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## **How Fatigue is related to other Somatic Symptoms**

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## Abstract

**Objective** In this study we assessed the relation between fatigue and somatic symptoms in healthy adolescents and adolescents with Chronic Fatigue Syndrome (CFS).

**Methods** 72 adolescents with Chronic Fatigue Syndrome were compared within a cross-sectional study design with 167 healthy controls. Fatigue and somatic complaints were measured using self-report questionnaires, respectively the subscale subjective fatigue of the Checklist Individual Strength (CIS-20) and the Children's Somatization Inventory.

**Results** Healthy adolescents reported the same somatic symptoms as adolescents with CFS, but with a lower score of severity. The top 10 of somatic complaints were the same: low energy, headache, heaviness in arms/legs, dizziness, sore muscles, hot/cold spells, weakness in body parts, pain in joints, nausea/upset stomach, back pain. There was a clear positive relation between log somatic symptoms and fatigue (linear regression coefficient: 0.041 points log somatic complaints per score point fatigue (95% Confidence Interval 0.033; 0.049, p-value < 0.001) which did not depend on disease status (interaction between CFS and fatigue: p-value 0.847).

**Conclusions** Our findings suggest a continuum with a gradual transition from fatigue with associated symptoms in healthy adolescents to the symptom complex of CFS.

## Introduction

Whether Chronic Fatigue Syndrome (CFS) is a distinct illness with its own causal processes is still a central question in research and clinical practice. The symptom complex is characterized by persistent debilitating fatigue causing a marked reduction of school and social activity. The minimal illness duration to fulfil criteria of the Centers for Disease Control and Prevention (CDC) is 6 months.<sup>1</sup> Recently developed clinical guidelines in the UK, however, concluded that the diagnosis should be based primarily on the impact of the condition and not require a specific illness duration.<sup>2</sup> Adolescents who suffer from CFS additionally report a variety of physical complaints such as headache, memory and concentration impairments and muscle and joint pain.<sup>2</sup> The symptom complex is not unique for CFS but overlaps with syndromes such as fibromyalgia and irritable bowel syndrome, equally ill-defined in terms of pathophysiology.<sup>3,4</sup>

This raises the question of how fatigue is related to other somatic symptoms in adolescents with CFS. Fatigue is not only a symptom of illness but also a common phenomenon in healthy adolescents. A recent prevalence study in the US established that 21 percent of the healthy adolescents experience fatigue.<sup>5</sup> Other somatic symptoms, like headache, stomach ache, back ache, dizziness, also occur in healthy adolescents, as recently published in a WHO report concerning the European Countries.<sup>6,7</sup>

We hypothesized that fatigue is proportionally related to other somatic symptoms, not only in adolescents with CFS but in healthy adolescents as well. Secondly, we hypothesized that CFS is positioned at the end of a continuous scale that includes the symptoms of healthy adolescents.

## Methods

A total of 132 adolescents (12-18 years) with severe fatigue were referred to a specific CFS clinic of the Department of General Paediatrics of the University Medical Center Utrecht between January 2001 and May 2004. All patients were Caucasian and 83 adolescents fulfilled the Centers for Disease Control and Prevention (CDC) criteria for CFS.<sup>1</sup> A child psychologist performed psychological examinations, using specific Dutch questionnaires for anxiety and depression in combination with an interview of both child and parent. Additional to the CDC exclusion criteria, patients with life long problems of somatisation (n=2) or an established diagnosis of a severe depression or a primary anxiety disorder dependent on pharmaceutical treatment (n=3) or severe somatic comorbidity (n=1) were excluded. Five adolescents refused to participate (2 on account of fatigue, 1 received no permission of the rehabilitation centre, 2 gave no reason). Individual measurements took place from 2002 to 2004 in separate rooms in the hospital. Of the remaining 72 adolescents, 66 fulfilled all CDC criteria for CFS at the moment of the research examinations: 6 months duration, debilitating fatigue particularly affecting school attendance, and a minimum of 4 side symptoms. Six patients had less than 4 side symptoms, but were still included.

As a reference group, 363 adolescents aged 12-18 years from a general secondary school, De Breul in the Dutch City of Zeist, were invited to participate. Inclusion criteria were age (12-18 years) and no current illness. 167 Adolescents (46%) agreed to participate and were examined during sessions at school in April 2002. All subjects were Caucasian.

Fatigue was measured with the subscale subjective fatigue of the self-report questionnaire Checklist Individual Strength-20 (CIS-20) consisting of 8 items about fatigue in the 2 weeks preceding the assessment, using a Likert scale (range: 1-7). The questionnaire has good reliability and discriminative validity.<sup>8</sup>

Somatic complaints were assessed with a validated Dutch translation of the Children's Somatization Inventory (CSI),<sup>9,10</sup> a self-report questionnaire, rating the presence of 35 somatic symptoms in the last 2 weeks using a 5-point Likert scale ranging from not at all (0) to a whole lot (4). This questionnaire was originally developed to measure somatization and includes many functional somatic symptoms and most symptoms mentioned in the CDC-criteria for Chronic Fatigue Syndrome<sup>1</sup> except for the symptoms: tender lymph nodes, unrefreshing sleep and post-exertion malaise. Two items from the CSI were omitted in the analysis: 'weakness in body parts' and 'low energy' because of overlap with the subscale subjective fatigue. We calculated the number of reported somatic symptoms irrespective of the severity (range 0-33). A total score, representing both number and severity of symptoms, was obtained by summing the ratings (range: 0-132 (33x4)). This total somatic

symptom score was judged as the best indicator of the burden of somatic symptoms, and was used in the analysis.

The medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from both adolescents and parents.

## Analysis

Of the relevant variables, group specific means and standard deviations were calculated for descriptive purposes.

The data were analysed with linear regression using the variable of interest as dependent variable and a group indicator (patient = 1, control = 0) as independent variable to explore group differences. Results are presented as linear regression coefficients representing mean differences between the CFS adolescents and the healthy controls for the investigated parameter with their corresponding 95% confidence intervals. The same models were used to adjust for age and gender.

Mean Likert scores for each somatic complaint were calculated and reported as a top-10 of somatic complaints.

To analyse the relation between fatigue and somatic complaints we performed a linear regression model with the somatic symptom score as the dependent variable and the fatigue score as an independent variable with adjustment for age and gender in the same model. The somatic symptom score was log transformed because its variance was not constant along different levels of the fatigue score. We tested for an interaction between CFS and fatigue scores by adding an interaction term in the regression model (interaction is calculated as the product of CFS status (yes or no) and fatigue scores).

For the graphical depiction of the results (figure 1) we calculated for each participant adjusted fatigue scores and adjusted somatic symptom score, to account for the slight difference in age and gender between the healthy adolescents and those with CFS. All these individuals scores were adjusted for age and gender within their original group (CFS or not).

The analyses were performed with the use of SPSS 12.0.1 statistical package for Windows.

## Results

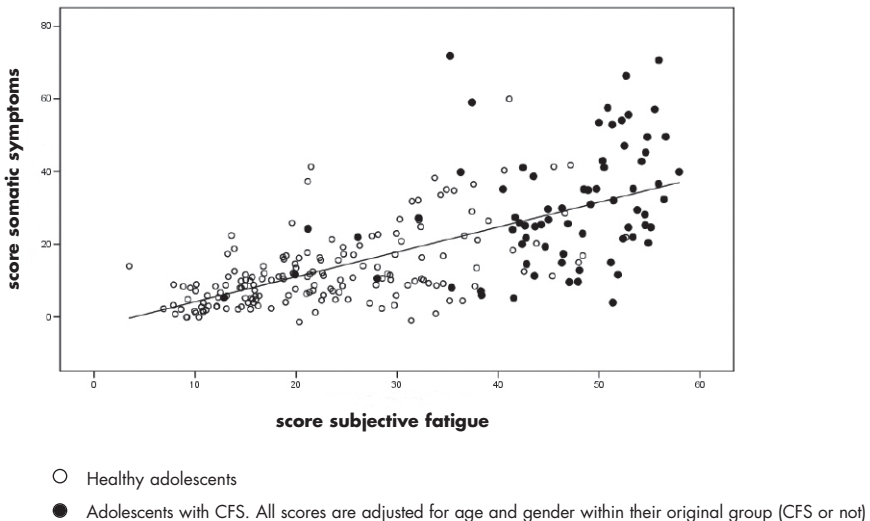
72 Patients (82% girls) and 167 controls (60% girls) were included. As shown in table 1 both the score on fatigue and somatic complaints, adjusted for the covariates age and gender, were significantly higher for the adolescents with CFS. The top 10 of somatic symptoms in the CFS adolescents was identical to the top 10 of somatic symptoms in healthy adolescents, except for 'sore muscles' in the top 10 of the CFS adolescents, which was substituted for 'stomach pain' in the top 10 of the healthy adolescents.

Fatigue and somatic complaints were positively related with a linear regression coefficient of 0.041 points log somatic complaints per score point fatigue (95% Confidence Interval 0.033; 0.049, p-value < 0.001) without a significant effect of interaction between fatigue score and CFS (p-value 0.847).

Eleven of the healthy adolescents showed a fatigue score  $\geq 40$ , corresponding with the fatigue score for adolescents with CFS. Their fatigue, however, did not result in severe disability, while 8 out of these 11 adolescents showed no school absence in the past 6 months, and only 3 had considerably school absence (5-50%): 1 because of multiple injuries, 1 because of an infectious illness, and 1 without reason.

### Figure 1 Relation between fatigue and somatic symptoms

Figure 1 represents the relationship between the fatigue score and the somatic complaints score for each individual. Each higher score point of fatigue resulted on average in a 0.57 higher score point of somatic complaints.



**Table 1 Characteristics and scores of CFS Adolescents and Healthy Controls**

	<b>32 CFS cases</b>	<b>167 healthy controls</b>	<b>Mean difference (95% CI)</b>	<b>Adjusted mean difference * (95% CI)</b>
Age (y)	16.0 (1.6)	15.5 (1.6)	0.5 (0.08; 0.97)	
Gender (% girls)	82	60	22 (10; 34)	
<b>Fatigue assessment</b>				
Subscale Subjective fatigue (CIS-20) (8 items; 7-points Likert Scale; 1-7; range 8-56)				
	46.1 (9.2)	22.9 (11.0)	23.2 (20.3; 26.1)	21.6 (18.7; 24.5)
<b>CDC criteria (range 0-8)</b>				
Number of reported CDC minor symptoms	5.7 (1.7)	Not specified		
<b>Children's Somatization Inventory</b> (33 items, 5-points Likert Scale 0-4)				
Total score (range 0-132)	30.2 (17.7)	12.4 (10.5)	17.8 (14.1; 21.4)	16.2 (12.6; 19.9)
Number of symptoms (range 0-33)	14.1 (6.0)	7.7 (5.0)	6.3 (4.8; 7.8)	5.8 (4.3; 7.3)
<b>Top 10 somatic complaints (range 0-4)</b>				
1. Low energy	2.7 (1.1)	1.3 (1.1)		
2. Headache	2.1 (1.4)	1.1 (1.1)		
3. Heaviness in arms/legs	1.9 (1.3)	0.4 (0.8)		
4. Dizziness	1.9 (1.5)	0.8 (1.0)		
5. Sore muscles	1.9 (1.4)	0.8 (0.9)		
6. Hot/cold spells	1.7 (1.3)	0.6 (1.0)		
7. Weakness in body parts	1.7 (1.3)	0.7 (1.1)		
8. Pain in joints	1.7 (1.4)	0.6 (1.0)		
9. Nausea/upset stomach	1.6 (1.4)	0.8 (1.0)		
10. Back pain	1.5 (1.3)	0.9 (1.2)		

\* adjusted for age and gender

Values are mean (SD)

95% CI = 95% confidence interval corresponding with a p-value &lt; 0.05



## Discussion

Healthy and CFS adolescents share a symptom complex, of which fatigue is the main symptom as low energy ranks first in the top 10 of symptoms in both groups. Additionally, a graded positive relationship between fatigue and other somatic complaints is established without a significant effect of interaction between CFS and fatigue. This might imply that the aetiology of experience of fatigue and other somatic symptoms is similar in healthy adolescents and in those with CFS. Our findings suggest a continuum with a gradual transition from fatigue with associated symptoms in healthy adolescents to the symptom complex of CFS.

Only 46% of the healthy adolescents invited to participate agreed, which may raise the question of whether this subgroup is sufficiently representative of the healthy adolescents. It is, however, unlikely that invitees reacted on the basis of specific associations between fatigue and somatic symptoms, in other words that the association between fatigue and somatic symptoms should be different among responders and non-responders.

Some healthy adolescents experience similar fatigue and associated symptoms as the adolescents with CFS but lack the effect on school attendance and do not view themselves as patients. This may reflect the fact that the identification of a symptom complex as abnormal and requiring medical examination is known to be related to the patient's health beliefs, former experiences, medical knowledge and norms and values in the family.<sup>11-16</sup> This emphasizes the need for a multidimensional approach with the identification of relevant illness beliefs and the medical and family history.

Biological formulations of the aetiology of these unexplained physical symptoms are scarce. Terminology is therefore predominantly descriptive in terms of symptoms. In general medicine CFS is categorized as one of the functional somatic syndromes, which is a non-stigmatizing and accepted description for adult patients.<sup>17</sup> An overall aetiological concept is still lacking. The findings of our study support the idea that a possible substrate for the experienced symptoms in CFS could be found in a mechanism which is present in all members of the population. A promising concept in this respect is interoception: "the sense of the physiological condition of the body."<sup>18</sup>

The recent guidelines of the Royal College of Paediatrics and Child Health propose to apply not a time criterion for the clinical diagnosis of CFS as opposed to the CDC- and the Oxford criteria.<sup>1, 19</sup> The degree of impairment as a consequence of the physical symptoms, is more critical to the diagnosis and treatment than the duration of symptoms. Positive recognition of the symptom complex may facilitate the process of making a diagnosis of CFS and may diminish the need for extensive investigations to exclude other diagnoses. The findings of our study support this positive recognition by viewing fatigue in combination with other somatic symptoms and not only in combination with the minor CDC criteria.

## References

- 1 Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953-9
- 2 Royal College of Paediatrics and Child Health. Evidence based guideline for the management of CFS/ME (chronic fatigue syndrome/myalgic encephalopathy) in children and young people. 2004
- 3 Nimnuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? *J Psychosom Res* 2001;51:549-57
- 4 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999;354:936-9
- 5 Rhee H, Miles MS, Halpern CT, Holditch-Davis D. Prevalence of recurrent physical symptoms in U.S. adolescents. *Pediatr Nurs* 2005;31:314-9, 350
- 6 Viner R, Christie D. Fatigue and somatic symptoms. *BMJ* 2005;330:1012-5
- 7 WHO-Europe. Health Policy for Children & Adolescents, no. 4. 1-248.2002
- 8 Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383-92
- 9 Walker LS, Garber J, Greene JW. Somatization symptoms in pediatric abdominal pain patients: relation to chronicity of abdominal pain and parent somatization. *J Abnorm Child Psychol* 1991;19:379-94
- 10 Meesters C, Muris P, Ghys A, Reumerman T, Rooijmans M. The Children's Somatization Inventory: further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. *J Pediatr Psychol* 2003;28:413-22
- 11 Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. *Ann Intern Med* 2001;134:917-25
- 12 Campo JV, Fritsch SL. Somatization in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1994;33:1223-35
- 13 Crushell E, Rowland M, Doherty M, Gormally S, Harty S, Bourke B et al. Importance of parental conceptual model of illness in severe recurrent abdominal pain. *Pediatrics* 2003;112:1368-72
- 14 Schor EL. Family pediatrics: report of the Task Force on the Family. *Pediatrics* 2003;111:1541-71
- 15 Ogden J. What do symptoms mean? *BMJ* 2003;327:409-10
- 16 van de Putte EM, Engelbert RH, Kuis W, Sinnema G, Kimpfen JL, Uiterwaal CS. Chronic fatigue syndrome and health control in adolescents and parents. *Arch Dis Child* 2005;90:1020-4

- 17 Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L et al. What should we say to patients with symptoms unexplained by disease? The “number needed to offend”. *BMJ* 2002;325:1449-50
- 18 Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002;3:655-66
- 19 Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A et al. A report-chronic fatigue syndrome: guidelines for research. *J R Soc Med* 1991;84:118-21

