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# Mirrored Symptoms in Mother and Child With Chronic Fatigue Syndrome

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## ABSTRACT

**OBJECTIVE.** Our aim with this study was to assess the relation between chronic fatigue syndrome in adolescents and fatigue and associated symptoms in their fathers and mothers, more specifically the presence of chronic fatigue syndrome-like symptoms and psychological distress.

**METHOD.** In this cross-sectional study, 40 adolescents with chronic fatigue syndrome according to the Centers for Disease Control and Prevention criteria were compared with 36 healthy control subjects and their respective parents. Questionnaires regarding fatigue (Checklist Individual Strength), fatigue-associated symptoms, and psychopathology (Symptom Checklist-90) were applied to the children and their parents.

**RESULTS.** Psychological distress in the mother corresponds with an adjusted odds ratio of 5.6 for the presence of CFS in the child. The presence of fatigue in the mother and dimensional assessment of fatigue with the Checklist Individual Strength revealed odds ratios of, respectively, 5.29 and 2.86 for the presence of chronic fatigue syndrome in the child. An increase of 1 SD of the hours spent by the working mother outside the home reduced the risk for chronic fatigue syndrome in their child with 61%. The fathers did not show any risk indicator for chronic fatigue syndrome in their child.

**CONCLUSIONS.** Mothers of adolescents with chronic fatigue syndrome exhibit fatigue and psychological symptoms similar to their child in contrast with the fathers. The striking difference between the absent association in fathers and the evident association in mothers suggests that the shared symptom complex of mother and child is the result of an interplay between genetic vulnerability and environmental factors.

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### Key Words

chronic fatigue syndrome, familial aggregation, family health, risk, psychopathology

### Abbreviations

CFS—chronic fatigue syndrome  
 CDC—Centers for Disease Control and Prevention  
 CIS-20—Checklist Individual Strength  
 SCL-90-R—revised Symptom Checklist  
 CDI—Children's Depression Inventory  
 OR—odds ratio  
 95% CI—95% confidence interval

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**A** MAJOR CONSENSUS in modern pediatric practice is that a child's health is profoundly influenced by family structure, family dynamics, and family functioning.<sup>1</sup> Nevertheless, remarkably little is known about family health and about how families develop illness-promoting or illness-preventing strategies.<sup>2</sup> Especially in unexplained illnesses, these family factors could elucidate part of the complex multifactorial etiology. Chronic fatigue syndrome (CFS) is such an illness and is characterized by chronic disabling fatigue, pain, sleep difficulties, and cognitive impairment. CFS is not restricted to adults but is increasingly recognized in adolescents and children.<sup>3</sup>

Fatigue seems to aggregate in families. In a large study of twins aged over 50, Hickie found that familial aggregation of fatigue of at least 1 month's duration seemed to be largely the result of genetic factors with a 2.5 times higher concordance rate in monozygotic twins than in dizygotic twins.<sup>4</sup> These results resemble those of a child twin study, in which the parents' reports of disabling fatigue of 1 month's duration in their children revealed a concordance rate of 0.75 in monozygotic twins versus 0.47 in dizygotic twins.<sup>5</sup>

Not only fatigue but also CFS aggregates in families. Buchwald performed a large twin study on chronic fatigue and CFS, and revealed a concordance rate for CFS of 0.55 in monozygotic and 0.19 in dizygotic twins,<sup>6</sup> confirming the familial aggregation of CFS and suggesting that genes may play a role. In a family history study of CFS, results based on subjects' reports of illness in first-degree relatives suggested that relatives of patients with CFS had significantly higher rates of CFS than relatives of a patient with another chronic illness.<sup>7</sup> Garalda<sup>8</sup> found more health problems in a cross-sectional study in the families of adolescents with a history of CFS than in the families of healthy control subjects, but it is not clear whether these health problems were CFS-like. Several years earlier, Bell<sup>9</sup> estimated from a cluster of 21 pediatric cases of CFS that familial CFS is a major risk factor for pediatric CFS.

All these findings suggest a familial predisposition for CFS of varying intensities but do not discriminate between a distinct incidence for the fatigue symptoms in fathers or mothers.

Because fatigue is necessarily associated with other somatic symptoms<sup>10</sup> and often is accompanied by depression and anxiety,<sup>11</sup> a family survey should deal with this cluster of symptoms.

The aim of this study was to assess the relation between CFS in adolescents and fatigue and associated symptoms in fathers and mothers, more specifically the presence of CFS-like symptoms and psychologic distress.

## METHODS

### Population

A total of 70 adolescents (aged 12–18 years) was referred with severe fatigue to a specific CFS clinic of the Uni-

versity Medical Center Utrecht between June 2003 and September 2004. All patients were investigated by a pediatrician and the final diagnosis of CFS was established by 1 pediatrician (E.v.d.P.) in 47 adolescents after medical and psychologic examinations using specific Dutch questionnaires for anxiety and depression in combination with an interview of both child and parent. Additional to the Centers for Disease Control and Prevention (CDC) exclusion criteria, patients with somatic comorbidity interfering with fatigue were excluded ( $N = 4$  [1 hyperhomocysteinemia, 1 celiac disease, 1 irritable bowel syndrome, and 1 delayed-phase sleep syndrome]). One patient was excluded because of severe depression requiring pharmaceutical treatment. Two adolescents refused to participate. Of the remaining 40 included adolescents, 36 fulfilled all criteria for CFS of the CDC.<sup>10</sup> Four patients had <4 side symptoms but were nevertheless included. The mean number of the 8 CDC side symptoms was 5.2 (SD: 1.6). Forty mothers and 34 fathers participated. The remaining 6 fathers lost contact with their child after a divorce.

As a reference group, 102 adolescents aged 12 to 18 years from a secondary school were invited to participate with their parents. Families with an adoptive child or a child with a chronic illness were excluded ( $n = 3$ ). From the remaining 99 adolescents, 36 adolescents (37%) agreed to participate, including 4 pairs of siblings. Two fathers and 2 mothers refused to participate, leaving 30 mothers and 30 fathers for participation.

### Self-Report Measures

Fatigue was assessed dimensionally in all participants with the Checklist Individual Strength (CIS-20), which asks about fatigue in the 2 weeks before the assessment. There are 4 subscales: subjective experience of fatigue, concentration, motivation, and physical activity, each item scored on a Likert scale (scored 1–7). A high score indicates a high level of subjective fatigue and concentration problems and a low level of motivation and physical activity. The internal consistency is high as is the discriminative validity for CFS.<sup>12</sup>

The revised Symptom Checklist (SCL-90-R), a 90-item self-report scale, was used to assess current psychologic distress in parents on 9 subscales: somatization, obsession, interpersonal sensitivity, depression, anxiety, aggression, phobia, paranoia, psychoticism, and additional items.<sup>13–15</sup> The questionnaire asks about the presence of a symptom in the preceding week, including the day of assessment, on a 5-point Likert scale (range: 1–5). The higher the score, the more psychologic distress.

A general questionnaire was applied to all parents regarding demographic data (eg, age, household size), hours of paid work, and current presence of fatigue and the 8 CDC symptoms for CFS (yes/no).

A sleep questionnaire was applied to all participants to measure sleep in the 2 weeks before the assessment

with 14 dichotomic scored items. The total score is a measure of sleep quality; the higher the score, the poorer the quality.<sup>16</sup>

Depression in adolescents was measured with a validated Dutch translation of the Children's Depression Inventory (CDI).<sup>17,18</sup> The CDI quantifies depressive symptoms in the past 2 weeks and consists of 27 items rated on a 3-point scale (range: 0–2).

Assessment of trait anxiety in adolescents was performed with a Dutch translation of the Spielberger State-Trait Anxiety Inventory for Children.<sup>19,20</sup> The Spielberger State-Trait Anxiety Inventory for Children consists of 20 statements on a 3-point scale that assess the level of anxiety a person reports as generally characteristic of himself or herself (disposition).

Somatic complaints were assessed with a validated Dutch translation of the Children's Somatization Inventory), a self-report questionnaire rating the presence of each of 35 somatic symptoms in the preceding 2 weeks using a 5-point Likert scale ranging from "not at all" to "a whole lot" (range: 0–4).<sup>21,22</sup>

All questionnaires were completed individually in separate rooms in a university building in May through August 2004. The adolescents completed the questionnaires on average in 30 minutes and the parents in 20 minutes.

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

### Statistical Analysis

Of the relevant variables, group-specific means and SDs or proportions were calculated for descriptive purposes.

The data were analyzed 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 pre-

sented as linear regression coefficients representing mean differences between the adolescents with CFS and the healthy control subjects for the investigated parameter with their corresponding 95% confidence intervals (CIs). The same models were used to adjust for possible confounding factors.

The magnitude of the associations between parental risk indicators and CFS in their offspring was quantified by estimating odds ratios (ORs) and respective 95% CIs using binary logistic regression with CFS (yes/no) as the dependent variable and the factors of interest as the independent variable. These factors were transformed into *z* scores to obtain relative risks per SD difference. The adjusted OR was quantified in the same model by adding possible confounding factors as covariates (age and gender of the child and the age of the parent concerned).

To account for possible differential nonresponse of the control group, we checked for the presence of fatigue and past or present psychologic treatment in the nonresponding parents (63 families) and adolescents (results from the Fatigue in Teenagers-I study 2002).<sup>23</sup>

### RESULTS

Table 1 shows that both adolescent groups had the same gender composition, but the CFS adolescents were slightly younger (16 vs 16.8 years). Both groups came from a high percentage of intact families with exactly the same number of siblings.

Evidently, the patients with CFS showed a higher score on all the subscales of the CIS-20 than the healthy adolescents. Sleeping problems were more prominent in the CFS group as were somatic complaints. Anxiety was more manifest in the adolescents with CFS just like depression. The mean CDI score for depression in the adolescents with CFS (11.7) is below that for a depressive disorder, which is 22.8 in a Dutch and Belgian reference sample of 18 children with a depressive disorder.

**TABLE 1** Characteristics of Adolescents With CFS and Healthy Control Subjects

	CFS (n = 40)	Healthy (n = 36)	Difference (95% CI)	P	Adjusted Difference (95% CI) <sup>a</sup>	P
Mean symptom duration (SD), mo	23.4 (11.3)	NA				
Age, mean (SD), y	16.0 (1.5)	16.8 (1.4)	0.8 (–1.5 to –0.1)	0.019		
Gender, % girls	78	67	11 (–10 to 31)	0.298		
Intact families, %	82	93	–9 (–27 to 5)	0.185		
Household size (No. of children), mean (SD)	2.5 (0.8)	2.5 (0.8)	0 (–0.3 to 0.3)	0.954		
Fatigue assessment, mean (SD)						
Total score CIS-20 (20 items; 20–140)	101.8 (17.8)	48.0 (18.8)	53.9 (45.5 to 62.2)	0.0001	50.8 (42.4 to 59.2)	.0001
Score subjective fatigue subscale (8 items; 8–56)	46.9 (7.4)	19.4 (10.0)	27.5 (23.5 to 31.5)	0.0001	26.0 (21.9 to 30.0)	.0001
Sleep problems (14 items; 0–14)	6.2 (3.2)	2.8 (2.9)	3.4 (2.0 to 4.8)	0.0001	3.4 (1.9 to 4.9)	.0001
Somatic complaints (CIS 35 items; 0–140)	35.6 (20.1)	13.0 (9.3)	22.6 (15.5 to 29.7)	0.0001	19.9 (12.6 to 27.1)	.0001
Psychologic adjustment, mean (SD)						
Anxiety disposition (Spielberger State-Trait Anxiety Inventory for Children; 20 items; 20–60)	36.9 (7.8)	30.3 (6.4)	6.6 (3.3 to 9.9)	0.0001	5.9 (2.5 to 9.3)	.001
Depression disposition (CDI; 27 items; 0–54)	11.7 (6.1)	5.6 (4.4)	6.1 (3.7 to 8.5)	0.0001	6.1 (3.5 to 8.7)	.0001

<sup>a</sup> Adjusted for age and gender.

der.<sup>24</sup> A cutoff score of  $\geq 16$  is proposed as predictive of a depressive disorder.<sup>24</sup> In our study, only 1 of the healthy adolescents scored  $\geq 16$  compared with 6 of the adolescents with CFS.

All differences between the healthy adolescents and the adolescents with CFS were statistically significant, and adjusting for age and gender did not influence the results.

The comparisons of the characteristics of the mothers and the fathers are shown separately in Table 2 and Table 3, respectively. Mothers of adolescents with CFS differed from mothers of healthy adolescents in all measurements of fatigue and fatigue-associated symptoms, including sleep. Nine mothers even fulfilled CDC criteria for CFS.<sup>10</sup> The presence of fatigue in the mother and dimensional assessment of fatigue with the CIS-20 revealed an OR of, respectively, 5.3 (95% CI: 1.3 to 21.2) and 2.9 (95% CI: 1.4 to 5.8) for the presence of CFS in the child. Self-reported psychologic distress was significantly higher, especially in the subscales somatization, depression, and anxiety. Psychologic distress in the mother corresponded with a 5.6 times higher chance for the presence of CFS in the child (95% CI: 1.9 to 16.8) with depression as the main risk factor.

An increase of 1 SD of the hours spent by the working mother outside the home reduced the risk for CFS in their child with 61% (OR: 0.39; 95% CI: 0.20 to 0.75). None of the ORs of the same variables of the fathers were different from 1.

The nonresponding mothers ( $n = 63$ ) of the control group mentioned fatigue in 19% and psychologic treatment in 13% (compared with, respectively, 17% and 13% of the responding mothers in this study). The nonresponding adolescents were more fatigued (CIS-20 score: 55.7) than the responding adolescents, leading to a nonsignificant difference in the CIS-20 score of  $-7.7$  (95% CI:  $-15.7$  to  $0.2$ ;  $P = .06$ ).

## DISCUSSION

This is the first study comparing families with a physician-diagnosed CFS proband with healthy families. Our study revealed a shared symptom complex of fatigue, fatigue-associated symptoms, and psychologic distress between adolescents with CFS and their mothers. A similar association between adolescents with CFS and their fathers was not found.

Associated emotional distress and psychopathology are commonly reported in adults and children with CFS.<sup>25-27</sup> The origin of this psychologic morbidity in CFS has not yet been clarified. Possibly it shares a common etiology with CFS or one is the result of the other. It is remarkable, however, that in our study, the same symptom complex is uncovered in both mother and child. The striking difference between the absent association in fathers and the evident association in mothers suggests that the shared symptom complex of mother and child is the result of an interplay between genetic susceptibility and environmental factors. It may point to a gene-environment interaction in which the child not only inherits the genetic characteristics of the mother, but these maternal characteristics also function as environmental factors for the child.

There is evidence for genetic factors to play a role in the cause of CFS. All twin studies on CFS or less strictly defined fatigue reveal a higher concordance rate among monozygotic twins.<sup>4-6</sup> Female gender is a risk factor for CFS as is clear from prevalence studies and from the twin studies. If CFS is assumed to be a multifactorial illness, monogenetic inheritance will be unlikely. The twin study of Hickie et al revealed independent genetic factors for fatigue only (44%) and common genetic factors for psychologic distress and fatigue.<sup>4</sup> Accordingly, mothers and children may share a genetic tendency for fatigue and psychologic distress and a genetic susceptibility to environmental influences both beyond and within the family. The nature of this susceptibility is

**TABLE 2** ORs for Characteristics of Mothers and the Presence of CFS in the Adolescent

	CFS ( $n = 40$ )	Healthy ( $n = 30$ )	OR <sub>uni</sub> (95% CI)	<i>P</i>	OR <sub>adj</sub> <sup>a</sup> (95% CI)	<i>P</i>
Age, mean (SD), y	45.1 (4.9)	47.4 (3.1)	0.6 (0.3 to 1.0)	.041	0.8 (0.4 to 1.6)	.533
Measures of psychologic distress						
SCL-90, mean (SD)	128.1 (29.4)	111.9 (16.1)	2.5 (1.2 to 5.2)	.016	5.6 (1.9 to 16.8)	.002
Depression, mean (SD)	20.2 (6.0)	16.5 (3.0)	3.0 (1.4 to 6.6)	.006	8.4 (2.2 to 31.6)	.002
Anxiety, mean (SD)	13.1 (3.8)	11.6 (2.0)	1.9 (0.9 to 3.6)	.074	3.0 (1.1 to 8.0)	.034
Somatization, mean (SD)	18.7 (6.5)	15.7 (3.7)	2.0 (1.0 to 3.9)	.037	3.1 (1.3 to 7.4)	.010
Measures of fatigue and fatigue-related symptoms						
Subjective fatigue, mean (SD)	28.5 (13.4)	19.2 (7.7)	2.0 (1.2 to 3.5)	.015	2.2 (1.2 to 4.2)	.015
CIS-20, mean (SD)	60.7 (27.6)	43.1 (12.4)	2.5 (1.3 to 4.7)	.004	2.9 (1.4 to 5.8)	.004
Fatigue present, <i>n</i> (%)	45 (50)	17 (38)	4.1 (1.3 to 12.9)	.016	5.3 (1.3 to 21.2)	.019
No. of CDC criteria present (SD)	2.4 (2.4)	1.0 (1.7)	1.4 (1.1 to 1.9)	.016	1.5 (1.1 to 2.2)	.020
Sleep score, mean (SD)	4.2 (3.7)	2.3 (2.7)	1.9 (1.1 to 3.4)	.027	2.2 (1.2 to 4.3)	.015
Daily work outside the home, mean (SD), h/wk	14.3 (13.0)	24.5 (8.6)	0.4 (0.2 to 0.7)	.002	0.4 (0.2 to 0.8)	.005

<sup>a</sup>OR<sub>adj</sub> was adjusted for age and gender of the child and age of the parent.

**TABLE 3 ORs for Characteristics of Fathers and the Presence of CFS in the Adolescent**

	CFS (n = 40)	Healthy (n = 30)	OR <sub>uni</sub> (95% CI)	P	OR <sub>adj</sub> (95% CI) <sup>a</sup>	P
Age, mean (SD), y	48.2 (4.7)	50.3 (3.3)	0.6 (0.3 to 1.0)	.060	0.6 (0.3 to 1.2)	.147
Measures of psychologic distress						
SCL-90, mean (SD)	112.0 (23.8)	112.7 (18.5)	1.0 (0.6 to 1.6)	.896	1.1 (0.6 to 1.9)	.794
Measures of fatigue and fatigue-related symptoms						
Subjective fatigue, mean (SD)	21.1 (10.8)	20.3 (17.7)				
CIS-20, mean (SD)	49.2 (20.5)	48.9 (28.4)	1.0 (0.6 to 1.7)	.955	1.2 (0.7 to 2.2)	.465
Fatigue present, n (%)	24 (43.1)	26 (44)	0.9 (0.3 to 2.7)	.831	1.1 (0.3 to 4.1)	.891
No. of CDC criteria present, mean (SD)	1.1 (1.4)	1.0 (1.5)	1.0 (0.7 to 1.4)	.940	1.2 (0.8 to 1.7)	.476
Sleep score, mean (SD)	2.0 (2.9)	1.4 (1.6)	1.3 (0.8 to 2.3)	.328	1.4 (0.8 to 2.5)	.314
Daily work outside the house, mean (SD), h/wk	34.4 (12.6)	31.9 (17.8)	1.2 (0.7 to 2.1)	.548	1.2 (0.6 to 2.3)	.606

<sup>a</sup> OR<sub>adj</sub> was adjusted for age and gender of the child and age of the parent.

unknown and genetic research is hampered by the lack of a possible biologic substrate, an endophenotype, for the symptoms of CFS. Occasionally, one causal biologic factor for CFS has been explored, like homozygosity for the serine allele of the CBG gene.<sup>28</sup>

Potential shared environmental factors beyond the family are infections, like Epstein-Barr virus and other enteroviruses and herpesviruses, or intolerance to certain chemicals.<sup>29-31</sup> However, these external environmental factors are potentially harmful for all family members and do not explain the difference in risk indicators between fathers and mothers, which means that other risk factors are necessarily involved for developing CFS.

Shared environmental factors within the family are illness attitudes, illness beliefs, and illness behavior. It has been shown that parental reinforcement of illness behavior is higher in children with CFS compared with children with juvenile rheumatoid arthritis. The parent (not explicitly the mother or the father) of teens with CFS experienced more concern and behaved in a more protective fashion with their teens, thereby reinforcing their illness behavior.<sup>32</sup> Viewed in this respect, the striking lower amount of working hours in mothers with an adolescent with CFS, with consequently more time to spend within the family with their ill child, could be quite relevant.

Another explanation for the shared symptom complex between mother and child is the possibility that the symptoms seen in the child are a reaction to a primary illness of the mother. The cross-sectional design of our study makes causal inference from the results impossible. However, we know from other studies in depressed mothers that their children are at increased risk for a series of behavioral disorders and depression through different mechanisms, like reduction of parental tolerance, social problem-solving, and coping skills.<sup>33,34</sup> However, a recently published longitudinal study on risk factors for CFS did not reveal preceding maternal psychopathology or parental illness (measured with the General Health Questionnaire) as risk factors for the

lifetime prevalence of self-reported CFS.<sup>27</sup> The time interval between the measurement of maternal psychopathology (at age 10 and 15 of the child) and that of lifetime prevalence of CFS (at the age of 30) was large. A smaller time interval is perhaps necessary to reveal these maternal symptoms as risk factors for CFS in their children.

Finally, the established symptoms in the mothers of adolescents with CFS may constitute a reaction of the mother to the illness of the child. From other chronic illnesses in children, we know that a reactive pattern predominated by depressive symptoms of the mother is possible, especially at the start of the illness.<sup>35</sup> From this study, we cannot conclude whether the health symptoms in the mother of an adolescent with adolescent are specific or also apply to mothers of children with other chronic illnesses. A recent study of Rangel suggests that the pattern of emotional reactions and health problems is quite specific for the parents of the child with CFS in comparison with juvenile rheumatoid arthritis and emotional disorders.<sup>36</sup> She found more psychopathology in CFS families than in families with a child with juvenile rheumatoid arthritis. A distinction between the parents was not made. The CFS families exhibited a pattern of emotional overinvolvement compared with the parents of a child with juvenile rheumatoid arthritis.<sup>36</sup> Another, retrospective study also established this maternal overprotectiveness in patients with CFS.<sup>37</sup>

## CONCLUSIONS

The clustering of symptoms in mother and child suggests genetic transfer and gene-environment interaction. The preferential choice of treatment for CFS at this time is cognitive behavioral therapy. A randomized, controlled trial in adolescents established a recovery rate of ~60%.<sup>38</sup> It is not clear which factors influence this recovery rate. Purely behavioral models of treatment of the adolescents with CFS may neglect these risk indicators in the mother and thereby overlook these potentially important perpetuating factors.

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