Issues in Estimating Rates of Pediatric Chronic Fatigue Syndrome and Myalgic Encephalomyelitis in a Community-Based Sample

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Abstract

Background: There is a need to examine the prevalence of pediatric chronic fatigue syndrome (CFS) and Myalgic Encephalomyelitis (ME) in the general community, as well as the relative frequency of CFS and ME among various groups (e.g., different age groups, genders, racial/ethnic groups, and socioeconomic strata) and to compare these individuals with community controls.

Objectives: In the present study, we describe an ongoing NIH-funded study which will answer basic epidemiologic pediatric issues for pediatric CFS and ME.

Materials and Methods: We used a multiple-stage design, beginning with a brief screening for CFS- and ME-like symptomatology, followed by a more rigorous medical and psychiatric diagnostic evaluation.

Results: We provide two case studies showing the types of data we are collecting, and how the data are being used to inform diagnostic decisions.

Conclusions: Our methods will allow us to determine the prevalence of pediatric CFS and ME status in the general community.

Keywords: Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, Epidemiology, Case Definition

1. Background

Chronic fatigue syndrome (CFS) and Myalgic Encephalomyelitis (ME) cause significant impairment to children's and adolescents' lives, including physical functioning, school attendance and performance, and extracurricular activities (1). Katz et al. (2) reported that six months following acute infectious mononucleosis, 13% of adolescents met criteria for CFS. Krilov et al. (3) found that only 14% of adolescents with CFS attended school regularly after onset. Dowsett and Colby (4) found CFS to be the most common cause of prolonged medical leave from school among adolescents. In a 25-year follow up of a sample of pediatric patients with CFS and ME, Brown et al. (5) found that even those patients that had improved still showed significantly more impairment on 23 of the 25 outcome variables evaluated compared to a healthy control group.

Epidemiology summarizes information about the distribution of illness and allows investigators to make inferences about risk and causal factors (6). In the U.S., the Centers for Disease Control (CDC) conducted a surveillance study (7) and estimated that among adolescents aged 12 - 17;

2.7 per 100,000 had CFS, indicating that CFS was a relatively rare disorder among youth. A major limitation of the Gunn et al. (7) study and a comparable study in Australia (8) was that the patients were identified through physician referral; therefore, members of the community that do not or cannot access medical care were not included.

The CDC conducted another study involving referrals from school nurses from junior and senior high schools in Wichita, Kansas, and Reno, Nevada and a prevalence of 24.0 per 100,000 was calculated for the 12 to 17 year old age group (9). As in other medical referral studies, the gatekeeper methodology, as well as reliance on previous diagnoses by physicians (rather than current evaluations), limited the validity of these findings. Another CDC study included within the Dobbins et al. (9) report involved a community-based investigation conducted in San Francisco, California. This study employed random digit dialing to households as a means of identifying children and adolescents with CFS-like illness. In adolescents aged 12 - 17, 116.4 per 100,000 were diagnosed with CFS-like conditions, although these self-reports were not confirmed with medical assessments. Another CDC prevalence study by Jones et al. (10) made use of a random digit dialing survey of the

residents of Wichita, Kansas. The prevalence of CFS-like illness was 338 per 100,000, but this study also did not include a medical evaluation of the pediatric sample. In the Netherlands, Nijhof et al. (11) reported a mid-range prevalence rate of 111 patients with CFS per 100,000 in a survey of general practitioners, but that study only had a 41% participation rate among the physicians. A more recent study in Great Britain by Collin et al. (12) found a 1.9% CFS prevalence rate among 16-year-olds, but data were based on self-reports without a medical examination.

One problem with population based efforts (13) is that the small number of identified patients with CFS resulted in very wide confidence intervals around the prevalence estimates. For example, in the Rimes et al. (13) study of British general practitioners, the point prevalence of pediatric CFS was 0.5%, but the 95% confidence interval around this ranged from 0.01 to 0.9, which would result in estimates of anywhere between 10 and 900 per 100,000. Thus, the true prevalence rate is unclear. Also, physician samples tend to be biased, generally under-estimating the true prevalence rate.

Children and adolescents with CFS and ME may be misdiagnosed or undiagnosed, have poor access to healthcare, or have a physician who discounts their symptoms (14). In addition, characteristics from adult CFS and ME studies might not apply to youth, as children may experience different symptoms than adults (15); symptoms such as rashes, abdominal pain, and orthostatic intolerance symptoms (16) may be frequently present in pediatric CFS and ME but are not as common in adults. Basic sociodemographic characteristics of pediatric CFS and ME in the general population have thus not been reliably identified (17).

In one pilot community-based epidemiological study of adult CFS (18), Jordan et al. (19) were able to collect data using a pediatric screening questionnaire administered to a sample of adult respondents. Parents reported that 4.4% of children experienced fatigue, and 2.0% had CFS-like symptoms. Only 2 children were found to have CFS upon medical examination, and the resulting prevalence was 60 per 100,000 or .06% (in contrast to .42% for adults). This study encountered a number of problems including using what was then an adult definition of CFS (20) and considerable time having elapsed between the telephone screen and medical examination. To date, existing studies of CFS and ME in youth have lacked the ability to rigorously estimate the overall prevalence of pediatric CFS or ME.

2. Objectives

Our community-based, NIH-funded study is using a multiple-stage design, beginning with a brief telephone screening for CFS- and ME- like symptomatology, followed by a more rigorous diagnostic evaluation to determine the prevalence of pediatric CFS and ME. This methodology has been previously used in the investigation of other disorders that are thought to be relatively uncommon (21).

The present community-based sample is generated in two stages. In stage 1, we contact households in the Chicago metropolitan area and screen for CFS and ME-like profiles in children and youth. On average, 1.8 children per household are screened. The screening questionnaire thus creates 2 groups: pre-screen positives and pre-screen negatives/controls. The parent/guardian(s) who are interested are asked to bring their child to the Ann and Robert H. Lurie Children's hospital of Chicago (henceforth called Lurie Children's outpatient clinic) for evaluation (stage 2).

Children participating in Stage 2 have a comprehensive physical examination, including a structured medical history assessment, blood work, urine analysis, and a saliva sample taken. In addition, both the parent/legal guardian and the child fill out several questionnaires related to the child's health and activity levels, as well as self-report measures of behavior and psychosocial functioning. Next, a psychiatric interview is completed with the parent/legal guardian and the child separately to determine the child's overall mental health functioning. Finally, the child is asked to wear an actigraph monitor for 24 hours to measure their activity levels.

3. Materials and Methods

During the Stage 1 screen, we ask a parent/legal guardian from each household if there is a youth in the household and ask permission to screen for pediatric CFS- and ME-like illness. The parent/legal guardian respondents are then interviewed regarding the health status of their children and adolescents (ages 5 - 17) in the household, using the Pediatric Screening Questionnaire. This questionnaire consists of three parts. First, there are questions to determine if any of the children or teenagers (ages 5 - 17 years) in the household are experiencing significant fatigue. The second part assesses whether any of the children are experiencing disruption in their school activities or performance due to fatigue or cognitive difficulties. The third part of the questionnaire presents a list of CFS- and ME-related symptoms common in children with CFS and ME proposed by Bell (22) and Jason et al. (23), and symptoms from the current CFS and ME criteria (20, 24, 25). In this article, we present the summarized information from two cases: a child who is screen positive (CFS- and ME-like) and one who is screen negative (healthy).

Children and adolescents who screen positive for either significant fatigue or school/learning/memory problems, and have cardinal CFS and ME symptoms are se-

lected for further evaluation (stage 2). This in-depth screening consists of a semi-structured psychiatric interview administered to the child and separately to the parent/legal guardian during a single in-person assessment session using the K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version) (26). The K-SADS is an appropriate structured interview schedule for children and adolescents, and has good psychometric properties.

Participants enter their responses directly into RED-Cap, a secure, web-based application for building and managing online surveys and databases. The DePaul Symptom Questionnaire (DSQ) is a self-report measure of CFS and ME symptomatology and illness history. This questionnaire provides a standardized method for assessing the dimensions of various case definitions, including the Fukuda et al. (20) CFS criteria, Canadian Clinical criteria (24), ME International Consensus criteria (25), and Institute of Medicine (IOM) criteria (27). We obtain case definition fulfillment based on the child and parent/guardian reports in the DSQ and the parent's responses to the Pediatric Screening Questionnaire. We also obtain parent/guardian and child ratings to all symptoms included in the DSQ, and items that score a 2 on frequency (occurring at least half the time) and 2 on severity (moderate) are highlighted (see Tabulation 5, Appendices 1 and 2).

The caretaker and child also complete the Child Health Questionnaire (28), an instrument that assesses physical and psychosocial well-being, as well as the following scales: The Autonomic Symptom Checklist is based on a validated questionnaire called the Autonomic Symptom Profile (29), and has been validated for CFS. Krupp et al.'s (30) Fatigue Severity Scale is used to measure fatigue. This scale includes 9 items rated on 7-point scales and is sensitive to different aspects and gradations of fatigue severity. The number of days attending school over the past week is recorded, as well as the number of hours each day that the child attended school. Physical activity during both productive and leisure time, as well as inactivity, is assessed for the six months prior to the evaluation using the Modifiable Activity Questionnaire (31). Finally, as a measure of physical activity, participants wear an actigraph for 24 hours (32).

Following the completion of these measures, the children and adolescents undergo a medical history interview and a complete physical examination and laboratory screening (including a complete blood count, blood chemistries, thyroid screen, inflammatory markers, urinalysis and other testing based on risk factors, e.g., pregnancy test, urine drug screen, HIV serology) at Lurie Children's outpatient clinic by one of us (BZK) to rule out other disorders that may cause fatigue (such as anemia, diabetes or hypothyroidism). Blood and saliva samples are stored

for further research.

3.1. Diagnosis

At the end of Stage 2, a team of physicians are responsible for making final diagnoses. Two physicians independently rate each file. The physician raters are unbiased because they do not meet the participants, and are instead only reviewing the information we've collected. We use three different case definitions including the Fukuda et al. (20) criteria with revisions recommended by Reeves et al. (33), the Pediatric Criteria developed by an international study group (23) and recommended by the international association of CFS/ME, and the recently published IOM criteria (27). These three case definitions are described below.

3.2. Fukuda et al. criteria (20)

To be diagnosed using the Fukuda et al. (20) criteria, participants need to experience persistent or relapsing fatigue for a period of six or more months concurrent with at least four of eight somatic symptoms that do not predate the fatigue. These symptoms include: sore throat, lymph node pain, muscle pain, joint pain, post-exertional malaise, headaches of a new or different type, memory and concentration difficulties, and unrefreshing sleep. Participants also need to experience substantial reductions in occupational, educational or personal activities as a result of the illness. Substantial reductions in functioning are being measured by the Child Health Questionnaire (28) subscales and the child's self-reported level of functioning, which is measured on a 7-point scale (1="I am not able to go to school (work) or do anything, and I am bedridden", 7="I can attend school (work) and do all activities without any problems with my energy"). In addition, to meet criteria, the youth must not have any exclusionary medical or psychiatric illnesses, as defined by Reeves et al. (33).

3.3. Pediatric Criteria (23)

This case definition is modeled after the Canadian Clinical case definition (24), and subjects with CFS are divided into severe and moderate categories. To be diagnosed with Severe Pediatric criteria (23), participants need to have unexplained, persistent or relapsing chronic fatigue over the past 3 months that was not the result of ongoing exertion and was not substantially alleviated by rest. Participants also have to experience substantial reduction in previous levels of educational, social and personal activities. Substantial reductions in functioning are measured by the Child Health Questionnaire (28) subscales and the child's self-reported level of functioning. These adolescents need to have the following symptoms: post-exertional malaise, unrefreshing sleep or disturbance of

sleep quantity, pain (myofascial, joint, abdominal and/or head pain), two or more neurocognitive manifestations, and one symptom from two of the following three categories: autonomic manifestations, neuroendocrine manifestations, or immunologic manifestations. Frequency and severity ratings of moderate or severe (a rating of 2 or higher indicating the symptom occurred at least half the time and was of moderate or greater severity) are needed as well. For the Moderate Clinical criteria (34), adolescents need to report five out of the six classic symptoms (fatigue, post-exertional malaise, unrefreshing sleep, pain, neurocognitive manifestations, and symptoms in at least 1 of the 3 following categories: autonomic, neuroendocrine, and immunologic).

3.4. IOM Criteria

The IOM (27) clinical criteria were operationalized by having youth meet the following four criteria: Substantial reductions in functioning was measured by the Child Health Questionnaire (28) subscales and the child's self-reported level of functioning. Next, post-exertional malaise items included: soreness after mild activity, drained/sick after mild activity, minimum exercise makes tired, muscle weakness, dead/heavy feeling after exercise, and mentally tired after the slightest effort. The third area involves sleep dysfunction symptoms, which can include: unrefreshing sleep, problems staying asleep, problems falling asleep, waking up early, and need to nap daily. Finally, youth needed to have either cognitive impairment or orthostatic intolerance. Neurocognitive items included: difficulty paying attention, difficulty expressing thoughts, problems remembering, absent-mindedness, only being able to focus on one thing at a time, slowness of thought, difficulty understanding, and difficulty paying attention. Orthostatic intolerance was defined as either dizziness/fainting, shortness of breath, unsteadiness, irregular heartbeat, or chest pain.

4. Results

4.1. Case A: Screen Positive

Case A is a 14-year-old African-American female in the 9th grade. During the initial prescreening questionnaire (Tabulation 1, Appendix 1), her Aunt/legal guardian reported that she experienced constant and severe fatigue for over 6 months, and often fell asleep during class. The child pushes herself to be active and participate in gym class; however, her Aunt specified that she cannot exercise for more than 20 minutes at a time before experiencing body aches. We were also informed that headaches, stomach aches, and joint/muscle pain occur frequently,
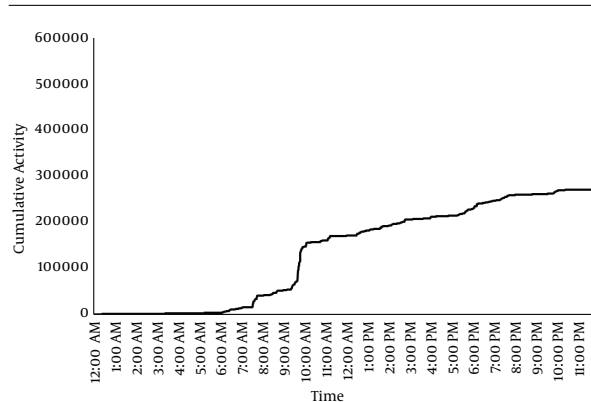

Figure 1. Actigraph Data (24 Hours) of Case A

and that she has moderate to severe neurocognitive difficulties most of the time.

During stage 2, the child received her comprehensive physical examination and psychiatric assessment (Tabulation 2, Appendix 1). The K-SADS interview with the child and her Aunt revealed that the child experienced multiple traumas (e.g., mother passing away, abuse/neglect by father), yet she did not meet criteria for Post-Traumatic Stress Disorder. The child did not have any exclusionary conditions to explain her illness.

Results from the health measures are in Tabulation 3, Appendix 1. The Child Health Questionnaire showed that the child reports were consistently below the norms for youth her age, yet were only statistically significantly decreased on the bodily pain subscale. On the other hand, the aunt's responses indicated the child was significantly below the norms for 8 out of 12 subscales. Subscales in which the aunt rated the child to be significantly below the norm are highlighted. The child experienced high levels of autonomic symptoms on the Autonomic Symptom Checklist, even higher than the average adolescent with ME or CFS. Further, her score of 51 on the Fatigue Severity Scale indicating extremely high levels of fatigue (where scores of greater than 36 indicate severe fatigue).

Tabulation 4, Appendix 1 provides information on activity and functioning. Though she is able to attend school full-time and participate in some activities, the child reported that she has no energy left for anything else. In addition, the objective actigraphy data indicates the child is doing far less activity throughout the day than the healthy control participant (Case B; see next section) (Figure 1).

Tabulation 5, Appendix 1 displays the child's and Aunt's responses to the DePaul Symptom Questionnaire (DSQ). Symptoms that are highlighted were reported to occur at least half the time and of moderate severity by one or both

respondents. The most frequent and severe symptoms were within the post-exertional malaise, pain, and neurocognitive symptom domains. Based on the child's symptomatology identified in the DSQ, she fulfilled diagnostic criteria for the Fukuda et al. (20) and IOM (27) case definitions, as well as Severe Pediatric criteria (23). In Tabulation 6, Appendix 1, the specific dimensions that the child met for each criteria are highlighted. There were few discrepancies in symptomatology between the child and her aunt except within the autonomic symptom domain, in which the child indicated she experienced shortness of breath at a frequency of 2 (i.e., about half the time) and a severity of 2 (i.e., medium problem). Thus, according to the aunt's report, she met the Moderate Pediatric criteria rather than Severe Pediatric criteria.

4.2. Case B: Screen Negative

Case B is a 13-year-old African American male in 7th grade who was reported to be quite active during the initial prescreening questionnaire (Tabulation 1, Appendix 2). His mother told us that he often works out at the gym where he uses exercise machines. Additionally, we were informed that the child did not experience any symptoms assessed by the Pediatric Screening Questionnaire.

The physical exam and K-SADS indicated the child's mental and physical health were unremarkable (Tabulation 2, Appendix 2). During the K-SADS interview in Stage 2, the mother reported that the child excels academically and socially. He also enjoys playing football, soccer, and video games. His scores were within normal ranges on the Child Health Questionnaire, Autonomic Symptom Checklist, and Fatigue Severity Scale (Tabulation 3, Appendix 2). Further, he is able to attend school full time and reported that he is not limited in functioning as a result of symptoms (Tabulation 4, Appendix 2). Actigraphy data mirrored the reports of the child's activity levels and shows that he is active throughout the day (Tabulation 4, Appendix 2) (Figure 2).

The parent and child responses to the DSQ (Tabulation 5, Appendix 2) show the child experiences an upset stomach/stomach pain, headaches, and shortness of breath at a frequency of 1 (i.e., hardly ever). However, both the child and his mother rated these symptoms at a severity of 0 (i.e., no problem). "Allergies" was the only symptom the child rated at a frequency of 2 (e.g., half the time), while his mother reported the frequency of his allergies as 1 (i.e., hardly ever). Again, both respondents reported that the child's allergies were a severity of 0 (e.g., no problem). The few symptoms that were endorsed by the parent and/or child followed this pattern, indicating the child's symptoms occur infrequently and are not problematic. As evident in Tabulation 6, Appendix 2, the child did not meet the
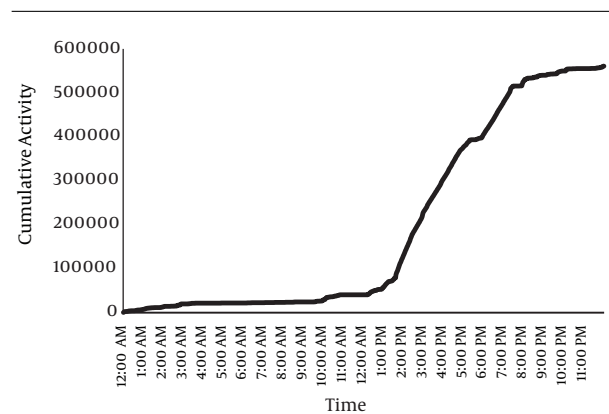

Figure 2. Actigraph Data (24 Hours) of Case B

Fukuda criteria (20), the criteria of the IOM (27), or the Pediatric criteria (23). Overall, the child is a high-functioning and healthy 13-year-old.

5. Discussion

Data from a community-based epidemiologic study of pediatric CFS are needed to better understand the prevalence of this illness as well as the sociodemographic characteristics of pediatric patients. At present, data derive mostly from treatment centers, and it is quite likely that findings from community-based settings will be different. The current article describes our approach to collecting data, as well as the instruments we are using to make diagnostic decisions. Our hope is that the methods and measures we are using are instructive to the larger field for assessing youth with CFS.

As we collect and analyze data in this epidemiologic trial, we continue to face challenges in attempting to implement the various case definitions that have been proposed. For example, we have assessed youth who seem to be active in sports, and due to this experience a number of symptoms that fit criteria, such as that of the IOM, which at present also allow no exclusionary illnesses. In a sense, case definitions need to take into account the many reasons that youth can become symptomatic, and whereas some symptoms are experienced by most youth, most of them are not sick or disabled.

Ultimately, both researchers and clinicians will need to decide which case definition to use for clinical and study purposes. There are now multiple case definitions, and there is need for a consensus definition for clinical as well as research purposes. Aside from the two detailed cases studies presented, we have also examined youth who present with a wide range of reasons for their impairment,

and it is possible that different case definitions will select different youth. For example, some youth fulfilled the IOM (27) case definition, but also had exclusionary conditions so did not meet the Fukuda et al. (20) or Canadian (24) criteria. In addition, as we screen youth, a number met criteria for one or more case definitions, but some seemed too active to be given a diagnosis of CFS or ME (e.g., one child played soccer every day which causes joint/muscle pain, while another child's symptoms were due to the fact that she plays water polo 3 hours daily). The child who played soccer came home exhausted and appeared to have major cognitive problems in the evening due to exhaustion, and also evidenced significant evening post-exertional malaise. He then had to stay up late to complete his homework and, as a result, did not get enough sleep and evidenced sleep difficulties. While this child might have met one of the case definitions, it was apparent that he was a healthy child who was over doing his level of sports involvement and did have CFS or ME.

Other children met the Fukuda et al. (20) less effective than the criteria but did not endorse post-exertional malaise (e.g., one child felt better after exercise). A variety of other reasons seemed to well describe other youth's symptoms, including: health (e.g., medication for depression caused one child headaches and was related to his inactivity/unwillingness to be involved in activities), long day/busy schedule (some children were very busy or had long days, or were involved in a lot of activities during school and after), poor sleep hygiene (e.g., some children had difficulty regulating their sleep schedule, and this is leading to fatigue or other symptoms), mild symptomatology (e.g., some children's symptoms were mostly mild and/or occur infrequently), lack of parental concern (e.g., some parents felt that their children's fatigue was normal for the amount of activity they are doing), weight (e.g., the child's BMI is 31.9, the 96th percentile for age, indicating obesity), poor diet (e.g., one child had fatigue due to not eating properly), and inactivity (e.g., one child was inactive by choice, preferred to play video games, and was not interested in physical activity). According to the IOM (27) definition, such issues are classified as co-morbidities, whereas for the Fukuda et al. (20) and Carruthers et al. (24) criteria, they would be more likely to be considered exclusionary. More work needs to be conducted comparing the different case definitions. There are few studies in the pediatric literature that have made these types of comparisons. However, in one study, Jason et al. (6) compared two case definitions in a group of 33 children and adolescents thought to have pediatric CFS and 21 without. Findings suggested the Fukuda et al. (20) criteria are less effective than the Pediatric criteria in correctly diagnosing pediatric CFS.

Another key issue is whether youth need to have 3 or 6 months of symptoms. The Canadian criteria suggest that children with symptoms lasting more than three months can be diagnosed with the illness (24). In support of this, Fowler et al. (35) did not find differences between 8 - 17 year olds with 3 versus 6 months of chronic fatigue. We think there is merit to indicating which children have the illness for 3 or 6 months.

In summary, our study is currently in progress, and we continue to deal with diagnostic challenges in categorizing youth with CFS or ME. Decisions need to be made about which case definitions to use if we are to have better prevalence data (36). Some youth might meet more general clinical criteria, such as that proposed by the IOM (27), whereas other youth might meet more restrictive criteria, which excludes those with other illnesses or conditions. Hopefully, our study will advance the field as we improve efforts to identify youth with CFS and ME in the general population.

Supplements

Supplementary material(s) is available at below link: http://avicennajnpp.com/?page=download&file_id=58015

Footnotes

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