the present study was joint pain. Of the HCs, only 10% reported joint pain more frequently than once a month, versus 70% of the adolescents with CFS.

Pain severity and interference in daily life

From HCs we know that physical activity has an important pain protective effect,[52] and Crawley and Stern[5] have shown that impaired physical function is associated with higher levels of fatigue, pain and low mood. Complicating this, pain thresholds in patients with CFS have been found to decrease after physical exercises,[56] which may lead to a fear avoidance behaviour. This phenomenon illustrates how several contributing factors may influence the pain condition.

Although average Pain Severity Scores were relatively moderate in the CFS group (table 3), healthcare providers should bear in mind that the total sum of pain and fatigue over time might represent a heavy burden with serious long-term consequences.[48] Large studies on pain in children and adolescents have demonstrated substantial reductions in quality of life (QOL).[50 57 58] In our study, the adolescents reported that pain interfered with school, general activity and mood; however, we cannot conclude from this study that pain has a causal effect, because it could be the other way around. Particularly interference with school attendance has been shown to strongly affect QOL in adolescents with CFS.[55 59] Some of our patients felt it was difficult to assess the interference of pain, and to separate what was caused by fatigue and what was caused by pain, and the second part of BPI (mapping the interference of pain) has for that reason been criticised.[27] Although the participants were told to concentrate on pain and not the fatigue, we realise that QOL is most likely to be affected by both.

It is important to bear in mind that the economical differences between social classes are not as pronounced in Norwegian society as in other Western societies, and all individuals in Norway have equal access to medical care; and using level of education as a surrogate for social class, we still found no difference between the two groups.

Strengths and limitations

This is one of the first studies to include a broader focus on pain in adolescents with CFS, and to test pressure-provoked pain in adolescents with CFS and in healthy adolescents. The relatively large sample of patients together with few missing data strengthens the study, making it possible to generalise the results. The wide inclusion criteria suggest generalisability to the population of adolescents with CFS referred to paediatric care. Only two patients reported a short disease duration between 3 and 6 months,[15] and the results should be generalisable to populations with a more persistent CFS condition (more than 6 months). The NorCAPITAL study did have one clear selection bias, as the study only included patients who were able to attend our research clinic; and the results cannot be extrapolated to the most seriously affected CFS adolescents. One question from the original BPI questionnaire was removed and this might have affected the psychometric property. However, Cronbach's α computed for BPI interference scores demonstrated strong internal consistency for both cases and controls. The results could have been influenced by confounding factors such as anxiety and depression. In a previous paper from our research group, on the same group of patients, however, we did not find depression to be a confounding factor.[15] The control group of adolescents is smaller than the CFS group, and the study might have benefitted from a larger sample of controls. Power calculation from a previous study,[47] however, gives reasons to assume that our

samples were sufficient to discover significantly and clinically interesting group differences.[15]

CONCLUSION

We found a higher prevalence of severe pain among adolescents with CFS and lowered pain thresholds compared with HCs. The total sum of bodily symptoms represented a heavy burden with great functional consequences. The large sample of patients together with few missing data strengthens the study, making it possible to generalise the results.

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