CHALLENGING CASE: CHRONIC DISEASE—DEVELOPMENTAL AND BEHAVIORAL IMPLICATIONS

Twelve-Year-Old Girl with Chronic Fatigue, School Absence, and Fluctuating Somatic Symptoms*

CASE

Celia is a 12-year-old white girl with a 5-month history of chronic fatigue associated with a variety of intermittent medical diagnoses, including an initial episode of sinusitis that led to hospitalization for severe pain and intravenous antibiotics, recurrent headaches, migratory arthralgia without specific signs of arthritis, and recurrences of Clostridium difficile enterocolitis. During this period, she continued to gain weight. Extensive laboratory tests for an underlying disorder, including studies for an immunologic deficiency, collagen-vascular disease, and chronic infectious process, failed to reveal a cause except for studies of Epstein-Barr virus (EBV) status. During a 3-week period in the 2nd month of her illness, the IgM antibody to the EBV capsid antigen was in a low-positive range on two occasions. During the same time period, the IgG antibody increased from low-positive to mid-positive. Celia was encouraged to return to school because it seemed to her primary care pediatrician that between illness episodes, she was in good health. Her persistent refusal to attend school was supported by her parents. Before her illness, she was a popular, straight A student who spent 4 to 5 hours doing homework each night. An educational assessment 1 year before the illness demonstrated aptitude tests in the average range without a learning disability. At the onset of the illness, she was running for class president, participating in a gymnastic tournament, and taking dance lessons twice a week. These activities ceased for the next 5 months. Two older siblings and a younger sibling were in good health and doing well in school. Her parents had achieved significant financial success in a family business and frequently expressed high expectations for success among the children. At physical examination, there was an absence of focal findings. Her height and weight were at the 60th percentile. Sexual maturation was Tanner 3. She was cooperative, quiet, and reserved. Verbal responses were short and limited in scope. She said that “I want to go back to school and be with my friends, but I’m not well enough.” She had lost interest in her many extracurricular activities. Her parents refused a referral for psychotherapy.

Dr. Martin T. Stein

Fatigue refers to the perception of exhaustion and weariness. It is a subjective feeling reported by patients with a wide spectrum of acute and chronic conditions. Among children and adolescents, it is common and usually self-limiting. When fatigue is a part of a symptom complex during an acute illness (e.g., streptococcal pharyngitis or acute hepatitis) or the result of sleep deprivation associated with preparation for a school play, the etiology is often apparent. When fatigue, however, is one of several symptoms of longer duration as observed in Celia, the etiology may be elusive to the clinician.

Two decades ago, Dr. Morris Green developed a table that outlined the multiple disorders in which chronic fatigue was a prominent symptom.¹ The differential diagnosis included disorders in every organ system, as well as psychosocial and environmental factors. A complete medical, psychosocial, and environmental history, a physical examination, and limited laboratory tests, supported by the history and physical examination, usually was sufficient to lead to a discovery of the cause of fatigue in an individual patient. The table has been updated to include diseases identified since the initial publication, but the model remains the same (Table 1).

Chronic fatigue syndrome (CFS) is a symptom complex that was described initially in young adults with a debilitating form of fatigue associated with focal, but nonspecific, complaints and constitutional symptoms.²,³ The symptoms were typically abrupt at onset after an acute viral illness and lasting for months to years. A limited number of reports have described a similar condition in adolescent patients.⁴,⁵ The existence of the entity in childhood is controversial.⁶

The patient described in this challenging case developed symptoms at the potentially vulnerable period between childhood and adolescence. The pattern of episodic organic diagnoses, with a background of persistent fatigue, delayed the recognition of CFS. Even when the diagnosis of CFS was established, management was difficult.

Two clinicians have been invited to comment on both the diagnostic and management issues. Dr. Lewis First is Chairman and Professor of Pediatrics at the University of Vermont. As an academic generalist, he is known as a master clinician with the comprehensive perspective of a primary care physician. Dr. Stanford Friedman is Professor of Pediatrics in the Division of Adolescent Medicine at the Albert Einstein College of Medicine/Montefiore Medical Center. He has contributed significantly to the
development of two pediatric specialties—adolescent medicine and developmental-behavioral pediatrics.

**Martin T. Stein, MD**
Professor of Pediatrics
University of California, San Diego
San Diego, California

**REFERENCES**


**Dr. Lewis R. First**

No topic can be more tiring to pediatricians, let alone children and their families, than the topic of fatigue, especially chronic fatigue. Although the peer-reviewed literature continues to argue whether or not “chronic fatigue syndrome” in children should be considered a “real” entity,1,2 the Centers for Disease Control (CDC) have declared a working definition for chronic fatigue syndrome (CFS), which is presented in Table 2.3 Modifications of this working definition for children have been described and continue to be discussed among experts in the field.4 Although not enough data are provided to determine if Celia meets the CDC’s working definition of

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**TABLE 1. Chronic Fatigue in Children and Adolescents**

<table>
<thead>
<tr>
<th>Emotional Factors</th>
<th>Collagen vascular disease</th>
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<tbody>
<tr>
<td>Depression</td>
<td>Lupus erythematosus</td>
</tr>
<tr>
<td>School refusal</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Grief reaction (e.g., hyperventilation)</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Panic attack (e.g., hyperventilation)</td>
<td>Allergic conditions</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>“Tension-fatigue” syndrome</td>
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<tr>
<td>Infectious hepatitis</td>
<td>Sleep disorders</td>
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<tr>
<td>Chronic aggressive hepatitis</td>
<td>Insufficient sleep</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Chronic infections in general</td>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>Hematology/oncology</td>
<td>Cyanotic chronic heart disease</td>
</tr>
<tr>
<td>Anemia</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Sarcoïdosis</td>
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<tr>
<td>Endocrine disorders</td>
<td>Myasthenia gravis</td>
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<td>Cushing’s disease</td>
<td>Chronic renal disease</td>
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<td>Addison’s disease</td>
<td>Chronic pulmonary disease</td>
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<td>Hypothyroidism</td>
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<td>Hyperthyroidism</td>
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<td>Primary hyperaldosteronism</td>
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**TABLE 2. The Working Case Definition of Chronic Fatigue Syndrome**

Pt meets CDC criteria if:

1. Both major criteria are met
2. 8 minor criteria or 6 minor and 2 physical criteria

**Major criteria**

1. Persistent or relapsing fatigue severe enough to decrease activity by at least 50% for at least 6 months
2. Exclusion of other systemic diseases (including psychiatric illness)

**Physical finding criteria**

1. Low-grade fevers (99.7–101.5°F orally)
2. Nonexudative pharyngitis
3. Tender or palpable cervical or axillary lymph nodes (<2 cm diameter)

**Minor criteria**

1. Fatigue that is less than 50% debilitating for >6 mo
2. Generalized headaches (new but chronic)
3. History of painful lymph nodes
4. History of low-grade fevers
5. Unexplained muscle weakness
6. Myalgias
7. Migratory arthralgias
8. Sleep disturbance (hypersomnia or insomnia)
9. Acute or subacute onset
10. Neuropsychiatric symptoms (including photophobia, forgetfulness, confusion, difficulty concentrating, reactive depression)

CFS, from the information provided it certainly remains prominent in our differential diagnosis.

Although Celia has clearly experienced an acute episode of an Epstein-Barr virus (EBV) infection during the course of her illness, it is difficult to attribute her 5 months of fatigue to this virus. In fact, EBV does not appear to be a specific causal entity for CFS, inasmuch as 90% of adults will subsequently demonstrate a positive IgG to EBV (like Celia), but most will never complain of chronic fatigue. Seeing EBV in the case description also raises the possibility that it, as well as many other conditions besides CFS, could contribute to a child feeling tired. In evaluating children and adolescents with chronic fatigue, I have witnessed common diagnoses such as anemia, pregnancy, eating disorders and drug use, as well as less common diagnoses, such as collagen vascular, endocrinologic, metabolic, oncologic, and neurologic diseases. In addition, primary depression, anxiety, school phobia, and delayed sleep phase disorders all can manifest as, or worsen, fatigue in children. In fact, one arrives at the diagnosis of CFS for Celia only by excluding a broad differential such as that noted above.

It is interesting to note that there are a number of studies in the literature seeking a single infectious entity for CFS, but none have been successful in doing this. Likewise, a variety of immunologic studies have been performed, none of which provides a characteristic immunodeficiency profile for these children. It is also important to note that the psychiatric profile of children with chronic fatigue is different from those who present with classic primary depression or anxiety. The chronic fatigue child is usually frustrated with the fatigue and wants to talk with you about it, whereas the primarily depressed child is quiet and lets her parents do the talking. Depression or anxiety can certainly result from experiencing months of fatigue, which may be Celia’s case. Sleep studies also differ in these children, in that children who demonstrate chronic fatigue seem to have difficulty in the non-rapid eye movement phases of sleep, whereas those who have primary mood disorders, such as depression, will have difficulties within the rapid eye movement phases of sleep.

One notable subset of fatigued patients that has recently gained attention have been those children who are predisposed to neurally mediated hypotension, such that they will have abnormal tilt table tests when challenged. This subset of fatigued adults and adolescents has been observed to benefit from treatment with mineralocorticoids and beta-blockers. Certainly in a child such as Celia, it might be useful at least to see if she fits into that category provided that pharmacologic treatment is available.

Celia and her parents do demonstrate the characteristic profile of families who present with concerns about CFS. These children are often high achievers in families that are striving for success. There is no question that once a child like Celia has missed a significant amount of time away from school, the thought of needing to make up so much missed work and extracurricular activities makes recovery even more difficult. This is an important factor for child health care providers who must recognize the signs of fatigue setting in so as to activate an appropriate therapeutic plan before anxiety or depression make things worse.

We have found success with the fatigued children we see by telling them that the fatigue is a real symptom but that “you need to control the fatigue rather than have the fatigue control you.” If the child or adolescent does wish to control the fatigue, they are more apt to be willing to participate in some form of counseling that may include cognitive behavioral therapy, psychotherapy, or simple relaxation techniques to reduce anxiety and stress. Our recovery program also usually includes some form of physical therapy or exercise and attention to adequate nutrition. The child who participates in a weekly or bi-weekly counseling program centering around gaining control over the activities that she or he would like to do is most likely to resume normal activities more quickly than those who will not. In addition, the hiring of a tutor and/or having the child attend some, if not all, classes during the day are other ways to ensure a quicker recovery.

Fortunately, the epidemiologic data that exists regarding prognosis in children and adolescents with CFS is more optimistic than that in the adult literature. Children who receive some form of counseling and gain control over how they are dealing with their fatigue are more apt to go on and lead active lives as older adolescents and young adults. In fact, children like Celia and her parents need to know that CFS in children is not a disease of severe morbidity or mortality. They need to understand that the fatigue is real just like the sensation of pain is real, but that the good news is that there is no life-threatening cause that requires significant surgical or pharmacologic attention. Although parents will seek pharmacologic treatment, there is no study that suggests that pharmacology by itself (without counseling) is successful in alleviating the chronic fatigue such as that described in the case above (unless neurally mediated hypotension is determined to be the cause of Celia’s symptoms).

It is equally important that the pediatrician continue to speak with and see the child on a monthly basis, assess the status of the treatment plan as suggested above, and validate the reality of the fatigue as well as improvements or worsening during the previous month.

LEWIS R. FIRST, MD
Professor and Chairman,
Department of Pediatrics, College of Medicine
University of Vermont
Burlington, Vermont

REFERENCES
4. Feder HM, Dworin PH, Orkin C: Outcome of 48 pediatric patients with...

Dr. Stanford B. Friedman

Several points need to be made before this brief discussion of the psychological issues pertinent in this 12-year-old girl with chronic fatigue. First, the recent medical history of Celia is consistent with the primary manifestation of chronic fatigue syndrome (CFS), namely, severe fatigue of more than 6 months duration limiting activity to less than 50% of premorbid function.1 Second, the laboratory data are suggestive, but not diagnostic, of active Epstein-Barr virus (EBV) infection. Third, the link between EBV infection and the symptoms of CFS is tenuous, at best. Lastly, in cases such as this, there is an understandable temptation to intensively hunt for a single (physical) cause for the multiple symptoms and complaints.

However, this case is best understood using a biopsychosocial model of etiology,2 focusing on the interaction of physical and psychosocial factors, and avoiding an “either-or” approach to the etiology of this girl’s symptoms. Rather, the etiology of Celia’s medical problems and symptoms may be viewed as multiple biological and psychosocial factors interacting over time, and this concept should be communicated to the family.

How, with this approach, might one make sense of this girl’s medical history? I think we can assume as factual her initial diagnosis of acute sinusitis and that the diagnosis was confirmed by appropriate radiographs and laboratory studies. Although the symptoms associated with this illness, and later medical difficulties, were apparently not severe enough to result in weight loss, they nevertheless may have triggered persistent fatigue and withdrawal from her usual activities, including school and numerous extracurricular activities. One explanation for this sequence of events is that her symptoms secondary to physical illness became the model for later symptomatology, suggesting a process similar to a conversion reaction.3 A potential vulnerability to this process is that girls at Celia’s pubertal stage (Tanner 3) are particularly prone to develop, usually self-limited, conversion symptoms. This is because of the psychological issues associated with pubertal development.

In our own experience,4,5 in evaluating over 50 adolescents with the referring diagnosis of CFS, we have been impressed with the importance of family dynamics in understanding the persistence of symptoms beyond an initial illness. In many of the families, the adolescent appears to be overprotected, with difficulty in separating from parents. Yet, parents often have high expectations of their teenager, particularly in the area of academic performance. This parenting style may be associated with the adolescent “overachieving” in school, relative to his or her estimated ability. A particularly difficult time may occur during the beginning months of junior or senior high school, when there is an increase in academic demands and a decrease in individualized attention from teachers. In our study population, there was a high incidence of marital discord, which perhaps accounted in part for intense parental attention to their child’s productivity.

These family dynamics have led us to conclude that school frequently is increasingly stressful to these adolescents, resulting in a strong, though characteristically unconscious, inclination to avoid attending school; avoidance of school and remaining at home thus may be considered an important “secondary gain” to the patient.

With Celia, it is important to focus on her straight A average, despite tests demonstrating “average range” of academic aptitude. She is described as spending 4 to 5 hours each night on homework, which despite a general belief that children and adolescents spend many hours doing homework, is excessive. One can speculate that Celia may well have been attempting to continue to meet her parents’ “high expectations,” which became increasingly difficult as she left the elementary school environment. Her refusal to attend school was supported by her parents, which may have reflected their wish to remain close to their “sick child,” as well as the realization that their child’s academic performance might have the best chance of remaining “straight A” with home tutoring.

Celia’s withdrawal from social and extracurricular activities is of concern, because, even in the presence of fatigue, adolescents diagnosed with CFS typically maintain their participation in such activities. Many studies, most involving adult patients, have noted the similarities of symptoms of patients with depression and those diagnosed with CFS. Indeed, the question has been raised whether CFS is a manifestation of depression, and the overlap of symptoms has been noted in the pediatric literature.6–8 Further evidence to support the diagnosis of depression should be sought, such as a family history of depression.

There also should be further exploration of the family, with a focus on the parental expectations of Celia and their interactions with her and her siblings. The fact that the other children are doing well in school may actually add to the pressure put on Celia, although the lack of identified psychological problems in them probably reflects some basic strengths within this family. However, as our experience has suggested marital discord in many families with an adolescent diagnosed with CFS, it is important also to explore the marital relationship of Celia’s parents.

Referral for psychotherapy seems premature. My approach to management would initially be twofold: First, it is critical to have Celia return to school as soon as possible. This may entail attendance only a few hours per day at first, ideally after a conference at Celia’s school, involving school personnel, Celia and her parents, and the pediatrician. The decisions regarding school attendance should be made by the pediatrician and/or the school nurse, not the parents.
The second component of management, in my opinion, would be for the pediatrician to have several sessions with Celia and her parents. The goals would be to obtain further understanding of this family, and, if appropriate, to modify the parents' academic expectations of Celia. Their expectations need to be consistent with her innate abilities and the priorities given her other activities (e.g., social, extracurricular activities). Further attention also should be given to her depressive symptomatology, and should such symptoms continue to dominate her clinical picture, then referral should be recommended. After the family sessions, referral to a psychotherapist will now be more accepted both by Celia and her parents.

**REFERENCES**


**TABLE 3.** Chronic Fatigue in an Adolescent: Historical and Diagnostic Clues

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Possible Diagnosis</th>
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<tbody>
<tr>
<td>Sexually active; delayed menstruation</td>
<td>Pregnancy</td>
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<tr>
<td>Desire to lose excessive amount of weight; excessive exercise; voluntary vomiting or laxative use; fear of fatness; persistent concern with body shape</td>
<td>Eating disorder</td>
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<td>History of drug use; change in behavior; lack of motivation or interest in activities previously enjoyed; decreased academic achievement</td>
<td>Substance abuse</td>
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<tr>
<td>Feeling of sadness; loss of pleasure; apathy; agitation; sleep disturbance; crying; decreased concentration; family history of depression</td>
<td>Major depressive disorder or sadness problem</td>
</tr>
<tr>
<td>School refusal; social withdrawal; fear; shortness of breath; palpitations; dizziness; separation problems; nervousness and worry; avoidance behavior; family history of anxiety</td>
<td>Generalized anxiety disorder or anxiety problem</td>
</tr>
<tr>
<td>Staying home from school or sent home from school for physical symptoms of emotional origin</td>
<td>School avoidance</td>
</tr>
<tr>
<td>Tendency to stay up late, sleep in, and/or take late afternoon nap; difficulty getting up in morning and going to school; sleeping into late afternoon on weekends (catch-up sleep)</td>
<td>Delayed sleep phase syndrome</td>
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<tr>
<td>Chronic fatigue associated with high achievement goals in family and child</td>
<td>Chronic fatigue syndrome</td>
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<tr>
<td>High academic expectations</td>
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<tr>
<td>Wants to talk about fatigue</td>
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<tr>
<td>Wants to continue regular activities</td>
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<tr>
<td>Overprotective parent</td>
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<td>Difficulty with separations</td>
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<td>Marital discord</td>
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Dr. Martin T. Stein

Most “new” diseases only appear new as a result of an altered definition or set of criteria, more sophisticated diagnostic tests, or a refined recognition of a rare disorder. Attention deficit/hyperactivity disorder, hemolytic-uremic syndrome, and pervasive developmental delay, respectively, are examples of this phenomenon. The recognition of chronic fatigue syndrome (CFS) is also not a recent discovery. Chronic fatigue in a patient without a clearly defined “organic” etiology was apparent to nineteenth century clinicians under the name of “neurasthenia.” Characteristically seen in young women, neurasthenia was associated in some patients with a diagnosis of hysteria, neurosis, and depression. Neither the etiology nor the clinical course were clearly defined.

The late twentieth century “discovery” of CFS evolved out of an observation of young adults who experienced persistent fatigue after infectious mononucleosis. Subsequently, many other patients without clinical or serologic evidence of an Epstein-Barr virus (EBV) infection were found to have similar postviral symptoms. The criteria for CFS was developed out of the need to correctly diagnose, study, and treat patients with long-standing fatigue associated with other symptoms, with or without evidence of a previous viral infection. Currently, most adolescents and young adults with CFS do not demonstrate immunologic evidence of an infectious process. Celia’s EBV antibody pattern is consistent with an EBV infection, but as Dr. First points out, it is difficult to connect serologic evidence with symptoms of CFS in an individual patient.

Both commentaries mentioned a wide variety of conditions that may be found in an adolescent with chronic fatigue. They were among the list of possibilities outlined in Table 1. In addition, both Dr. First
Dr. Friedman recorded clinically useful clues to alternative diagnoses that might be found in the course of a medical history (Table 3).

Dr. Friedman observed that a continuous search for a physical cause in a patient like Celia may not have a therapeutic benefit once an appropriate medical evaluation has been completed, and a physical cause has not been found. Alternatively, he recommends a focus on the interactions between physical and psychosocial factors as a way to frame the troubling symptoms in discussions with the parents and the patient. The biopsychosocial model of disease, as developed and elaborated by George Engle, is an effective way to conceptualize a disorder like CFS, as well as a way to help patients understand mind-body connections. For some families, this form of cognitive therapy may act as an entry point to the acceptance of certain therapeutic strategies, such as progressive relaxation, mental imaging, and physical therapy, including massage and exercise programs. For other patients, an acceptance of physical and psychological interactions may help them to carry out the recommendation, in Dr. First’s potentially powerful words, “you need to control the fatigue rather than have the fatigue control you.” A modification of a method to control pain in children with recurrent abdominal pain, by the imaginary use of pain control knobs on a spaceship as described by Zeltzer and colleagues in a previous Challenging Case in this Journal, may be an effective method to gain control of chronic fatigue.

CFS can be an emotionally overwhelming experience for both the patient and family. Similar to most chronic disorders, allowing the youth and parents an opportunity to express their feelings, frustrations, and hopes in a supportive clinical environment is usually therapeutic. Once the diagnosis is established, the urge “to do another test” in the quest to discover a physical cause should be suppressed unless new symptoms or new information surface that suggest an alternative diagnosis. The astute clinician will remain open to a new hypothesis (psychological or physical) but, simultaneously, help the family avoid unwarranted expense and doctor-shopping.

An active and continuous search for strengths in the patient and the family may provide clues to a helpful intervention. The engagement of other relatives, clergy, and community organizations (e.g., the YMCA for exercise and socialization, or a community volunteer project) may alleviate some stress and offer a new direction for the adolescent. Finally, regularly scheduled office visits to monitor symptoms, coordinate care, and build a therapeutic relationship between the clinician, patient, and parents need to be ongoing.

REFERENCES
Twelve-Year-Old Girl with Chronic Fatigue, School Absence, and Fluctuating Somatic Symptoms
Martin T. Stein, Lewis R. First and Stanford B. Friedman
*Pediatrics* 2001;107;953

<table>
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