BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005920
Article Type:	Research
Date Submitted by the Author:	17-Jun-2014
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Paediatrics
Keywords:	Pain management < ANAESTHETICS, PAIN MANAGEMENT, PUBLIC HEALTH

Title Page

Pain and Pain Thresholds in Adolescents with Chronic Fatigue Syndrome

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Abbreviations: BPI- Brief Pain Inventory; CFS-Chronic fatigue syndrome; HC- Healthy Controls; NRS-Numeric Rating Scale; PPT-Pressure Pain Threshold; QoL- Quality of Life

Key Words: adolescents, pain threshold, Chronic fatigue syndrome, public health nurse, and pediatrician

Clinical Trials, NCT01040429; The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial (Nor CAPITAL) www.clinicaltrials.gov.

Length of article: 3251 words

What's known on this subject: Pain is an important symptom in chronic fatigue syndrome (CFS). However, this pain is poorly understood and little explored in adolescents with CFS.

What does this study add: The study describes the pain prevalence and severity in adolescents with CFS and demonstrates that they are significantly more interfered by pain compared to healthy adolescents in terms of pain frequency, pain severity, functional interference and pressure pain threshold (PPT).

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ABSTRACT

Background and 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 the 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 healthy controls, aged 12 to 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 to HC ($p<0.001$). The Pain Severity Score and Pain Interference Score were significantly higher in adolescents with CFS compared to 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 HC ($p<0.001$).

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

Strengths and limitations

- This is the first study to test pressure-provoked pain in both adolescents with CFS and in healthy adolescents
- The relatively large sample of patients, together with few missing data strengthens the study
- 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 larges 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. According to US Centers for Disease Control (1994), a CFS diagnosis requires three criteria: 1) severe chronic fatigue for six or more consecutive months, 2) fatigue that significantly interferes with daily activities and 3) at least four out of eight other symptoms: post-exertional malaise lasting more than 24 hours, unrefreshing sleep, significant impairment of short-term memory or concentration, muscle pain, pain in the joints without swelling or redness, headaches of a new type, pattern, or severity, tender lymph nodes in the neck or armpit, and a sore throat that is frequent or recurring. Five out of these eight symptoms, are about pain,[3]. For some patients the ongoing pain is even more disabling than fatigue,[4] and is associated with poor physical function,[5]. Although some definitions emphasize pain as an important component,[3, 6], it is often ignored by clinicians and researchers,[7], and little progress has been made in understanding the pain component in patient with CFS,[8]. Patients with CFS report increased sensitivity to stimuli like light and sound,[9], and some researchers have hypothesized that the pain is caused by increased sensitivity of the nervous system,[10-12], defined as an "increased responsiveness to normal or sub-threshold input",[13]. Based upon the theory of the Cognitive activation theory of stress (CATS) the sustained arousal theory was suggested as a mechanism for the development of CFS, resulting in several bodily symptoms, including pain,[14]. Hypersensitivity, measured by means of pressure is investigated in the adult CFS population, but only with a small number of patients,[12]; however, to our knowledge, this has not been studied in adolescents. So far, the pain research on adolescents with CFS has focused on the cluster of symptoms characterizing CFS,[1, 15-17]. One way to detect if there is an increased sensitivity is to compare pressure pain thresholds (PPT) in symptomatic and asymptomatic

areas in CFS patients to HCs,[7]. The International Association for the Study of Pain's (IASP) definition of pain emphasizes that pain is a complex concept,[18]. 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 to healthy adolescents, and more specifically explore: 1) the prevalence and location of pain symptoms, 2) pain severity and its functional interference on everyday life and 3) baseline pressure pain thresholds (PPTs).

MATERIAL 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,[9].

Participants

CFS patients

One hundred and twenty adolescents with CFS and 39 adolescents, without any known health problems, were recruited between March 2010 and March 2012. All pediatric departments in Norwegian hospitals (n=20), as well as primary care pediatricians and general practitioners, were invited to refer adolescents with CFS, aged 12 to 18, years to a central Norwegian department of pediatrics. The 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,[19, 20] a "broad" case definition with three 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 pre-specified criteria for inclusion (Table 1) were included in the Nor CAPITAL 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 has to be present for the diagnosis with CFS. At present, there is no evidence for an obvious cut-off for the number of symptoms,[19].

Table 1. Criteria for inclusion and exclusion

	CFS patients	**Healthy control subjects**
Inclusion criteria:	Persisting or constantly relapsing fatigue lasting 3 months or more. Functional disability resulting from fatigue to a degree that prevent normal school attendance Age ≥ 12 and < 18 years	Age ≥ 12 years 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 Pheocromocytoma Evidence of reduced cerebral and/or peripheral circulation due to vessel disease Polyneuropathy Renal insufficiency Known hypersensitivity towards clonidine or inert substances (lactose, saccarose) in capsula Abnormal ECG (apart from ectopic beats)	Another chronic disease Permanent use of drugs (including hormones)

	Supine heart rate < 50 beats/min
	Supine systolic blood pressure < 85 mmHg
	Upright systolic blood pressure fall > 30 mmHg

The criteria are designed for the randomized 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).

In our study, there was no difference between patients and controls regarding socioeconomic status (Table 2). It is important to bear in mind that the economical differences between social classes are not as pronounced in the Norwegian society as in other Western societies, and all individuals in Norway have equal access to medical care. However, using level of education as a surrogate for social class, we still found no difference between the two groups.

Table 2. Demographic data and adherence to specific CFS criteria (Fukuda, 1994).

		CFS patients	controls
Male-	no (%)	34 (28)	11 (28.2)
Female-	no (%)	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)	n.a.
Fukuda-criteria	no (%)	88 (75)	n.a.
Lives with both parents	no (%)	85 (73)	26 (70)
Parents highest education			
Primary school	no (%)	5 (4.3)	0 (0)
Secondary school	no (%)	30 (26)	8 (23)
Lower University	no (%)	34 (29)	9 (23)
Higher University	no (%)	48 (41)	19 (54)

A control group of healthy adolescents

To recruit a control group of healthy adolescents, information of the study was sent to the 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,[9].

Measures

Brief Pain Inventory (BPI):

To assess pain, the Brief Pain Inventory (BPI) was used,[21]. BPI assesses the intensities of pain and to what extent pain interferes with different aspects of life,[22]. The Norwegian version of BPI has been validated in cancer pain patients,[23], several chronic non- malign and musculoskeletal disorders,[24, 25], and in youths with neuromuscular diseases,[26].

In order to reduce the total burden of questions, we removed the question about pain interference with sleep. 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,[24]. 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 alpha 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 Nor CAPITAL study,[9], 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 has shown to be

reliable in measuring pain in children and adolescents,[27]. 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 pre- stamped envelopes within a few weeks. All measures were done at baseline, eight weeks after inclusion, and 30 weeks after inclusion. Only the baseline data are presented here.

Pressure pain threshold

The pressure pain threshold (PPT) is a reliable variable to test for hyperalgesia in superficial structures like skin, nails and underlying muscles,[28]. The pain threshold is defined by IASP (1986) as "the minimum intensity of a stimulus that is perceived as painful.",[13]. To investigate if there are group differences in pressure-provoked pain, the 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, USA). For pressure measurements, we selected three pre-defined sites: 1) the fingernail of the third finger, 2) skin superficial to the trapezius (ascending part) and 3) supraspinatus muscles bilaterally. We intended to measure PPTs both at places where people commonly have pain (trapezius and supraspinatus), and places that rarely hurt (fingernails). Reduced thresholds on both symptomatic and asymptomatic/remote places may indicate a general sensitization,[12]. The pressure stimuli were applied twice to each spot with increasing intensity until the pressure pain threshold was reached. For each person we assessed all sites in the same order. The participants were instructed to indicate the pain threshold by saying, "stop". In between the two measurements, they filled in the BPI assessment form, which took about ten minutes to fulfill.

Ethical considerations

The study was approved by Norwegian Social Science Data Service (NSD) and by the Norwegian Regional Committee for Medical and Health Research Ethics (REK). Participation

in the project required informed consent by the adolescent and by his or her 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 differences were therefore analyzed by a non- parametric test (Mann Whitney Wilkoxon-test). For frequency differences between the groups, the Chi-square 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*-test.

To assess internal consistency of the instruments, Cronbach's alpha was computed separately for cases and controls. Alpha >0.7 was considered acceptable,[29]. 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, version IBM Statistics 20.

RESULTS

In the whole sample (including the CFS and the control group), about 25% were males and 75% females. The age ranged from 12 -18 years (Table 2). There were almost no missing data in any of the data sets (details are given in Tables 3 and 4). There were no statistically significant differences between cases and controls conserning possible confounders (age, BMI and gender distribution).

Table 3. Frequency of pain episodes in different locations among CFS patients and healthy controls

	CFS patients n= 120 (%)				Healthy controls n=39 (%)			
Frequency	Head	Abdomen	Joints	Muscles	Head	Abdomen	Joints	Muscles
0-1 t/mo	9 (8)	30 (25)	36 (30)	21 (18)	18 (46)	20 (51)	35 (90)	26 (67)

2-3 t/mo	28 (23)	30 (25)	19 (16)	20 (17)	14 (36)	15 (39)	2(5)	7 (18)
1-2 t/w	28 (23)	21 (18)	24 (20)	24 (20)	4 (10)	1 (3)	0	2 (5)
3-5 t/w	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
mo= month, w= week

Table 4. Pain Intensity, Severity and Interference scores among CFS patients and healthy controls

	CFS patients			Healthy controls			*p*-value*
	N	Median	(Range)	n	Median	(Range)	
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 to:							
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)	
Enjoy 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

Pain prevalence and distribution

The frequency data from the CFS Symptom Inventory showed that adolescents with CFS were weekly seriously influenced by pain (Table 3). Summing up the categories 3, 4 and 5 in Table 2, almost all adolescents with CFS vs. one third of the HC reported pain during the previous week, and the group difference was statistically 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 HC (13%), followed by pain in muscles (11%) and abdominal pain (6%). No HC 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 (Figure 1).

Figure 1. Number of body sites mapped as painful among CFS patients and healthy controls (insert)

Pain severity and functional interference

CFS patients demonstrated higher Pain Severity Scores (p <0.001) and Pain Interference scores (p <0.001) than HCs. Among the CFS patients, pain interfered most with attendance at school and general activity (Table 4). Ability to enjoy life, however, was one of the life domains that was least affected by pain, both among CFS patients and 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 on pain severity while four on pain interference, reflecting the large variation in the normal population.

Pressure pain thresholds

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

DISCUSSION

This study shows that adolescents with CFS have significantly lower pain thresholds than a 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 cases.

Hypersensitivity and frequency of pain

We found significantly lower PPTs among adolescents with CFS compared with HCs at all three sites (trapezius and supraspinatus muscles and nails) and in both symptomatic and asymptomatic places. This finding could indicate a more general sensitization of the nervous system,[30]. General hypersensitivity has been suggested as a reason for pain among CFS patients, as it has for chronic widespread pain,[10] and fibromyalgia,[31]. Our own research group found significantly higher sensitivity scores among adolescents with CFS and hypothesizes that the hypersensitivity could be an effect of sustained arousal,[9]. Other researchers have highlighted altered pain inhibition as a potential factor in patients with generalized pain,[32]. Patients with CFS have also reported being more sensitive to other sensory stimulations like light and sound,[9, 33]. Thus, it might be the case that adolescents with CFS are more sensitive to all 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 do not predict the response to, for instance, thermal stimuli.

Researchers have suggested that CFS patients are genetically more prone to develop the disease,[14], and epidemiological studies have demonstrated a genetic predisposition to chronic pain,[34]. The factors and processes for pain among CFS patients remain unclear, but in other populations, pain beliefs, feelings, understanding of pain and psychosocial factors have been found to influence the perception of pain,[35]. In patient with fibromyalgia Turk et

al. (2003) showed that fear of movement maintains the pain experience and increases the disability,[35]. There is no obvious reason to believe that this is not the case for adolescents with CFS. A multidimensional perspective of CFS is in line with the sustained arousal theory, acknowledging the impact of cognitive processes on physiological responses and thereby opposing a fundamental dichotomy between bodily and mental processes,[14]. A multidimensional perspective and a bio-psychosocial approach for this group of patients are in line with other studies,[36, 37]. 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. As far as we know, there is no published study focusing on this aspect.

As the present study shows, almost all adolescents with CFS suffered from weekly pain, and pain on a daily basis was a problem for a large proportion of the patients. The CFS patients reported significantly more pain compared with the HC, but interestingly, they reported pain in the same places as the HCs did, although the pain frequency was higher. In both groups, headache was the most common pain followed by abdominal pain. Of the CFS patients, 67% experienced weekly headache and of these 27% had headache every day. For the HCs, these numbers were respectively 13% and 3%. Pain is indeed a common problem among teenagers in general,[38-41]; 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,[40]. In our study 49% reported abdominal pain every week. Such a high proportion of recurrent abdominal pain (49%) has also been reported in a study on CFS adolescents from the UK,[42]. The same authors have in a previous study demonstrated same somatic symptoms among HCs and adolescents with CFS, although with a lower degree of severity,[43]; headache and sore muscles were among the top ten bodily complaints. The largest group difference in the present study was joint pain. Of the HCs, only 10% reported pain more frequently than once a month, vs. 70% of the adolescents with CFS.

Pain severity and interference in daily life

From healthy controls we know that physical activity has an important pain protective effect,[40], and Crawley and Stern (2009) have shown that impaired physical function is associated with higher levels of fatigue, pain and low mood,[5]. Complicating this, pain thresholds in patients with CFS have been found to decrease after physical exercises,[44], and patients may easily develop a fear of movement behavior. This illustrates how several contributing factors may influence the pain condition.

Although average Pain Severity Scores were relatively moderate in the CFS group (table 4), health care 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,[37]. In larger studies on children and adolescents with long-lasting pain, pain has been associated with substantial reductions in health- related quality of life (QoL),[38, 45, 46]. In our study, the pain influenced school attendance, general activity and mood. Particularly interference on school attendance has been shown to strongly affect the quality of life in adolescents with CFS,[43, 47]. 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 criticized,[23]. Although the participants were told to concentrate on pain and not the fatigue, we realize that fatigue may still a confounding factor and daily life was most likely to be affected by both.

Strengths and limitations

This is the first study to include a broader focus on pain in adolescents with CFS, and to test pressure-provoked pain in both adolescents with CFS and in healthy adolescents. The relatively large sample of patients together with few missing data strengthen the study. The wide inclusion criteria suggest generalizability to the population of adolescents with CFS

referred to pediatric care. Only two patients reported a short disease duration between three and six month,[9], and the results should be generalizable to populations with a more chronic CFS condition (more than six months). The Nor CAPITAL 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, hence we performed a factor analysis on BPI interference scores showing a strong internal consistency for both cases and controls. The control group of adolescents is smaller than the CFS group, and the study could have benefited from a larger sample of controls, even if a power calculation based upon previous studies,[36] give reasons to assume that the samples would be sufficient to discover significantly and clinically interesting group differences,[9].

CONCLUSION

We found a higher prevalence of severe pain among adolescents with CFS and lowered pain thresholds compared to healthy controls. Pain has great functional consequences and the total sum of bodily symptoms is a heavy burden.

Acknowledgments

Kari Gjersum, Berit Widerøe Njølstad, Adelheid Holm, Marianne Svendsen, Anne Marie Halstensen, Kristin Villa, Esther Gangsø, Hamsana Chandrakumar, Anna Marie Thorendal Ryenbakken all participants and their parents/next-of-kin.

The information reported in this manuscript has not been presented in any other journal.
The authors have no financial relationship nor any other conflict of interest to disclose.

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Acknowledgments:

Kari Gjersum provided secretarial assistance, Berit Widerøe Njølstad, MA; Adelheid Holm, RN; Marianne Svendsen, BSc; Anne Marie Halstensen, RN; Kristin Villa, RN; Esther Gangsø, BSc; Hamsana Chandrakumar, BSc and Anna Marie Thorendal Ryenbakken provided practical assistance.

Competing interests: To the author's knowledge, no conflict of interest, financial or other, exists.

Funding/Support: As part of the Nor CAPITAL-project this study was funded by Health South-East Hospital Trust, the University of Oslo, Oslo and Akesrhus University College of Applied Sciences, the Norwegian Competence Network of Pediatric Pharmacotherapy, Simon Fougner Hartman's Family Foundation, and Eckbo's Family Foundation funded this study.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

No additional data available.

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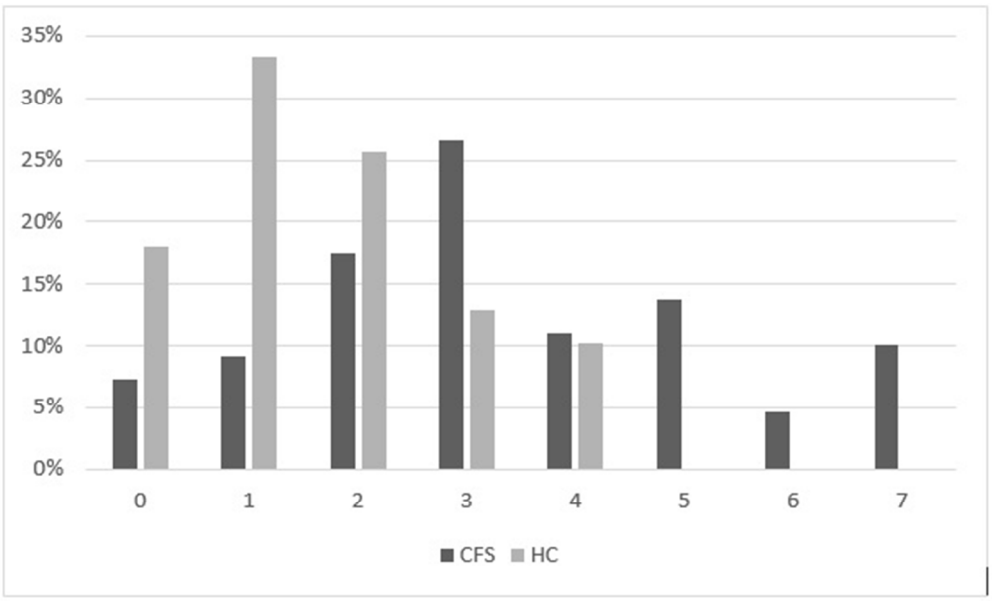

129x77mm (120 x 120 DPI)

BMJ Open

Pain and Pressure Pain Thresholds in Adolescents with Chronic Fatigue Syndrome and Healthy Controls; a cross sectional study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005920.R1
Article Type:	Research
Date Submitted by the Author:	09-Aug-2014
Complete List of Authors:	Winger, Anette; Oslo and Akershus University College of Applied Sciences, Kvarstein, Gunnvald; University of Tromsø, the Article University of Norway, Department of Clinical Medicine Wyller, Vegard; University of Oslo, Medical Faculty Sulheim, Dag; Lillehammer County Hospital, Lillehammer, Department of Pediatrics, Norway Fagermoen, Even; University of Oslo, Medical Faculty Småstuen, Milada; Oslo and Akershus University College of Applied Sciences, Helseth, Sølvi; Oslo and Akershus University College of Applied Sciences,
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Public health
Keywords:	Pain management < ANAESTHETICS, PAIN MANAGEMENT, PUBLIC HEALTH

Title Page

Pain and Pressure Pain Thresholds in Adolescents with Chronic Fatigue Syndrome and Healthy Controls; a cross sectional study

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Abbreviations: BPI- Brief Pain Inventory; CFS-Chronic fatigue syndrome; HC- Healthy Controls; NRS-Numeric Rating Scale; PPT-Pressure Pain Threshold; QoL- Quality of Life

Key Words: adolescents, pain threshold, Chronic fatigue syndrome, public health nurse, and pediatrician

Clinical Trials, NCT01040429; The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial (Nor CAPITAL) www.clinicaltrials.gov.

Length of article: 3706 words

What's known on this subject: Pain is an important symptom in chronic fatigue syndrome (CFS). However, this pain is poorly understood and little explored in adolescents with CFS.

What does this study add: The study describes the pain prevalence and severity in adolescents with CFS and demonstrates that they are significantly more interfered by pain compared to healthy adolescents in terms of pain frequency, pain severity, functional

interference and pressure pain threshold (PPT).

Pain and Pressure Pain Thresholds in Adolescents with Chronic Fatigue Syndrome and Healthy Controls; a cross sectional study

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 the 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 to 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 to HCs ($p<0.001$). The Pain Severity Score and Pain Interference Score were significantly higher in adolescents with CFS compared to 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 to HCs. The mechanisms, however, are still obscure. Large longitudinal population surveys are warranted measuring pain thresholds prior to the onset of CFS.

Strengths and limitations

- This is one of the first large studies to test and to discuss pressure-provoked pain in both adolescents with CFS and healthy adolescents.
- The relatively large sample of patients together with few missing data strengthen the study and make it possible to generalize 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 six or more consecutive months, 2) fatigue that significantly interferes with daily activities and 3) at least four out of eight accompanying symptoms. Five out of these eight symptoms, are about 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 the 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 etiology,[9]. For children and adolescents there are specific recommendations with a broad case definition, requiring three months of unexplained disabling, chronic/relapsing fatigue of new onset,[10, 11]. Although some definitions emphasize 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 like light and sound,[15], and some researchers have hypothesized 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 upon the theory of the Cognitive activation theory of stress (CATS) 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 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. (2005), finding that there is considerably lowered pressure pain threshold (PPT) in adolescents with CFS compared to a group of healthy controls,[21]; 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 characterizing 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 CFS patients to HCs,[13]. The International Association for the Study of Pain's (IASP) definition of pain emphasizes that pain is a complex concept,[24]. Thus, there is a need for a broad approach to understand pain in patients with CFS.

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

MATERIAL 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

CFS patients

One hundred and twenty adolescents with CFS and 39 adolescents without any known health problem, were recruited between March 2010 and March 2012. All pediatric departments in Norwegian hospitals (n=20), as well as primary care pediatricians and general practitioners, were invited to refer adolescents with CFS (Table 1). The 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 three 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 pre-specified criteria for inclusion (Table 1) were included in the Nor CAPITAL 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 with CFS. At present, there is no evidence for an obvious cut-off for the number of symptoms,[11].

Table 1. Criteria for inclusion and exclusion

	CFS patients	**Healthy control subjects**
Inclusion criteria:	Persisting or constantly relapsing fatigue lasting 3 months or more. Functional disability resulting from fatigue to a degree that prevent normal school attendance Age ≥ 12 and < 18 years	Age ≥ 12 years 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	Another chronic disease Permanent use of drugs (including hormones)

	Pheocromocytoma
	Evidence of reduced cerebral and/or peripheral circulation due to vessel disease
	Polyneuropathy
	Renal insufficiency
	Known hypersensitivity towards clonidine or inert substances (lactose, saccarose) in capsula
	Abnormal ECG (apart from ectopic beats)
	Supine heart rate < 50 beats/min Supine systolic blood pressure < 85 mmHg Upright systolic blood pressure fall > 30 mmHg

The criteria are designed for the randomized 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).

Table 2. Demographic data and adherence to specific CFS criteria (Fukuda, 1994).

		CFS patients 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)	n.a.
Fukuda-criteria	n (%)	88 (75)	n.a.
Lives with both parents	n (%)	85 (73)	26 (70)
Parents highest education			
Primary school	n (%)	5 (4.3)	0 (0)
Secondary school	n (%)	30 (26)	8 (23)
Lower University	n (%)	34 (29)	9 (23)
Higher University	n (%)	48 (41)	19 (54)

n=number of individuals

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 (BPI)

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 alpha 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 Nor CAPITAL 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 pre- stamped envelopes within a few weeks. All measures were done at baseline, eight 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 hyperalgesia in superficial structures like 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, USA). Values are presented in Newton (N). The intensity was increased until the pressure pain threshold was reached. For each person we assessed all sites in the same order. We intended to measure PPTs both at places where people commonly have pain (trapezius and supraspinatus), and places that rarely hurt (fingernails) and selected three pre-defined sites: 1) the fingernail of the third finger, 2) skin superficial to the trapezius (ascending part) and 3) supraspinatus muscles bilaterally. Reduced thresholds on both symptomatic and asymptomatic/remote places may indicate a general sensitization,[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 ten minutes to complete. The researcher was not blinded regarding CFS patients and HCs.

Ethical considerations

The study was approved by Norwegian Social Science Data Service (NSD) and by the Norwegian Regional Committee for Medical and Health Research Ethics (REK). Participation in the project required informed consent by the adolescent and by his or her 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 differences were therefore analyzed by a non- parametric test (Mann Whitney Wilkoxon-test). For frequency differences between the groups, the Chi-square test was applied. An average of two pain pressure thresholds 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*-test.

To assess internal consistency of the instruments, Cronbach's alpha was computed separately for cases and controls. Alpha >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, version IBM Statistics 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 3 and 4).

There were no statistically significant differences between cases and controls concerning possible confounders (age, BMI and gender distribution), and there was no difference between patients and controls regarding socioeconomic status (Table 2).

Table 3. Frequency of pain episodes in different locations among CFS patients and healthy controls

	CFS patients n= 120 (%)				Healthy controls n=39 (%)			
Frequency	Head	Abdomen	Joints	Muscles	Head	Abdomen	Joints	Muscles
0-1 t/mo	9 (8)	30 (25)	36 (30)	21 (18)	18 (46)	20 (51)	35 (90)	26 (67)
2-3 t/mo	28 (23)	30 (25)	19 (16)	20 (17)	14 (36)	15 (39)	2(5)	7 (18)
1-2 t/w	28 (23)	21 (18)	24 (20)	24 (20)	4 (10)	1 (3)	0	2 (5)
3-5 t/w	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
mo= month, w= week

Table 4. Pain Intensity, Severity and Interference scores among CFS patients and healthy controls

	CFS patients		Healthy controls		*p*-value*
	n	Median (Range)	n	Median (Range)	
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 to:					
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)	
Enjoy 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

Pain prevalence and distribution

The frequency data from the CFS Symptom Inventory showed that adolescents with CFS were weekly seriously influenced by pain (Table 3). Summing up the categories 3, 4 and 5 in Table 3 (1-2t/w, 3-5t/w and ~every day), almost all adolescents with CFS vs. 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).

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

	CFS Patients 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)

n=number of individuals. 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.

Pain severity and functional interference

CFS patients demonstrated higher Pain Severity Scores (p <0.001) and Pain Interference scores (p <0.001) than HCs. Among the CFS patients, pain interfered most with attendance at school and general activity (Table 4). Ability to enjoy life, however, was one of the life domains that was least affected by pain, both among CFS patients and 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, PPT were significantly lower (all p< 0.001) among CFS patients than HCs. For the trapezius muscle the mean values were 15.4, 95%CI [14.1- 16.8] and 24.5,

95%CI [21.0- 28.0] for cases and controls, respectively. On fingernails 18.5, 95%CI [16.9-20.0] for cases and 30.8, 95%CI [26.5- 35.4] for controls. Concerning supraspinatus muscle the mean values were 17.1, 95%CI [15.6-18.6] for cases and 27.7, 95%CI [23.3- 31.6] for controls. The values show that PPT was as much as 50% lower in patients with CFS than in HCs, both at locations that usually are painful (muscles) and in areas that usually are not reported painful (finger nails). There were no missing data for HCs and for CFS patients' data was missing for one individual.

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 both symptomatic and asymptomatic places could indicate a more general sensitization of the nervous system,[38]. Lowered PPT in asymptomatic areas, indicating general sensitization, has also been found in patients with Ehler-Danlos syndrome,[36]. General hypersensitivity has been suggested as a reason for pain among CFS patients, 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 hypothesizes 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 generalized pain,[40]. Patients with CFS have also reported being more sensitive to other sensory stimulations like 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 born in mind that lowered PPT only reflects increased sensitivity to mechanical stimuli, and do not predict the response to, for instance, thermal stimuli.

Researchers have suggested that CFS patients 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 CFS patients 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 patient with fibromyalgia Turk et al. (2003) showed that fear of movement maintains the pain experience and increases the disability,[43]. 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. (2008) demonstrate a clear association between pain catastrophizing, pain severity and activity limitation/participation,[45]. There is no obvious reason to believe that this is not the case for adolescents with CFS. Negative thoughts may also develop when the patients do not understand the etiology 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 behavior therapy for CFS has shown to be effective in improving fatigue and pain in both adult 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 from one study (published as editorial letter 2013), showing improvement in pain and pain

threshold after successful cognitive behavior 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 quarter 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 weekly bases, but the rate was 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 ten bodily complaints. Our study confirm 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, vs. 70% of the adolescents with CFS.

Pain severity and interference in daily life

From healthy controls we know that physical activity has an important pain protective effect,[52], and Crawley and Stern (2009) have shown that impaired physical function is associated with higher levels of fatigue, pain and low mood,[5]. Complicating this, pain thresholds in patients with CFS have been found to decrease after physical exercises,[56],

which may lead to a fear avoidance behavior. 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 4), health care 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 children and adolescents, pain has 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 criticized,[27]. Although the participants were told to concentrate on pain and not the fatigue, we realize 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 the 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 both adolescents with CFS and in healthy adolescents. The relatively large sample of patients together with few missing data strengthen the study, making it possible to generalize the results. The wide inclusion criteria suggest

generalizability to the population of adolescents with CFS referred to pediatric care. Only two patients reported a short disease duration between three and six months,[15], and the results should be generalizable to populations with a more persistent CFS condition (more than six months). The Nor CAPITAL 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 alpha computed for BPI interference scores demonstrated strong internal consistency for both cases and controls. The results could have been influenced by confounding factors like 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 benefited 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 to healthy controls. The total sum of bodily symptoms represented a heavy burden with great functional consequences. The large sample of patients together with few missing data strengthen the study, making it possible to generalize the results.

Acknowledgments

Kari Gjersum, Berit Widerøe Njølstad, Adelheid Holm, Marianne Svendsen, Anne Marie Halstensen, Kristin Villa, Esther Gangsø, Hamsana Chandrakumar, Anna Marie Thorendal Ryenbakken all participants and their parents/next-of-kin.

The information reported in this manuscript has not been presented in any other journal.

The authors have no financial relationship nor any other conflict of interest to disclose.

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Acknowledgments:

Kari Gjersum provided secretarial assistance, Berit Widerøe Njølstad, MA; Adelheid Holm, RN; Marianne Svendsen, BSc; Anne Marie Halstensen, RN; Kristin Villa, RN; Esther Gangsø, BSc; Hamsana Chandrakumar, BSc and Anna Marie Thorendal Ryenbakken provided practical assistance.

Competing interests: To the author's knowledge, no conflict of interest, financial or other, exists.

Funding/Support: As part of the Nor CAPITAL-project this study was funded by Health South-East Hospital Trust, the University of Oslo, Oslo and Akesrhus University College of Applied Sciences, the Norwegian Competence Network of Pediatric Pharmacotherapy, Simon Fougner Hartman's Family Foundation, and Eckbo's Family Foundation funded this study.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: No additional data available.

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Title Page

Pain and Pressure Pain Thresholds in Adolescents with Chronic Fatigue Syndrome and Healthy Controls; a cross sectional study

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Abbreviations: BPI- Brief Pain Inventory; CFS-Chronic fatigue syndrome; HC- Healthy Controls; NRS-Numeric Rating Scale; PPT-Pressure Pain Threshold; QoL- Quality of Life

Key Words: adolescents, pain threshold, Chronic fatigue syndrome, public health nurse, and pediatrician

Clinical Trials, NCT01040429; The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial (Nor CAPITAL) www.clinicaltrials.gov.

Length of article: 3706 words

What's known on this subject: Pain is an important symptom in chronic fatigue syndrome (CFS). However, this pain is poorly understood and little explored in adolescents with CFS.

What does this study add: The study describes the pain prevalence and severity in adolescents with CFS and demonstrates that they are significantly more interfered by pain compared to healthy adolescents in terms of pain frequency, pain severity, functional

interference and pressure pain threshold (PPT).

Pain and Pressure Pain Thresholds in Adolescents with Chronic Fatigue Syndrome and Healthy Controls; a cross sectional study

ABSTRACT

Background and 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 the 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 to 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 to HCs ($p<0.001$). The Pain Severity Score and Pain Interference Score were significantly higher in adolescents with CFS compared to 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 to HCs. The mechanisms, however, are still obscure. Large longitudinal population surveys are warranted measuring pain thresholds prior to the onset of CFS.

Strengths and limitations

- This is one of the first large studies to test and to discuss pressure-provoked pain in both adolescents with CFS and healthy adolescents.
- The relatively large sample of patients together with few missing data strengthen the study and make it possible to generalize 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 six or more consecutive months, 2) fatigue that significantly interferes with daily activities and 3) at least four out of eight accompanying symptoms. Five out of these eight symptoms, are about 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 the 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 etiology,[9]. For children and adolescents there are specific recommendations with a broad case definition, requiring three months of unexplained disabling, chronic/relapsing fatigue of new onset,[10, 11]. Although some definitions emphasize 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 like light and sound,[15], and some researchers have hypothesized 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 upon the theory of the Cognitive activation theory of stress (CATS) 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 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. (2005), finding that there is considerably lowered pressure pain threshold (PPT) in adolescents with CFS compared to a group of healthy controls,[21]; 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 characterizing 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 CFS patients to HCs,[13]. The International Association for the Study of Pain's (IASP) definition of pain emphasizes that pain is a complex concept,[24]. Thus, there is a need for a broad approach to understand pain in patients with CFS.

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

MATERIAL 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

CFS patients

One hundred and twenty adolescents with CFS and 39 adolescents without any known health problem, were recruited between March 2010 and March 2012. All pediatric departments in Norwegian hospitals (n=20), as well as primary care pediatricians and general practitioners, were invited to refer adolescents with CFS (Table 1). The 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 three 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 pre-specified criteria for inclusion (Table 1) were included in the Nor CAPITAL 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 with CFS. At present, there is no evidence for an obvious cut-off for the number of symptoms,[11].

Table 1. Criteria for inclusion and exclusion

	CFS patients	**Healthy control subjects**
Inclusion criteria:	Persisting or constantly relapsing fatigue lasting 3 months or more. Functional disability resulting from fatigue to a degree that prevent normal school attendance Age ≥ 12 and < 18 years	Age ≥ 12 years 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	Another chronic disease Permanent use of drugs (including hormones)

	Pheocromocytoma
	Evidence of reduced cerebral and/or peripheral circulation due to vessel disease
	Polyneuropathy
	Renal insufficiency
	Known hypersensitivity towards clonidine or inert substances (lactose, saccarose) in capsula
	Abnormal ECG (apart from ectopic beats)
	Supine heart rate < 50 beats/min Supine systolic blood pressure < 85 mmHg Upright systolic blood pressure fall > 30 mmHg

The criteria are designed for the randomized 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).

Table 2. Demographic data and adherence to specific CFS criteria (Fukuda, 1994).

		CFS patients 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)	n.a.
Fukuda-criteria	n (%)	88 (75)	n.a.
Lives with both parents	n (%)	85 (73)	26 (70)
Parents highest education			
Primary school	n (%)	5 (4.3)	0 (0)
Secondary school	n (%)	30 (26)	8 (23)
Lower University	n (%)	34 (29)	9 (23)
Higher University	n (%)	48 (41)	19 (54)

n=number of individuals

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 (BPI)

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 alpha 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 Nor CAPITAL 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 pre- stamped envelopes within a few weeks. All measures were done at baseline, eight 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 hyperalgesia in superficial structures like 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, USA). Values are presented in Newton (N). The intensity was increased until the pressure pain threshold was reached. For each person we assessed all sites in the same order. We intended to measure PPTs both at places where people commonly have pain (trapezius and supraspinatus), and places that rarely hurt (fingernails) and selected three pre-defined sites: 1) the fingernail of the third finger, 2) skin superficial to the trapezius (ascending part) and 3) supraspinatus muscles bilaterally. Reduced thresholds on both symptomatic and asymptomatic/remote places may indicate a general sensitization,[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 ten minutes to complete. The researcher was not blinded regarding CFS patients and HCs.

Ethical considerations

The study was approved by Norwegian Social Science Data Service (NSD) and by the Norwegian Regional Committee for Medical and Health Research Ethics (REK). Participation in the project required informed consent by the adolescent and by his or her 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 differences were therefore analyzed by a non- parametric test (Mann Whitney Wilkoxon-test). For frequency differences between the groups, the Chi-square test was applied. An average of two pain pressure thresholds 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*-test.

To assess internal consistency of the instruments, Cronbach's alpha was computed separately for cases and controls. Alpha >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, version IBM Statistics 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 3 and 4).

There were no statistically significant differences between cases and controls concerning possible confounders (age, BMI and gender distribution), and there was no difference between patients and controls regarding socioeconomic status (Table 2).

Table 3. Frequency of pain episodes in different locations among CFS patients and healthy controls

	CFS patients n= 120 (%)				Healthy controls n=39 (%)			
Frequency	Head	Abdomen	Joints	Muscles	Head	Abdomen	Joints	Muscles
0-1 t/mo	9 (8)	30 (25)	36 (30)	21 (18)	18 (46)	20 (51)	35 (90)	26 (67)
2-3 t/mo	28 (23)	30 (25)	19 (16)	20 (17)	14 (36)	15 (39)	2(5)	7 (18)
1-2 t/w	28 (23)	21 (18)	24 (20)	24 (20)	4 (10)	1 (3)	0	2 (5)
3-5 t/w	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
mo= month, w= week

Table 4. Pain Intensity, Severity and Interference scores among CFS patients and healthy controls

	CFS patients		Healthy controls		*p*-value*
	n	Median (Range)	n	Median (Range)	
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 to:					
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)	
Enjoy 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

Pain prevalence and distribution

The frequency data from the CFS Symptom Inventory showed that adolescents with CFS were weekly seriously influenced by pain (Table 3). Summing up the categories 3, 4 and 5 in Table 3 (1-2t/w, 3-5t/w and ~every day), almost all adolescents with CFS vs. 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).

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

	CFS Patients 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)

n=number of individuals. 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.

Pain severity and functional interference

CFS patients demonstrated higher Pain Severity Scores (p <0.001) and Pain Interference scores (p <0.001) than HCs. Among the CFS patients, pain interfered most with attendance at school and general activity (Table 4). Ability to enjoy life, however, was one of the life domains that was least affected by pain, both among CFS patients and 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, PPT were significantly lower (all p< 0.001) among CFS patients than HCs. For the trapezius muscle the mean values were 15.4, 95%CI [14.1- 16.8] and 24.5,

95%CI [21.0- 28.0] for cases and controls, respectively. On fingernails 18.5, 95%CI [16.9-20.0] for cases and 30.8, 95%CI [26.5- 35.4] for controls. Concerning supraspinatus muscle the mean values were 17.1, 95%CI [15.6-18.6] for cases and 27.7, 95%CI [23.3- 31.6] for controls. The values show that PPT was as much as 50% lower in patients with CFS than in HCs, both at locations that usually are painful (muscles) and in areas that usually are not reported painful (finger nails). There were no missing data for HCs and for CFS patients' data was missing for one individual.

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 both symptomatic and asymptomatic places could indicate a more general sensitization of the nervous system,[38]. Lowered PPT in asymptomatic areas, indicating general sensitization, has also been found in patients with Ehler-Danlos syndrome,[36]. General hypersensitivity has been suggested as a reason for pain among CFS patients, 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 hypothesizes 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 generalized pain,[40]. Patients with CFS have also reported being more sensitive to other sensory stimulations like 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 born in mind that lowered PPT only reflects increased sensitivity to mechanical stimuli, and do not predict the response to, for instance, thermal stimuli.

Researchers have suggested that CFS patients 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 CFS patients 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 patient with fibromyalgia Turk et al. (2003) showed that fear of movement maintains the pain experience and increases the disability,[43]. 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. (2008) demonstrate a clear association between pain catastrophizing, pain severity and activity limitation/participation,[45]. There is no obvious reason to believe that this is not the case for adolescents with CFS. Negative thoughts may also develop when the patients do not understand the etiology 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 behavior therapy for CFS has shown to be effective in improving fatigue and pain in both adult 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 from one study (published as editorial letter 2013), showing improvement in pain and pain

threshold after successful cognitive behavior 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 quarter 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 weekly bases, but the rate was 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 ten bodily complaints. Our study confirm 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, vs. 70% of the adolescents with CFS.

Pain severity and interference in daily life

From healthy controls we know that physical activity has an important pain protective effect,[52], and Crawley and Stern (2009) have shown that impaired physical function is associated with higher levels of fatigue, pain and low mood,[5]. Complicating this, pain thresholds in patients with CFS have been found to decrease after physical exercises,[56],

which may lead to a fear avoidance behavior. 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 4), health care 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 children and adolescents, pain has 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 criticized,[27]. Although the participants were told to concentrate on pain and not the fatigue, we realize 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 the 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 both adolescents with CFS and in healthy adolescents. The relatively large sample of patients together with few missing data strengthen the study, making it possible to generalize the results. The wide inclusion criteria suggest

generalizability to the population of adolescents with CFS referred to pediatric care. Only two patients reported a short disease duration between three and six months,[15], and the results should be generalizable to populations with a more persistent CFS condition (more than six months). The Nor CAPITAL 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 alpha computed for BPI interference scores demonstrated strong internal consistency for both cases and controls. The results could have been influenced by confounding factors like 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 benefited 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 to healthy controls. The total sum of bodily symptoms represented a heavy burden with great functional consequences. The large sample of patients together with few missing data strengthen the study, making it possible to generalize the results.

Acknowledgments

Kari Gjersum, Berit Widerøe Njølstad, Adelheid Holm, Marianne Svendsen, Anne Marie Halstensen, Kristin Villa, Esther Gangsø, Hamsana Chandrakumar, Anna Marie Thorendal Ryenbakken all participants and their parents/next-of-kin.

The information reported in this manuscript has not been presented in any other journal.

The authors have no financial relationship nor any other conflict of interest to disclose.

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Acknowledgments:

Kari Gjersum provided secretarial assistance, Berit Widerøe Njølstad, MA; Adelheid Holm, RN; Marianne Svendsen, BSc; Anne Marie Halstensen, RN; Kristin Villa, RN; Esther Gangsø, BSc; Hamsana Chandrakumar, BSc and Anna Marie Thorendal Ryenbakken provided practical assistance.

Competing interests: To the author's knowledge, no conflict of interest, financial or other, exists.

Funding/Support: As part of the Nor CAPITAL-project this study was funded by Health South-East Hospital Trust, the University of Oslo, Oslo and Akesrhus University College of Applied Sciences, the Norwegian Competence Network of Pediatric Pharmacotherapy, Simon Fougner Hartman's Family Foundation, and Eckbo's Family Foundation funded this study.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

No additional data available.

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