Is Chronic Fatigue Syndrome a Connective Tissue Disorder?  
A Cross-Sectional Study in Adolescents

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ABSTRACT. Objectives. To investigate whether constitutional laxity of the connective tissues is more frequently present in adolescents with chronic fatigue syndrome (CFS) than in healthy controls. Increased joint hypermobility in patients with CFS has been previously described, as has lower blood pressure in fatigued individuals, which raises the question of whether constitutional laxity is a possible biological predisposing factor for CFS.

Design. Cross-sectional study.

Participants. Thirty-two adolescents with CFS (according to the criteria of the Centers for Disease Control and Prevention) referred to a tertiary hospital and 167 healthy controls.

Methods. The 32 adolescents with CFS were examined extensively regarding collagen-related parameters: joint mobility, blood pressure, arterial stiffness and arterial wall thickness, skin extensibility, and degradation products of collagen metabolism. Possible confounding factors (age, gender, height, weight, physical activity, muscle strength, diet, alcohol consumption, and cigarette smoking) were also measured. The results were compared with findings in 167 healthy adolescents who underwent the same examinations.

Results. Joint mobility, Beighton score, and collagen biochemistry, all indicators of connective tissue abnormality, were equal for both groups. Systolic blood pressure, however, was remarkably lower in patients with CFS (117.3 vs. 129.7 mm Hg; adjusted difference: −13.5 mm Hg; 95% confidence interval [CI]: −19.1, −7.0). Skin extensibility was higher in adolescents with CFS (mean z score: 0.5 vs. 0.1 SD; adjusted difference: 0.3 SD; 95% CI: 0.1, 0.5). Arterial stiffness, expressed as common carotid distension, was lower in adolescents with CFS, indicating stiffer arteries (670 vs 820 μm; adjusted difference: −110 μm; 95% CI: −220, −10). All analyses were adjusted for age, gender, body mass index, and physical activity. Additionally, arterial stiffness was adjusted for lumen diameter and pulse pressure.

Conclusions. These findings do not consistently point in the same direction of an abnormality in connective tissue. Patients with CFS did have lower blood pressure and more extensible skin but lacked the most important parameter indicating constitutional laxity, ie, joint hypermobility. Moreover, the collagen metabolism measured by crosslinks and hydroxyproline in urine, mainly reflecting bone resorption, was not different. The unexpected finding of stiffer arteries in patients with CFS warrants additional investigation. Pediatrics 2005; 115:e115–e122. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1515; chronic fatigue syndrome, connective tissue disease, cardiovascular factors, autonomic nervous system.

ABBREVIATIONS. CFS, chronic fatigue syndrome; EDS, Ehlers-Danlos syndrome; HP, hydroxylysylpyridinoline; LP, lysylpyridinoline; CDC, Centers for Disease Control and Prevention; CIMT, carotid intimal-medial thickness; Hyp, hydroxyproline; CIS-20, Checklist Individual Strength-20; CI, confidence interval.

C

eronic fatigue syndrome (CFS) is a frequently disabling illness of unknown etiology and variable prognosis. Scientific interest in the pathogenesis of this illness parallels the apparent increase in incidence.1,2 However, despite all scientific efforts, a plausible cause for CFS has not been established yet. Until now, there is insufficient support for either a purely somatic or psychic chain of causation. CFS is viewed as a multifactorial illness, and a distinction is made between constitutional, initiating, and perpetuating factors on both the biological and psychosocial levels.3

The prognosis for adolescents with CFS seems to be better than for adults, although as many as 44% of adolescents remain ill with significant symptoms, as observed in an 8-year follow-up study.4 This study focuses on a constitutional biological factor, which may partly explain the symptoms of fatigue and pain. The main question is whether constitutional laxity of the connective tissues is present more frequently in adolescents with CFS than in healthy controls. One of the reasons to perform this study was the previous finding of increased joint hypermobility in adolescents with CFS.5 Moreover, a former study in adolescents established the coexistence of CFS and Ehlers-Danlos syndrome (EDS) in a substantial part of the study population.6 Fatigue is not a diagnostic criterion in EDS and not often emphasized in the medical literature, likely because of the highly unspecific nature of the symptom fatigue.7 Also, in the more frequently diagnosed benign joint-hypermobility syndrome in childhood, fatigue is 1 of the clinical symptoms.8–10

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Additional motivation for the hypothesis that constitutional laxity may play a role in CFS comes from the finding that just like in EDS, the clinical symptoms in benign joint-hypermobility syndrome are not restricted to the musculoskeletal system. Other organs are possibly involved, such as blood vessels (with lower systolic and diastolic blood pressure), skin (with higher skin extensibility), and bone (with a lower quantitative ultrasound measurement). In addition, the patients with symptomatic generalized joint hypermobility have significantly lower excretion of urinary hydroxylsylpyridinoline (HP) crosslinks and lysylpyridinoline (LP) crosslinks. A relation between stiffness of joints and skin and blood pressure is not restricted to patients with a known collagen abnormality. Also, in healthy children we recently described a relation between stiffness of joints and laxity of skin and blood pressure. Stiffness of joints seems to reflect other systemic changes in connective tissue, and this putative multiple-organ involvement, together with the clinical finding of fatigue in collagen disorders, led to the main research question: Is constitutional laxity of the connective tissues a possible biological factor in CFS?

**METHODS**

**Population**

A group of 32 patients with CFS ranging in age from 12 to 18 years were included. These patients were referred to a specific CFS clinic of the University Medical Center Utrecht between January 2001 and May 2002. All patients were white and fulfilled the Centers for Disease Control and Prevention (CDC) criteria for CFS at the time of inclusion. Supplementary to the CDC exclusion criteria, patients with an established diagnosis of a connective tissue disease or disorders involving skin, joints, bone or joint hypermobility have significantly lower excretion of urinary hydroxylsylpyridinoline (HP) crosslinks and lysylpyridinoline (LP) crosslinks.

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**Measurements**

A team of 4 examiners (physiotherapists) and the principal investigator (E.M.v.d.P.) conducted all measurements. The 4 physiotherapists were unaware of the study hypothesis. The same investigator (E.M.v.d.P.) conducted all measurements. The 4 physiotherapists were unaware of the study hypothesis. The same investigator (E.M.v.d.P.) conducted all measurements. The 4 physiotherapists were unaware of the study hypothesis. The same investigator (E.M.v.d.P.) conducted all measurements. The 4 physiotherapists were unaware of the study hypothesis.

**TABLE 1. Order of Measurements**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Measurement</th>
<th>Examiner</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Rest</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Blood pressure</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Body height and body weight</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Bone density</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Skin extensibility (2 locations bilaterally)</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>Pain (2 locations bilaterally)</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>Joint mobility (34 joint motions in 9 joints bilaterally)</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>Myometry (4 locations bilaterally)</td>
<td>4</td>
</tr>
<tr>
<td>40</td>
<td>Ultrasonography carotid artery</td>
<td>5</td>
</tr>
<tr>
<td>60</td>
<td>Blood pressure</td>
<td>1</td>
</tr>
<tr>
<td>62</td>
<td>Questionnaires</td>
<td>1</td>
</tr>
<tr>
<td>80</td>
<td>Measurements completed</td>
<td>1</td>
</tr>
</tbody>
</table>
Results are presented as linear-regression coefficients representing the investigated parameter as a dependent (outcome) variable.

Subsequently, mean individual location instead of simply averaging all measurement results. or the number of SDs below or above the mean) for values at each location instead of simply averaging all measurement results. Subsequently, mean individual z scores were calculated by averaging z scores of all measured locations. These mean z scores, indicating individuals’ ranks in the distribution of joint mobility, skin extensibility, or muscle strength, were used for additional analysis.

The data were analyzed with linear regression using a group indicator (patient = 1, control = 0) as an independent variable and the investigated parameter as a dependent (outcome) variable. Results are presented as linear-regression coefficients representing mean group differences for the investigated parameter with their corresponding 95% confidence intervals (95% CIs). The same models were used to adjust for possible confounding factors such as age, gender, BMI, and physical activity. For evaluations of arterial stiffness, we constructed several parameters of stiffness to enable comparison with other studies. All these stiffness parameters are constructed as ratios in different formulas as we have described. However, in studies looking into etiology, analyses using ratios are difficult to interpret, because an observed relationship may be caused by the relation with the nominator, the denominator, or both. Therefore, a better approach in etiologic studies may be to use either the nominator or the denominator and adjust for the other factor in a regression model. Thus, we present the distension value (change in lumen diameter during the cardiac cycle), which is adjusted for pulse pressure and diastolic lumen diameter and additionally adjusted for age, gender, BMI, and physical activity, as the most appropriate measurement for stiff arteries in this etiologic study. A lower distension value inversely relates to a stiffer vessel, as do the cross-sectional compliance coefficient and the distensibility coefficient. The Peterson’s modulus is closely related to the inverse of the distensibility coefficient. Young’s elastic modulus provides direct information about the elastic properties of the wall material independent of the vessel geometry.

Statistical significance was considered to be reached when 95% CIs did not include the null value, corresponding with a P value < .05.

RESULTS

A summary of relevant characteristics of the adolescents with CFS is provided in Table 2. The majority of patients were females. There was considerable school absence and a high use of medication, and many patients were on a diet. Additionally, Table 2 shows a substantial use of health care services since the start of the symptoms, including psychotherapy and alternative treatment. Table 3 describes general characteristics of the adolescents with CFS and the controls. Both groups were comparable except for gender, BMI, and physical activity. Physical activity, computed in hours of physical activity per week, was 5.7 hours less in patients with CFS. Because gender, age, BMI, and physical activity may affect the studied collagen-related measurements, we considered...
them to be possible confounding factors. The patients with CFS showed a higher score on all the subscales of the CIS-20.

Table 4 shows the joint mobility in 5 bilateral joints in both groups and the mean (adjusted) difference in joint mobility between the adolescents with CFS and the healthy adolescents. There were no group differences in joint mobility in these 5 joints. The median Beighton score in the healthy adolescents was 2, similar to the median Beighton score in the CFS group. Comparison of the Beighton scores between the 2 groups in a linear-regression model (adjusted for age, gender, and BMI) showed no difference as well (regression coefficient: \(-0.35; 95\% \text{ CI}: -1.0, 0.3\)). Generalized joint hypermobility (Beighton score \(\geq 4\)) was present in 29 of 167 (17%) healthy adolescents, Beighton score in the healthy adolescents was 2, similar to the median Beighton score in the CFS group. Comparison of the Beighton scores between the 2 groups in a linear-regression model (adjusted for age, gender, and BMI) showed no difference as well (regression coefficient: \(-0.35; 95\% \text{ CI}: -1.0, 0.3\)). Generalized joint hypermobility (Beighton score \(\geq 4\)) was present in 29 of 167 (17%) healthy adolescents,
whereas in the CFS group, 3 of the 32 adolescents with CFS (9%) showed hypermobility.

Mean differences in indicators of organ stiffness between patients with CFS and controls are presented in Table 5. Joint mobility of all the 34 examined joints did not differ between patients and controls. A separate analysis of small and large joints did not change this result. The skin of patients with CFS was more extensible, and adjustment for age, gender, and BMI did not materially change this finding.

There was a significant difference in muscle strength between the adolescents with CFS and the healthy adolescents (mean difference in z score: −0.7; 95% CI: −1.0, −0.4), even when adjusted for age, gender, and BMI (mean difference in z score: −0.6; 95% CI: −0.9, −0.4).

There was a significant difference in systolic and diastolic blood pressure and pulse pressure between the groups at the start of the examination. Blood pressure levels were lower in patients with CFS (−13.5 adjusted difference in systolic blood pressure, −6.7 mm Hg adjusted difference in diastolic blood pressure), without any effect on the heart rate, which was similar for both groups at the start. At the end of the examination, the blood pressure was comparable for both groups, but the heart rate was faster for the CFS group (mean difference: 4.9; 95% CI: −0.1, 9.8). Arterial stiffness expressed as common carotid distension and adjusted for lumen diameter and pulse pressure showed that patients with CFS have a lower value of distension than controls, reflecting stiffer arteries. The analyses of the various arterial stiffness parameters point toward arterial stiffness in the patients with CFS compared with controls. Although some of the associations do not reach statistical significance, the consistency of the findings enhances the validity of the finding.

Arterial wall thickness, as determined by the common CIMT, was equal for both groups. The bone parameters showed that there was less stiffness of bones in patients with CFS. Adjusting for confounding factors, including physical inactivity, attenuated this difference.

There were no clear differences between the groups with regard to collagen biochemistry (Table 5).

The mean pain threshold differed considerably between patients with CFS and controls. After adjusting for age, gender, and BMI, this lower pain threshold for patients with CFS remained.

**DISCUSSION**

The results of our study do not consistently point toward an abnormality in connective tissue and therefore do not support the hypothesis that connective tissue laxity is a risk factor for the development of CFS in adolescents. Patients with CFS did have lower blood pressure during rest, more extensible skin, and less muscle strength but lacked the most important parameter indicating constitutional laxity: joint hypermobility. Another argument against constitutional laxity is the finding of an increased arterial stiffness in the patients with CFS. Moreover, the collagen metabolism measured by crosslinks and Hyp in urine, mainly reflecting bone resorption, did not differ between the 2 groups.

Before additional discussion about these results, some aspects of our study design need to be addressed. The cross-sectional design of our study limits causal interpretations. Furthermore, we attempted to measure all conceivable confounders of relations between stiffness parameters and disease status. However, we cannot exclude the possibility that there is residual confounding or unknown confounders. We do believe that we have sufficiently tackled problems with information bias, because examiners were blinded for other patient characteristics during measurement protocols.

Our results are incongruent with former studies with respect to joint mobility in adolescents with CFS. Whereas former studies established joint hypermobility in adolescents with CFS,5,6 we found a remarkably similar joint motion in adolescents with CFS and controls and a congruent Beighton score. The question is whether the CFS population under study is a representative sample of the CFS adolescent population in the Netherlands, which is estimated to consist of 2000 cases (the prevalence rate in the 5- to 15-year age group according to CDC criteria is 0.2 in Great Britain).26 Exact prevalence rates for the adolescent age group in the Netherlands are lacking. The Wilhelmina Children’s Hospital is a tertiary referral center for CFS (50 new patients with fatigue each year) and for children with joint hypermobility. A child with joint hypermobility initially referred to the department of pediatric physiotherapy for hyper-
This study we are not informed about minor psychological disturbances, and thus it is possible that the association between fatigue and blood pressure could be explained by unknown psychological factors.

Our study was explicitly not designed to study autonomic nervous dysfunction, which would have required appropriate measurements for the detection of orthostatic intolerance (e.g., tilt-table testing). However, the lower blood pressure in sitting position in patients with CFS may be explained by alterations in cardiovascular disease among patients with CFS. It is not been reported in the literature, nor has increased cardiovascular disease among patients with CFS. It is not been reported in the literature, nor has increased cardiovascular disease among patients with CFS.

The differences in systolic and diastolic blood pressure, which were evident only at the start of the examinations, are intriguing. The low blood pressure did not correlate with illness severity (CIS-20 score) or duration (Pearson correlation coefficients: 0.1 [P = 0.06] and -0.2 [P = 0.02], respectively), which makes a causal relationship between CFS and blood pressure not very likely. An association between systolic blood pressure and fatigue was established in a population study consisting of adult men and women with a linear trend showing more tiredness with lower systolic blood pressure. In a subsequently published cross-sectional study in civil servants, this strong association between tiredness and systolic blood pressure was reestablished but seemed confounded by minor psychological dysfunction. In this study we are not informed about minor psychological disturbances, and thus it is possible that the association between fatigue and blood pressure could be explained by unknown psychological factors.

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Opposite to the finding of this lower blood pressure is the unexpected finding that patients with CFS do seem to have stiffer arteries than controls, established with different parameters of arterial wall stiffness and adjusted for possible confounding factors (age, gender, BMI, physical activity, and lumen diameter and pulse pressure). This lifestyle factors were not incorporated into the regression model. An explanation for stiffer arteries in patients with CFS is not available yet. It has not been reported in the literature, nor has increased cardiovascular disease among patients with CFS. It is not been reported in the literature, nor has increased cardiovascular disease among patients with CFS.

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increased BMI\textsuperscript{30,31} and the decreased physical activity, but we adjusted for these possible confounding factors, as we did for lifestyle factors. There might be residual confounding in psychological factors, for example, the stress for patients with CFS to live with a disabling, unexplained condition.

The difference in arterial stiffness is not explained by arterial wall thickness, which was remarkably similar for both groups. Additional research is necessary to give more insight into this intriguing finding.

The difference in bone stiffness disappeared when we adjusted additionally for inactivity. Bone-resorption parameters in an overnight urine sample were the same for both groups. We could have expected a less active process of formation and resorption of bone in the patients with CFS, because of the inactivity, but this was not reflected in the data, possibly because of the large variation in these measurements between both groups.

The pain perception differed considerably between patients and controls. Although this was to be expected, because pain is a frequent complaint of patients with CFS, this is the first study to confirm this difference. Little is known about nociception, processing, cortical perception, and reporting of pain.\textsuperscript{32} It is surprising that the patients with CFS not only complain of more pain sensation on different locations but are also hypersensitive to visual,\textsuperscript{33} acoustic,\textsuperscript{34} and sensory signals. The processes underlying this increased sensory symptom perception in patients with CFS are not understood yet.

CONCLUSIONS

The findings of lower blood pressure, more extensible skin, arterial stiffening, and lower pain threshold in patients with CFS seem to be genuine but do not consistently point at a generalized abnormality in connective tissue. A more likely explanation is that these findings are caused by different mechanisms, such as complex disturbance of the autonomic nervous system in combination with a possible change in sensory symptom perception. More research is necessary to assess the pathogenicity of these findings and the reversibility after successful treatment of the adolescent with CFS.

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