Risk Factors Associated with Chronic Fatigue Syndrome in a Cluster of Pediatric Cases

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After seven pediatric cases of chronic fatigue syndrome (CFS) were diagnosed in a farming community in upstate New York, a questionnaire regarding symptoms and potential risk factors of CFS was distributed to all students enrolled in the same school district. Twenty-one students with symptoms of CFS were identified. Two controls per case matched for age and sex were randomly selected from questionnaire respondents. Health status was verified for all subjects by telephone, and diagnosis of CFS was confirmed by a physician. Information was collected on the following factors: symptoms of CFS among other family members; history of allergy/asthma; consumption of raw milk, raw eggs, raw cheese, or raw meat; water supply; exposure to animals; home heating source; proximity to farmland/orchards; tick bite; blood transfusion; camping; and appendicitis. Logistic-regression analyses indicated that the best model (characterized by symptoms among other family members, recent ingestion of raw milk, and history of allergy/asthma) produced significant estimates of relative risk ($P < .05$) of 35.9, 44.3, and 23.3, respectively, for the three factors (corrections were made for the effect of the other covariates). These data suggest that a combination of host and environmental factors, including an infectious agent or agents, are involved in the etiology of CFS.

In recent years, several investigators have described a chronic illness characterized by persistent fatigue, fever, myalgia, pharyngitis, headache, adenopathy, gastrointestinal symptoms, and neurologic problems [1–10]. Similar syndromes have been described on several occasions over the past 50 years [11–24]. In the United States this illness has been referred to as chronic mononucleosis [3], chronic mononucleosis-like syndrome [9], and chronic active Epstein-Barr virus syndrome [1]. Because of the uncertain etiology of this syndrome and the severity and chronic nature of the fatigue experienced by many patients, the illness has been renamed chronic fatigue syndrome (CFS) [25].

When several studies [1, 2, 5] described an association between CFS and persistently elevated serum titers of antibody to Epstein-Barr virus (EBV), CFS was thought to be a form of chronic infection due to EBV. Subsequent reports [3, 9] have demonstrated that elevated levels of antibody to EBV are not consistently found in persons with CFS and that levels of antibody to cytomegalovirus, measles virus, and herpesviruses 1 and 2 have been noted. These findings raise the possibility that an altered immunologic response is initiated by another stimulus or agent. A greater percentage of patients with this syndrome have a history of allergies than would be expected [1]. CFS is reported to occur more frequently in women (70%) than in men and in young and middle-aged adults more than in other age groups [1, 3, 26]. However, no exogenous risk factors for this illness have been identified.

Lyndonville, New York, is a village of ~950 persons at the center of the town of Yates, which has a population of 2,371. Virtually all children in the Lyndonville school district (n = 914) live in Yates or in parts of the three surrounding townships and attend Lyndonville Central School. The area is in the heart of upstate New York farmland and borders on the southern shore of Lake Ontario halfway between the cities of Niagara Falls and Rochester.

In November 1985 seven Lyndonville children (aged 10–16 years) from two families presented with fever, lymphadenopathy, arthralgias, hepatosplenomegaly, fatigue, headache, and malaise. The initial course lasted ~2 weeks, during which time the only abnormalities noted from laboratory studies were slightly elevated values in liver function tests. All children subsequently developed chronic pain in lymph nodes, joints, muscles, and upper abdomen. Headache, marked fatigue, facial rash on the cheeks, eye pain, and recurrent sore throat further characterized the ongoing symptomatology. The size of the liver and spleen and levels of alanine aminotransferase returned to normal, and fever disappeared. Extensive laboratory analyses were conducted, including serologic tests specific for *Brucella abortus, Brucella suis, Brucella melitensis*, and *Brucella canis; Coxiella burnetii*; cytomegalovirus; EBV; *Toxoplasma gondii; Borrelia burgdorferi*; human immunodeficiency virus (HIV); hepatitis B virus, parvovirus B-19; and *Francisella tularensis*. These and other tests (to determine liver function, complete blood cell count [CBC], erythrocyte sedimentation rate [ESR], antinuclear antibody

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[ANA], antistreptolysin O titer, rheumatoid factor, and febrile agglutinins) failed to reveal any etiologic agent that could explain the children's symptoms. The present study was conducted to identify other cases of CFS and to evaluate a number of possible risk factors.

Methods

Study population. As part of our study, a questionnaire regarding symptoms and possible risk factors of CFS was distributed in May 1987 to all 914 students in the Lyndonville Central School District (grades K–12). Of those students, 61% (561) responded with a completed questionnaire by June 1987, before any reports were published in three local newspapers or transmitted by radio or television. Thirty-three students with symptoms of CFS were identified and interviewed; these included the six index cases (one of the seven original patients had graduated and was not included in the study). A diagnosis of CFS was confirmed by a physician for 21 students after a complete history was obtained and a physical examination and routine laboratory evaluations (including tests for CBC, blood chemistry, thyroid function [T_3, T_4, and T_7], ESR, and ANA) were performed. Twelve students were found to have other diagnoses that could explain their symptoms and were excluded from the final CFS case group. For each child with CFS, two controls matched for age and sex were randomly selected from asymptomatic respondents. The health status of all controls was verified by a follow-up telephone call.

All patients who were diagnosed with CFS were thoroughly evaluated for evidence of other underlying disease that could explain their symptoms, such as chronic diseases that occur in pediatric populations or psychiatric or behavioral disorders. As part of this assessment, all case children and their parents were interviewed concerning family history of behavioral or psychiatric problems and the existence of any academic or social problems in the school setting before their illness. During the interview, case children and their parents were questioned extensively concerning recent trauma or stressful events that may have affected the child, such as separation or divorce of parents or death of a family member or a close friend. Medical records for each case child were reviewed for evidence of previous behavioral or psychiatric disorder or history of child abuse or neglect.

Our study was conducted before the 1988 publication of diagnostic criteria for CFS by Holmes et al. [25]. A retrospective review of the medical records for case children showed that all 21 cases included in our study met these diagnostic criteria for CFS. However, at the time this study was conducted, students were considered to have CFS if the following criteria were met: (1) a course of >6 months of continuous or relapsing symptoms; (2) no evidence of other underlying disease, psychiatric disorder, or pathology; (3) at least six of eight major chronic symptoms (fatigue, headache, abdominal pain, myalgia, pharyngitis, lymphatic pain, arthralgia, and neurologic symptoms) or at least five of those major symptoms and at least two of three minor symptoms (facial rash, dysuria, and ocular discomfort and/or photophobia).

Table 1. Prevalence of symptoms of CFS in case population (n = 21).

Symptoms	No. (%) with symptom
Major	
Fatigue	21 (100.0)
Headache	21 (100.0)
Abdominal pain	21 (100.0)
Myalgia/backache	21 (100.0)
Pharyngitis	20 (95.2)
Lymphatic pain	20 (95.2)
Arthralgia	19 (90.5)
Neurologic symptoms	18 (85.7)
Vertigo	13 (61.9)
Insomnia	8 (38.1)
Memory loss/poor concentration	14 (66.7)
Lightheadedness/fainting	2 (9.5)
Tinnitus	7 (33.3)
Parasthesias	8 (38.1)
Aphasia	5 (23.8)
Fasciculations	8 (38.1)
Choreiform movements	3 (14.3)
Minor	
Ocular discomfort/photophobia	18 (85.7)
Facial rash	17 (80.9)
Dysuria	7 (33.3)

Table 1 summarizes the prevalence of various symptoms of CFS in our case population. The types of symptoms seen in this pediatric cluster were similar to those reported by other authors [1–5, 9, 10]. Fatigue, abdominal pain, headache, and myalgia were noted in 100% of the cases. Pharyngitis, lymph node pain, and rash were noted in the majority of cases, as was a history of fevers, sweats, and/or chills. Neurologic symptoms were found in 18 of the 21 cases; memory loss/poor concentration and vertigo were among the symptoms reported most commonly.

Data collection and analysis. In addition to requesting information about symptoms of CFS, the questionnaires asked whether other family members had symptoms of CFS; whether the child had a history of allergies, asthma, or consumption of raw milk, raw meat, raw cheese, or raw eggs; and about water supply, exposure to animals, home heating source, proximity to farmland or orchards, tick bites, blood transfusion, camping, and appendicitis. This list was based on the symptoms noted in cases and was designed to include known risk factors in adults (history of allergies or asthma), possible exposure to toxins, exposure to known vectors of infectious disease, and possible exposure to enteric organisms known to be associated with postinfectious arthropathy syndromes. The associations among the possible risk factors and CFS were investigated via computation of relative risks [27], tests of significance [28], and stepwise linear logistic regression [29]; 95% confidence intervals were computed for all estimates of relative risk [28].

Results

Sixty-one percent (561 of 914) of the students responded. Since virtually all children in the district attend the Lyndonville Central School, we can extrapolate a prevalence of CFS of at least 2.3%, assuming that nonresponders were likely to be asymptomatic. Figure 1 contains information on the sex and age-at-onset distributions for the 21 case children. Age at onset of CFS ranged from 18 months to 15 years. The mean age of onset for the case population was 10.6 years, and the median age was 11 years, while the male-to-female ratio was 11:10. Figure 2 shows the distribution of cases of CFS by year of onset. For 96% of the cases (n = 20) the date of onset was since January 1982, and for 71% (n = 15) the date of onset was since January 1985.

The sociodemographic characteristics of case and control children are summarized in table 2. More than 95% of case children and >73% of control children lived in households where both parents were present. The rate of parental unemployment (9.5%) was equal for the two groups, and the types of parental employment were not significantly different. Nine of the cases occurred among siblings from three families. The remaining 12 case children were the only children at the time in each of their 12 respective families with symptoms that fit the CFS case definition. Each of the 42 control children represented a different family.

The results of univariate analysis for the multiple risk factors under investigation are presented in table 3. Highly significant positive associations were observed for the presence of other family members with symptoms of CFS, ingestion of raw milk either recently or in the past, ingestion of raw eggs, and history of allergies or asthma. Exposure to hot-air heating, the presence of cats on the property, and appendicitis also had significant positive associations with CFS. The presence of dogs in the house was inversely associated with CFS.

Stepwise linear logistic regression was performed to investigate further the association between CFS and the various risk factors. Table 4 summarizes the results of these analyses. The best logistic regression model included a constant

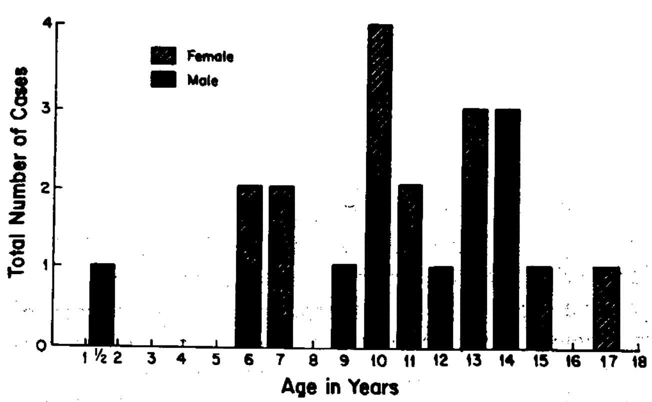

Figure 1. Distribution of cases by sex of child and age at onset of CFS.

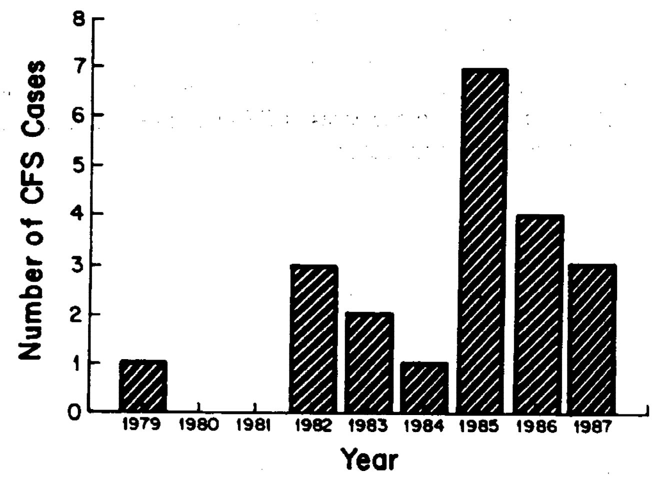

Figure 2. Year of onset of CFS (n = 21). The data for 1987 were collected from January through June only.

Table 2. Sociodemographic characteristics of children with CFS and control children.

Characteristic	No. (%) in indicated group* CFS	Control
Sex		
Male	11 (52.4)	22 (52.4)
Female	10 (47.6)	20 (47.6)
Total	21 (100)	42 (100)
Parental occupation†		
White-collar	4 (19.0)	5 (11.9)
Blue-collar	14 (66.7)	27 (64.3)
Farmer	1 (4.8)	4 (9.5)
Unemployed	2 (9.5)	4 (9.5)
Unknown	0 (. . .)	2 (4.8)
Total	21 (100)	42 (100)
Family status		
Two parents	20 (95.2)	31 (73.8)
Single parent	1 (4.8)	10 (23.8)
Unknown	0 (. . .)	1 (2.4)
Total	21 (100)	42 (100)
Age (y)		
Range	6–17	6–17
Mean	12.8	12.3
Median	13.0	13.0

* Except where indicated otherwise.
† Primary occupation of head of household at time of survey.

Table 3. Risk ratios for individual variables of exposure to disease.

Variable	No. in group with exposure: Case (n = 21)	Control (n = 42)	RR	95% CI
Food ingestion				
Raw milk, at any time	19	14	15.33*	3.45, 137.9
Raw milk, recently	17	4	33.27*	7.54, 258.18
Raw eggs	12	5	8.97*	2.38, 43.81
Raw shellfish	2	2	2.08	0.19, 23.22
Raw cheese	4	1	7.11	0.89, 244.29
Other family member with symptoms of CFS	16	2	48.60	9.43, 578.22
Allergies/asthma	15	7	11.29	3.10, 54.26
Private well at present	11	28	0.56	0.16, 1.82
Private well at any time	15	35	0.50	0.12, 2.05
Outdoor camping	20	31	4.99	0.82, 158.47
Proximity to orchards or farmland	15	31	0.87	0.24, 3.35
Exposure to animals in the house				
Dogs	5	26	0.21†	0.05, 0.71
Cats	8	21	0.63	0.18, 2.03
Fish	6	4	3.59	0.79, 19.23
Mice	1	2	1.19	0.03, 15.50
Birds	3	0	0.26	<0.01, 4.63
Hamsters	3	2	3.06	0.40, 31.84
Other	3	1	5.23	0.56, 183.48
Home heating source				
Oil	6	19	0.51	0.13, 1.69
Electricity	3	4	1.62	0.25, 9.73
Hot air	8	3	7.11†	1.57, 45.68
Wood	8	24	0.48	0.14, 1.53
Kerosene	3	11	0.52	0.09, 2.19
Natural gas	3	6	1.06	0.17, 5.32
Exposure to animals on property				
Cattle	2	6	0.72	0.08, 4.03
Horses	1	4	0.63	0.02, 5.10
Sheep	0	5	0.16	<0.01, 2.31
Swine	0	1	0.64	<0.01, 36.03
Cats	18	23	4.39†	1.12, 25.00
Dogs	16	34	0.74	0.18, 3.19
Ducks	4	9	0.91	0.19, 3.74
Goats	1	4	0.63	0.02, 5.10
Chickens	5	9	1.18	0.28, 4.64
Other	1	6	0.41	0.01, 2.87
Tick bite	1	3	0.83	0.02, 7.85
Blood transfusion	0	2	0.38	<0.01, 8.51
Appendicitis	4	0	21.86†	1.42, ∞

NOTE. RR = relative risk; CI = confidence interval.
* $P < .0005$.
† $P < .05$.

and these three variables: other family members with symptoms of CFS, recent ingestion of raw milk, and history of allergies or asthma. Risk estimates for all three factors were statistically significant ($P < .05$) after corrections were made for the effects of the other two covariates, and the resulting risk ratios were 35.9, 44.3, and 23.3, respectively. The other apparent risk factors identified during univariate analyses no longer appeared to be risk factors for CFS after controls for these three factors were implemented. Attempts to assess interactions among the three significant risk factors yielded results of zero cell frequencies and, in turn, the inability to compute model coefficients.

The 21 cases identified among students attending schools in the Lyndonville Central School District included six of the seven original index cases. The seventh case child had graduated before this study was conducted. A determination of whether risk factors identified for the 21 cases changed if the six index cases were eliminated from the case population was

Table 4. Results of logistic regression modeling.

Variable	Coefficients	RR	95% CI	P
Constant	−4.66	. . .	. . .	.0003
Other family member with symptoms of CFS	3.58	35.9	2.84, 488.5	.0071
Raw milk, recent ingestion	3.79	44.3	3.21, 606.5	.0046
Allergies or asthma	3.15	23.3	1.67, 327.3	.0192

NOTE. Each estimate of relative risk (RR) is adjusted for the other two variables. CI = confidence interval.

made by repeating univariate and logistic regression analyses that compared the 15 nonindex cases with controls. As in the original univariate analyses, significant positive associations were observed for the presence of other family members with symptoms of CFS, ingestion of raw milk either recently or in the past, ingestion of raw eggs, history of allergies or asthma, and appendicitis. Exposure to rabbits on the property and having fish in the house were also positively associated with CFS. The best logistic regression model once again included only a constant and the same three variables: other family members with symptoms of CFS, recent ingestion of raw milk, and history of allergies or asthma.

Discussion

Past research concerning CFS has been difficult because of the lack of clear-cut laboratory markers or an accepted clinical definition of this illness. CFS is reported to be most common in persons 25–40 years of age, and most studies have specifically selected adult subjects [1, 2, 10].

The children presented here fulfill the criteria recently published by Holmes et al. [25] for diagnosis of CFS in adults, and we believe that the diagnosis of CFS can be made on this basis. Our study was conducted in a defined rural population of children who ranged in age from 6 to 17 years at the time of the study. The majority of cases of CFS occurred in children ⩾10 years old. Although studies of adult populations report that most cases of CFS are in women (female-to-male ratio, ~3:1) [3], we found no gender differences in prevalence of CFS.

In our study population, ingestion of raw milk and the presence of a second family member with symptoms of CFS were both highly significant factors for cases as compared with matched controls. Furthermore, results of logistic regression modeling suggest that recent ingestion of raw milk and the presence of other family members with symptoms of CFS are separate risk factors for the illness. A history of allergies or asthma also was identified as a separate risk factor for CFS in this case population. The results of analyses that compared the 15 nonindex cases with controls suggest that the risk factors identified as part of this study could not be accounted for by inclusion of index cases in the study population.

Assessment of other risk factors appears to rule out the possibility that the association found between CFS and the ingestion of raw milk was coincidental due to environmental factors. Case children were not more likely than control children to live on farms, live near livestock, use water from private wells, live in homes heated with wood, or have animals in their homes. Since the raw milk consumed was of both bovine and caprine origins, from a number of different providers, and ingested over a span of several years, it is unlikely that a heat-labile toxin was the initiating mechanism. A more likely agent is some type of microorganism. Such a microorganism may effect disease in a variety of ways.

Raw milk has been well documented to be a perfect medium for transmission of a number of pathologic agents, including a host of viruses [30]. Recently, it has been shown that HIV may be transmitted through breast milk [31]. Many of the bacterial agents commonly found in raw milk have been ruled out as a cause of ongoing infection in our study population. However, our efforts did not include investigation of raw milk for rickettsiae, spirochetes, mycoplasmas, or viruses.

Alternatively, an organism present in raw milk may function as a cofactor to another agent or virus. It now appears that EBV is not the direct etiologic agent in the majority of cases of CFS [8, 9]. However, it is possible that one or more viruses that have yet to be identified may be involved in the etiology of this illness. If another virus is determined to be a primary etiologic agent of CFS, perhaps coinfection with an organism found in raw milk increases the risk of expression of disease. Onset of symptoms of CFS postdated the ingestion of raw milk in at least 19 cases. Data were not available for two cases. Lyndonville is a rural community where numerous dairy farmers make raw milk available to friends and neighbors for a fraction of the cost of processed milk, and many families from Lyndonville drink raw milk on a regular basis.

Our finding that risk of CFS increases when other family members are symptomatic may represent person-to-person transmission of an infectious agent, the presence of genetic factors responsible for increased expression of disease, or some environmental factor yet to be defined. These hypotheses require further exploration.

The fact that a history of allergies or asthma is also a risk factor for expression of disease may reflect relative immune dysfunction, which could be associated with decreased host defenses to an infectious agent, an augmented autoimmunologic response, or a connection with genetic predisposition.

Several studies have demonstrated associations between various autoimmune diseases and the presence of particular HLA antigens [32, 33]. Similarly, response of IgE to antigens appears to be linked to increased incidence of certain HLA haplotypes [34]. A limited number of studies have reported a higher-than-expected incidence of the HLA-D7 haplotype among patients with CFS [35]. One study found a weak, nonsignificant, increase in the HLA-B8 haplotype [24], while another study found no significant differences between the frequency distribution of various HLA haplotypes for patients with CFS and the previously published prevalence rates for specific HLA antigens [1]. However, in these latter two studies, the sample size was not sufficient to detect a weak association between CFS and HLA haplotype. Further study of HLA haplotypes among larger populations of patients with CFS may help elucidate the role of allergies and asthma as risk factors for this syndrome.

When interpreting these results, we must keep in mind that a small number of pediatric cases from one rural area were studied. While case and control children came from a defined cohort, our initial response rate from that cohort was only 62%. However, our data support the use of a specific definition for the syndrome. Our cases were carefully evaluated for the presence of other medical or psychiatric disorders that could explain their symptoms and were found to be similar to controls with regard to indicators of family stability and socioeconomic status. Finally, the presence of specific risk factors and the geographic and temporal clustering of cases strongly imply the presence of a specific, chronic illness.

The question remains whether these cases represent a real epidemic of CFS, as it is defined in the adult population, or a separate entity. Several cases of CFS in adults have been diagnosed in the Lyndonville area; these include parents of some of the children in our case population. However, we chose to limit our study to children because of the unique availability of this pediatric cluster and the clearly defined, accessible population represented by the students of the Lyndonville Central School District.

With the exception of the outbreak of CFS in the Lake Tahoe region of Nevada in 1985, most recent reports concerning CFS in the United States represent individual cases referred for evaluation from dispersed geographic areas. Further study will be necessary to determine whether the risk factors identified for this pediatric cluster are generalizable to adults in this community or to children or adults in other geographic locations who have CFS. CFS may have multiple etiologies that result in the same clinical syndrome. Alternatively, an endemic level of disease may exist that creates discrete clusters of epidemic disease, which may be studied more intensely. Epidemiologic studies such as this one may provide direction for further laboratory-based research and may lend additional insight into the pathogenic processes involved in the development and natural history of CFS.

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