ORIGINAL RESEARCH

A Pediatric Case Definition for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

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SUMMARY. For a diagnosis of chronic fatigue syndrome (CFS), most researchers use criteria that were developed by Fukuda et al. (1994), with modifications suggested by Reeves et al. (2003). However, this case definition was established for adults rather than children. A Canadian Case Definition (ME/CFS; Myalgic Encephalomyelitis/CFS) has recently been developed, with more specific inclusion criteria (Carruthers et al., 2003). Again, the primary aim of this case definition is to diagnose adult CFS. A significant problem in the literature is the lack of both a pediatric definition of ME/CFS and a reliable instrument to assess it. These deficiencies can lead to criterion variance problems resulting in studies labeling children with a wide variety of symptoms as having ME/CFS. Subsequently, comparisons between articles become more difficult, decreasing the possibility of conducting a meta-analysis. This article presents recommendations developed by the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group for a ME/CFS pediatric case definition. It is hoped that this pediatric case definition will lead to more appropriate identification of children and adolescents with ME/CFS. doi:10.1300/J092v13n02_01

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A PEDIATRIC CASE DEFINITION FOR ME/CFS

ME/CFS[1] is a persistent disabling disorder that is characterized by severe, overwhelming fatigue along with a number of other symptoms (Fukuda et al., 1994; Joyce et al., 1997). The origins and boundaries of the syndrome are still unclear (Jason et al., 2003; Komaroff & Buchwald, 1998). Illnesses that are consistent with ME/CFS definitely occur in adolescents and children (Breau et al., 1999; Jordan et al., 1997; Marshal, 1999; Wright & Beverly, 1998). However, the case definition was developed for adults (Fukuda et al., 1994) and may not be appropriate for use with children and adolescents. Currently, no ME/CFS case definition exists for children and adolescents. The lack of application of a consistent pediatric definition of ME/CFS and the lack of a reliable instrument to assess it (Jordan, Kolak, & Jason, 1997) might lead to studies which inaccurately label children with a wide variety of symptoms as having ME/CFS as well as possibly missing children who do have it.

In The Netherlands, a case definition was proposed in order to increase coherence in child ME/CFS (De Jong et al., 1997). According to this case definition, as with adult ME/CFS, no somatic or psychiatric condition should be able to explain the symptom pattern presented by the child/adolescent. In addition, there should be a distinct onset of the symptom pattern. In contrast to adult ME/CFS, where patients need to present a significant decrease in their physical functioning, children or adolescents are not able to compare premorbid or morbid physical functioning due to their lack of reference and due to their flexibility. Both are characteristics of the process of identify formation. Therefore, the assessment of leisure, social and educational activities are indispensable to being able to detect a decrease in their functionality.

There has been controversy over whether the assignment of a diagnosis of ME/CFS in children may lead to omissions or errors in the appropriate diagnostic evaluations of fatigued children (Harris & Taitz, 1989; Jones, 1997; Lask, & Dillon, 1990). Some believe that the diagnosis of ME/CFS in this age group should be considered only an interim diagnosis but not a definitive disease (Jones, 1997). Another concern about applying a ME/CFS diagnosis to a young child is the potential damage inflicted on a child by conferring a diagnosis that is open-ended. However, this possibility must be weighed against the advantages of naming the illness that may alleviate anxiety and uncertainty in both the child and family as well as having a clarifying impact on the school environment. These arguments do not address the reality that many clinicians are, indeed, faced with children with unexplained fatigue and other symptoms for which exhaustive medical and psychosocial evaluations have not revealed an acceptable explanation. In these children, no diagnosis may be made, often leading to the inappropriate assumption of malingering or diagnosis of psychiatric disease. These incorrect diagnoses may be more damaging than the diagnostic label of ME/CFS. It seems clear that for any child with a chronic illness, an ongoing diagnostic evaluation that involves looking for either primary causes of fatigue and other symptoms or complications of underlying process, is essential (Carter & Marshall, 1995). There is now enough clinical experience and research findings to put forward a case definition for children and adolescents.

One of the main goals of classifying any disease or illness is to group together patients who have an illness that may have many manifestations, but a common underlying pathophysiological pathway (Hartz et al., 1998). The benefit of classifying patients into diagnostic categories is that it facilitates communication among clinicians/researchers, selec-

tion of appropriate treatment methods, and prediction of response to treatment. Past experience has shown that even in cases where the underlying pathophysiological pathway has not been identified, research on the etiology and treatment of the illness has been facilitated by simply classifying these illnesses as syndromes of signs and symptoms (e.g., systemic lupus erythematosus or tuberculosis). One of the greatest sources of diagnostic unreliability is criterion variance, differences in the formal inclusion and exclusion criteria used by clinicians to classify patients into diagnostic categories (Spitzer et al., 1975). The addition of specific criteria and standardized measures with scoring guidelines would likely improve the reliability of diagnostic decisions by providing clinicians with objective standards to follow when assessing the various features of this syndrome (King & Jason, 2005). Collecting very careful clinical, family, and developmental histories is also important to ensure a differential diagnosis.

In order to address these important classification and diagnostic issues, this paper proposes a case definition for diagnosing ME/CFS in children and adolescents. It is hoped that this case definition for children and adolescents with ME/CFS will serve as a developmentally appropriate diagnostic tool for clinicians and researchers. Further, development of a pediatric definition of ME/CFS will allow for the application of consistent and objective criteria, and may serve to stimulate research which will then not only further test the validity of this case definition but also elucidate pathophysiology and improve treatment approaches.

DIAGNOSIS AND PROGNOSIS

It is critical that those conducting studies attempting to diagnose children with ME/CFS carry out a thorough evaluation, including a comprehensive medical and developmental history, physical examination, and laboratory tests to confirm diagnosis. The history should involve both of the parents as well as the child because children are still constructing their identity. Subsequently, they do not have a reference to which they can compare before and after situations.

Arav-Boger and Spirer (1995) describe the usual patient as being previously athletic and ambitious, upper middle-class, and having close relatives with ME/CFS. Similarly, while clinic and community samples have found more female than male adults with ME/CFS (Gunn et al., 1993; Jason et al., 1999), several studies involving children have shown an equal representation of females to males (e.g., Jordan et al., 1998). A

recent study by Van Hoof et al. (in press) shows the same gender representations compared to adults (80% females vs. 20% males) in adolescents. This finding might suggest that hormonal changes in adolescence trigger this difference in gender prevalence. Another recent study by Viner and Hotopf (2004) found that a higher risk of ME/CFS was associated with having a limiting longstanding condition in childhood, female sex, and high social class in childhood. Higher levels of exercise in childhood were associated with lower risk of ME/CFS.

Among adolescents, easy fatigability and disturbed learning and memorization are several of the primary characteristics of this syndrome (Miike et al., 2003). As is often so with adults, the fatigue may be quite severe to the point that "exhaustion" would be a more apt description. Another striking feature of this illness is the individuality of symptom patterns and unpredictability of symptom severity among youngsters with ME/CFS. The unpredictable fluctuation of symptom severity is one of the more stressful features for youth and family alike. Children may have a few good days and then end up in bed. When others see them on "good days," they might become confused or skeptical about the seriousness and debilitating effects of the illness. This can become a serious matter as it can lead to rejection of the diagnosis by school authorities and others and relentless pursuit of psychological explanations even to the point of inappropriately diagnosing Munchausen-by-proxy.

Children may experience different symptoms than adults with ME/CFS (Jordan et al., 1997). Symptoms such as rashes and abdominal pain may be frequently present in pediatric ME/CFS, but may not be as common in adults. Bell (1995b) reported that the three most common complaints, besides fatigue, in children and adolescents with ME/CFS were headaches, sleep disturbance, and cognitive difficulties. As children are still learning effective coping skills, they frequently react upon their complaints by increased irritability (Van Hoof & Maertens, 2002).

The prognosis for a child or adolescent diagnosed with ME/CFS has been considered to be better than with adults with this diagnosis (Arav-Boger & Spirer, 1995; Smith & Carter, 2003). While the condition has not been found to be progressive nor life-threatening (Carter et al., 1995), it is noteworthy that some children continue to experience significant fatigue and disability. It is possible that children who do not show any improvements over time have a more severe form of the illness or differ in other important genetic or biological ways. Bell (1995a) notes that this persistently disabled group tends to have fatigue and other symptoms that are worse from onset and result in severe activity limita-

tion. Recent guidelines for the management of patients with this condition have been published (Baumer, 2005).

DIFFERENTIATE BETWEEN DIAGNOSES

Formal psychological assessment may be useful in determining if a child's symptoms are attributable to factors such as a primary psychiatric disorder, school phobia, or family dysfunction (Jordan et al., 1998). One study (Pelcovitz et al., 1995) that examined psychological factors found that adolescent ME/CFS patients reported higher levels of internalizing symptoms (i.e., fearful, depressed, and overcontrolled behavior) than a comparison group of adolescent cancer patients. Another study (Smith et al., 1991) found that one third of the children and adolescents with ME/CFS met criteria for major depressive disorder as diagnosed by clinical interview. Similarly, Walford et al. (1993) compared three groups: children and adolescents with ME/CFS, cystic fibrosis and healthy controls. It was found that the ME/CFS group had significantly higher depression scores than other groups. Furthermore, significant social and academic impairment was present in the ME/CFS group. Although recurrent, medically unexplained physical symptoms are common in children and adolescents, somatization disorder that meets DSM-IV criteria is rare in this age group. Many of these studies have flaws within them, and they often do not clearly differentiate between pre-illness symptoms and post-illness symptoms, and therefore it is conceivable that higher rates of psychological problems are secondary to having ME/CFS.

In children and adolescents, school phobia or school refusal is another diagnostic category to be considered in differential diagnosis. However, school phobia can generally be distinguished from ME/CFS after a comprehensive evaluation, as once the child with school phobia is allowed to remain home, symptoms typically disappear, and there are usually no complaints on weekends or holidays or during the summer. Inquiring about hobbies/leisure activities is important in distinguishing school phobia (or social phobia) and CFS. The latter will have abandoned their hobbies and leisure activities. Some physicians have suggested that ME/CFS in children and adolescents is a physical manifestation of family dysfunction claiming that ME/CFS symptoms may be utilized by the child for primary or secondary gain, to cope with developmental issues or change, or to deal with family problems. However, Pelcovitz et al. (1995) found no differences between families of adolescents with

ME/CFS and families of adolescents with cancer and control families on family functioning measures and marital problems indices.

It should be noted that for children ill with this syndrome, after 6 months or so, friends often stop calling or visiting the youngster. If there are no peers, cousins or extended family or anyone close in age, the isolation can be devastating. Other changes and losses include no longer being able to participate in normal activities with peers, loss of self-confidence and self esteem if teachers and physicians are overly skeptical. School attendance then may not only be physically taxing but psychologically stressful as well.

PREVALENCE OF PEDIATRIC ME/CFS

Much of the epidemiological research to date has focused on adults, with minimal focus on children and adolescents. A study that ME/CFS-like illness, characterized by prolonged fatigue (= 1 month) accompanied by fever, decreased endurance with exertion, and pain symptoms, occurs at a rate of 4.4% among adolescents seen in primary care settings indicates that this syndrome is an important medical concern among youth (Mears et al., 2004). Whether or not the syndrome occurs as a readily recognizable illness in younger children is still an open question. The main reason to be cautious in this regard is that the diagnosis was based on patient complaints and the self-reported consequences of the illness.

Lloyd and associates (1990) included information regarding children of all ages in their published prevalence estimates from an Australian community population study. Prevalence estimates of 5.5 cases per 100,000 were determined for children ages 0 to 9 and 47.9 cases per 100,000 cases for children and adolescents aged 10 to 19. A major problem with the study that limits the validity of prevalence estimates was the low number of medical practitioners who participated and identified cases in their practices (11 out of 50 doctors participated). This problem may have been due to lack of information about the syndrome or doubts about the validity of ME/CFS. Given that the population in this study was obtained through physician referral, members of the community that do not or cannot access medical care for their symptoms were not included in the study.

The CDC has conducted several studies to estimate the prevalence of pediatric ME/CFS in different geographical areas (Dobbins et al., 1997). A surveillance study was performed in Atlanta, Reno, Grand Rapids,

and Wichita (Gunn et al., 1993). Local physicians identified and referred patients who fulfilled CDC diagnostic criteria for the syndrome. Only 44% of eligible physicians agreed to participate in the study. Based on the Holmes et al. (1988) definition, the authors estimated that among adolescents aged 12-17, 8.7 cases per 100,000 showed chronic fatigue symptomatology and 2.7 per 100,000 had ME/CFS. No inquiries regarding fatigue or ME/CFS symptoms were made regarding children under the age of 12.

Among a second generation of CDC studies was a community-based investigation conducted in San Francisco (Dobbins et al., 1997). This study employed random digit dialing to households as a means of identifying children and adolescents with chronic fatigue and ME/CFS-like illness. Estimates were made for children aged 2-11, indicating that 71.9 per 100,000 suffered symptoms of chronic fatigue, and 0 per 100,000 presented with ME/CFS-like symptoms. In adolescents aged 12-17, 465.7 per 100,000 were found to suffer chronic fatigue symptoms, and 116.4 per 100,000 were diagnosed with ME/CFS-like conditions. Jones et al. (2004) performed a random digit dialing survey of the residents of Wichita, Kansas. Adults identified fatigued adolescents in the household and answered questions relating to the child's health. Selected adolescents were invited to attend a clinic with a parent/guardian. After clinical evaluation they were classified as CFS or another fatigue state as defined in the 1994 CFS definition. The survey contacted 34,018 households with 90,316 residents. Of 8,586 adolescents, 138 had fatigue for more than one month, and most (107 or 78%) had chronic fatigue (more than 6 months) at some point during the 3 year follow up. The baseline weighted prevalence of CFS-like illness was 338 per 100,000. However, because these studies did not include a medical evaluation, the actual number of cases in that population could not be determined, and thus, only "ME/CFS-like" illness could be diagnosed.

The CDC conducted another study involving referrals from school nurses from junior and senior high schools in Wichita, Kansas, and Reno, Nevada. A prevalence of 24.0 per 100,000 ME/CFS was found for the 12 to 17 year old age group (Dobbins et al., 1997). As in other medical referral studies, the gatekeeper methodology, as well as reliance on previous diagnoses by physicians (rather than current evaluations), limited the reliability and generalizability of these findings. In a community-based study that occurred in Wichita, Kansas, Jones et al. (2004) estimated CFS-like pediatric prevalence rates to be 338 per 100,000, but no cases of CFS were found.

In a community epidemiology study in Chicago (Jason et al., 1999), a pediatric screening questionnaire was administered to the adult respondents at the completion of the adult ME/CFS screening questionnaire. Follow-up interviews were conducted with children and adolescents identified through the initial telephone screening process. Following the psychiatric assessment, children and adolescents underwent a complete physical examination with laboratory testing to diagnose the presence of ME/CFS and rule out exclusionary medical conditions (Fukuda et al., 1994). Physician reviews were completed on 34 screened positive cases and 23 screened negative cases. Results of physician review revealed a prevalence of .06%, or 60 cases per 100,000 (Jordan et al., 2006).

In addition, some of the published reports follow widely reported "epidemics" or cluster outbreaks of the syndrome (e.g., Bell et al., 1991). As the syndrome remains to be precisely defined, both in adults and children, such epidemics may be considered unique events at this time, as there is no conclusive evidence that the same illness process is at work in both the cluster outbreaks and isolated cases.

CHANGES FROM THE ADULT DEFINITION

The adult definition (Fukuda et al., 1994) has been used to diagnose pediatric samples. It is critical for future studies examining this disorder in pediatric populations that a consistent definition, which has been adapted from the adult definition to take into account special circumstances of children, be utilized. In addition to facilitating coherent research on this population, a case definition adapted for children will facilitate diagnosis and management by pediatricians and primary care physicians confronted with unexplained, chronic fatigue in children.

The definition presented in Table 1 has elements of the Fukuda et al. (1994) adult case definition, along with of recommendations of Reeves et al. (2003). We have also incorporated the structure of a new clinical case definition for ME/CFS that has been developed in Canada (Carruthers et al., 2003). We believe that requiring certain symptoms does provide more specification of critical symptoms for a case definition. However, we have tried to limit the types of symptoms within each of the Canadian criteria categories to allow investigators to more reliably categorize pediatric patients. We also believe that this case definition does reduce the prominence of the symptom fatigue and more explicitly highlights the importance of symptoms such as dizziness, decreased endurance with symptoms, pain, and flu-like symptoms. Indi-

TABLE 1. Definition of ME/CFS for Children

I. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue over the past 3 months that:
   - A. Is not the result of ongoing exertion
   - B. Is not substantially alleviated by rest
   - C. Results in substantial reduction in previous levels of educational, social and personal activities
   - D. Must persist or reoccur for at least three months

II. The concurrent occurrence of the following classic ME/CFS symptoms, which must have persisted or recurred during the past three months of illness (symptoms may predate the reported onset of fatigue).

   A. Post-exertional malaise and/or post-exertional fatigue.

      With activity (it need not be strenuous and may include walking up a flight of stairs, using a computer, or reading a book), there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 24 hours or longer.

   B. Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance.

      May include prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening), and/or day/night reversal.

   C. Pain (or discomfort) that is often widespread and migratory in nature. At least one symptom from any of the following:

      Myofascial and/or joint pain (Myofascial pain can include deep pain, muscle twitches, or achy and sore muscles. Pain, stiffness, or tenderness may occur in any joint but must be present in more than one joint and lacking edema or other signs of inflammation.)

      Abdominal and/or head pain (May experience eye pain/sensitivity to bright light, stomach pain, nausea, vomiting, or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines.)

   D. Two or more neurocognitive manifestations:

      Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis)
      Difficulty focusing (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli in a classroom, or to focus on reading, computer/work activity, or television programs)
      Difficulty finding the right word
      Frequently forget what wanted to say
      Absent mindedness
      Slowness of thought
      Difficulty recalling information
      Need to focus on one thing at a time
      Trouble expressing thought
      Difficulty comprehending information
      Frequently lose train of thought
      New trouble with math or other educational subjects

E. At least one symptom from two of the following three categories:

1. Autonomic manifestations: Neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on the feet–disturbed balance, shortness of breath.

2. Neuroendocrine manifestations: Recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change-loss of appetite or abnormal appetite, worsening of symptoms with stress.

3. Immune manifestations: Recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation–generally minimal swelling noted, new sensitivities to food, odors, or chemicals.

III. Exclusionary conditions:
- A. Any active medical condition that may explain the presence of chronic fatigue, such as:
  1. Untreated hypothyroidism
  2. Sleep apnea
  3. Narcolepsy
  4. Malignancies
  5. Leukemia
  6. Unresolved hepatitis
  7. Multiple Sclerosis
  8. Juvenile rheumatoid arthritis
  9. Lupus erythematosus
  10. HIV/AIDS
  11. Severe obesity (BMI greater than 40)
  12. Celiac disease
  13. Lyme disease

- B. Some active psychiatric conditions that may explain the presence of chronic fatigue, such as:
  1. Childhood schizophrenia or psychotic disorders
  2. Bipolar disorder
  3. Active alcohol or substance abuse–except as below:
     a) Alcohol or substance abuse that has been successfully treated and resolved should not be considered exclusionary.
  4. Active anorexia nervosa or bulimia nervosa–except as below:
     a) Eating disorders that have been treated and resolved should not be considered exclusionary.
  5. Depressive disorders

IV. May have presence of concomitant disorders that do not adequately explain fatigue, and are, therefore, not necessarily exclusionary.
  1. Psychiatric diagnoses such as:
     a) School phobia
     b) Separation anxiety
     c) Anxiety disorders
     d) Somatoform disorders
     e) Depressive disorders

TABLE 1 (continued)

2. Other conditions defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, such as:
   a) Multiple food and/or chemical sensitivity
   b) Fibromyalgia
3. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented.
4. Any condition, that was treated with definitive therapy before development of chronic symptomatic sequelae.
5. Any isolated and unexplained physical examination, laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition.

rectly, fatigue will accompany such infectious or neurological illnesses, but may not be the main focus.

Several changes were made to adult case definition based on the conception that the diagnosis of ME/CFS in children should be made based upon the symptom complex present at the time of evaluation.

First, the adult definition requires that the fatigue not be lifelong and that it be of a new and definite onset. In a revision of the Fukuda et al. (1994) criteria, Reeves et al. (2003) state that only participants who recount having always felt severely fatigued should be excluded as having "lifelong" fatigue. We also decided to not use this criterion in formulating the diagnostic criteria for children for two reasons. First, children and their families may not be able to pinpoint a definite onset because, in up to 25% of pediatric cases, the onset is insidious rather than sudden (Bell, 1992). Second, children may not be able to compare their current functioning with a healthy baseline as, due to developmental events and progress, they may not have a comparable period with which to compare their current functioning. Further, children themselves may be unable to judge onset because variations in cognitive development might affect their ability to remember their functioning at previous points in time. Finally, children may be more adaptable than adults and, consequently able to make accommodations for their fatigue and other symptoms (Bell, 1995b). On the other hand, inquiring about hobbies, social and leisure activities can provide an indication of the time wherein complaints started to significantly influence daily activities. Clinical practice shows that ME/CFS patients abandon their hobbies, social and leisure activities in order to keep up at school. This process starts when the first school demonstrates a decline in performance. Subsequently, parents will encourage their children to perform better and conse-

quently to spend more time in order to achieve higher levels of functioning at school. Therefore, although no exact onset can be identified by the child or parents, through the assessment process, it is often possible to pinpoint the time point when the fatigue started to interfere with the children's daily functioning.

Similarly, the provision that the symptoms such as sore throat or memory impairment not predate the fatigue has also been modified. It has been found that, in children with an insidious onset, such symptoms may in fact predate fatigue. Alternatively, children may have a history of sore throats, ear infections, or upper respiratory infections as part of the usual childhood series of illnesses. However, these illnesses may make it difficult to tease out the onset of ME/CFS symptoms. In addition, parents and children may not be aware of the fatigue but may notice other symptoms. Furthermore, children may also present as irritable rather than fatigued, and it may be difficult to date the onset of this symptom. The symptoms present at the time of diagnosis should, however, be associated in a complex of symptoms that occurs repetitively or chronically.

Second, debate has also occurred regarding the six-month requirement for the fatigue and other symptoms (Kulig, 1991; Vereker, 1992). The Canadian criteria suggest that children with symptoms lasting more than three months duration can be diagnosed with the illness (Carruthers et al., 2004). We agree with this notion, as Fowler et al. (2005) did not find differences between 8-17 years olds with 3 versus 6 months of chronic fatigue. Overall, the criterion regarding the duration of the symptoms varies from two weeks to six months (Van Hoof & Maertens, 2002). Arbitrarily, we propose to diagnose a CFS-like condition after 1 to 2 months of duration. After three months, ME/CFS can be diagnosed. In clinical practice, however, it often takes more than one year before a ME/CFS diagnosis is given to children and adolescents (Van Hoof et al., in press).

Third, the threshold number of four symptoms has been changed, as we now adopt a similar system to that used with the Canadian ME/CFS criteria of symptom clusters. Appendix A provides a copy of the Pediatric ME/CFS Questionnaire, which provides a way of gathering this information to help diagnose pediatric ME/CFS. It is generally recommended that adolescents age 12 and older fill it out themselves, and parents can assist or fill it out for the children 11 and under, although adherence to this guideline would vary depending on the comprehension level of the individual child. It is possible that more than one person (e.g., child only, parent only, both parents, other primary caregiver)

could fill out the Questionnaire. Some clinicians feel that it is almost never acceptable to only involve one parent in doing a child/adolescent evaluation, because a limited and sometimes inaccurate view of the child and family often results from questioning only one parent. Research by Jones et al. (2004) revealed that significant differences exists between parental and children's descriptions of the illness. Thus, whenever possible, information from both parents should be collected. Further, it may be appropriate to gather information from grandparents, extended family members, or other caregivers if they are in close contact with the young person.

For a diagnosis of pediatric ME/CFS, the following five classic ME/CFS symptom categories must occur (see Table 1). Post-exertional malaise, the first criteria symptom, must occur with loss of physical or mental stamina, rapid muscle or cognitive fatigability (or easy distraction as the behavioral component of cognitive fatigability). The second symptom category is unrefreshing sleep, or disturbance of sleep quantity or rhythm. The third symptom category requires that the young person exhibit either 1. myofascial pain, 2. joint pain, 3. abdominal and/or 4. head pain. The fourth symptom category is the occurrence of two or more neurocognitive manifestations. Finally, the fifth symptom category requires at least one symptom from two of the following three subcategories: 1. Autonomic manifestations, or 2. Neuroendocrine manifestations, or 3. Immune manifestations. For those patients who do not have the minimum duration of 3 or more months for the 5 classic ME/CFS symptom categories, the diagnosis should be ME/CFS-like. In contrast, there are a small number of patients with no pain or sleep dysfunction, and some pediatric cases might have only 2 to 4 ME/CFS classic symptom categories above. For these individuals, a diagnosis of atypical pediatric ME/CFS can be given. Those individuals with pediatric ME/CFS as well as atypical pediatric ME/CFS and pediatric ME/CFS-like are important to study.

Some support for the inclusion of these symptoms emerged from Rowe and Rowe's (2002) confirmatory factor analysis, which found muscle pain and fatigue, neurocognitive, abdominal head and chest pain, neurophysiological, and immunological factors. Abdominal symptoms have been added to the list, and this is supported by the work by Rowe and Rowe (2002). Autonomic symptoms have also been added, and this is supported by the Canadian case definition, (Carruthers et al., 2003), which pointed to autonomic manifestations (neurally mediated hypotension, light headedness). In addition, a study by Jason, Torres-Harding et al. (2002) found a symptom currently not part of the Fukuda

criteria, shortness of breath, did differentiate the groups in adults with ME/CFS. Given that autonomic manifestations might play a role in pediatric neurally mediated hypotension, which has been connected to ME/CFS (Poole et al., 2000), this symptom was also included. Overall, De Becker et al. validated the importance of the general, cognitive and musculoskeletal symptoms. These symptom factor scores were associated with differentiation of both the Holmes and Fukuda defined CFS patients from non-CFS patients (De Becker et al., 2001).

It is important that each of the symptoms should be either moderate or severe, but this "severity index" has not been well defined in previous criteria. We now specify that symptoms that are present be rated on the following scale: 1 = not present, 3 = moderate, 7 = severe. Symptoms need to be rated at moderate or severe (e.g., 5 or higher) to meet criteria. The rating scale, rather than a simple yes/no dichotomy, will facilitate accurate diagnosis in the research setting for several reasons. First, it will eliminate false positives on a dichotomous symptom checklist, as most of these symptoms are common to a variety of childhood illnesses, although not to a moderate or severe degree. Second, it will assist the rater, who when faced with a dichotomous choice, may choose "no" if the symptoms are present sometimes or are not severe. Finally, the rating scale will increase the amount of information gathered about each symptom. This will also allow better comparison over time, as symptom severity may wax and wane. In addition, providing information concerning the date of onset of the symptoms might allow investigators to better understand the progression of this illness. This type scoring design allows a dimensional diagnostic evaluation based upon the presence of the symptoms and a traditional ICD-10 categorical diagnosis. This scoring design is implemented because in diagnosing, it is important to take into account both the presence of the symptoms as well as the distress they create.

Fourth, the Canadian ME/CFS clinical case definition (Carruthers et al., 2003) states that the concurrent occurrence of the symptoms must have persisted or recurred during six or more consecutive months of illness. We think it is better to indicate the past 3 months, as we are attempting to diagnose current ME/CFS in pediatric cases. In addition, it is clear that the symptoms need not be continuous for the three-month period and may predate the onset of the recognized fatigue. However, it is unclear what is meant by "persisted or recurred" during the past three months. This is a rather complex concept and can lead to unreliability unless the criterion is better specified. We now operationalize this phrase by assessing how often the patient has experienced the symptom

over the past 3 months using the following 7 point scale, from 1 = hardly ever to 7 = every day). To be counted as "persisted or recurred," the individual would have to indicate a score of at least 4.

In addition to including criteria to determine the meaning of substantial reductions in activity, associated criteria are needed to assess issues of illness severity and remission states. Borrowing from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) (American Psychiatric Association, 1994) terminology and the CFS clinical case definition developed by Lapp and Cheney (1995), patients' severity of symptoms might be classified as follows: (A) minimal (just enough symptoms to meet the diagnosis, particularly occurring with exertion, usually able to attend school); (B) mild (few symptoms in excess of those in the diagnosis, occurring even at rest, may be able to attend school part of the time); (C) moderate (many symptoms in excess of those in the diagnosis, moderate symptoms at rest that become severe with effort, unable to attend school); (D) severe (often housebound or bedbound); (E) in partial remission (full criteria for the syndrome were previously met, but currently only a few symptoms remain with effort, able to attend school regularly); and (F) in full remission (no longer any symptoms, even with effort, able to attend school). For individuals who require a more differentiated way of classifying patients' severity of illness, we suggest using the AYME Functional Ability Scale (2005).

Fifth, exclusionary medical diagnoses include genetic and other disorders usually first evident in childhood that would explain the fatigue and symptoms, as well as those exclusionary medical diagnoses enumerated in the adult definition. Medical diagnoses that have been adequately treated (e.g., Lyme disease) or that are not likely to cause fatigue should not be considered exclusionary. One change, however, revolves around the depression diagnosis. In the Fukuda et al. (1994) adult definition, melancholic and psychotic depression are considered exclusionary conditions, primarily due to the findings that melancholic and psychotic processes represent distinct biological or endocrinological processes and may respond well to antidepressant or anti-psychotic medications (Robbins et al.,1989; Schulkin, 1994). Depression is less common in childhood, compared with adolescence, and symptoms may differ between these two age groups. Depressed pre-pubertal children are more likely to present with psychomotor agitation, symptoms of phobic and separation anxiety, and somatic complaints. Adolescents with depression, on the other hand, are more likely to present with symptoms such as anhedonia, hypersomnia, weight loss or gain, hopelessness, and lethal suicide attempts. The two groups of depressed youth

do not differ on symptoms such as depressed mood, guilt, fatigue, or negative self-image (Compas et al., 1993). As symptoms of depression overlap with those of ME/CFS (Hawk et al., in press), a careful evaluation must be conducted by the physician, with close attention to the differing developmental presentations (Jason, 1997). Inquiring about hobbies and leisure activities is important in distinguishing depression and ME/CFS. Those with the latter diagnosis will have abandoned their hobbies and leisure activities. In particular, if adolescents are sick, not diagnosed, and not believed, the youngsters could become depressed and anxious. Further inquiring about depressive or anxious feelings will reveal an underlying frustration as a result of loosing control rather than a negative self-image. Furthermore, if children experience frequent absences, but no "diagnosis" and no extra help or support, they will have to struggle to catch up when they have to return to school, and this can also lead to depression and anxiety. Thus, depressive feelings should not be considered necessarily exclusionary, as it may co-exist with ME/CFS, particularly if it is a reactive depression to the losses incurred by the illness. There could be a strong feeling of disappointment in ME/CFS children towards their support and peer group as they can not explain the child's condition. This differentiation may also be assisted by evaluating the course of both the depressive symptoms and fatigue symptoms, to determine whether depression and fatigue co-vary or appear to be separate diagnostic entities. However, depression is one of the major entities to be considered during differential diagnosis, and, when it may better explain the fatigue and child's symptom patterns, may be the appropriate diagnosis rather than ME/CFS.

Reeves et al. (2003) has recommended that major depressive disorder with melancholic features, anorexia nervosa, or bulimia, not be considered exclusionary if these conditions have been resolved for more than 5 years before the onset of the current illness. We believe that pediatric psychotic disorders of any variety continue to be exclusionary. In addition, eating disorders (i.e., anorexia nervosa and bulimia nervosa) and substance abuse have been qualified to be exclusionary only if the diagnosis is current; a diagnosis of melancholic depression, substance abuse or eating disorder that has been appropriately treated and resolved should not be considered exclusionary.

Table 1 also lists disorders that should not necessarily be considered exclusionary, although they may present comorbidly with ME/CFS. Such disorders include school phobia, separation anxiety disorder, and fibromyalgia. School phobia and separation anxiety disorder are two disorders that should be carefully considered in the differential diagno-

sis. When school phobia or separation anxiety disorder predate the fatigue and other symptoms, it is possible that a diagnosis of ME/CFS is inappropriate and that the symptoms are better explained by a psychological disorder. Children with school phobia may be differentiated from children with ME/CFS in that the former typically feel ill in the morning but recover once allowed to remain home from school (Pilkington & Piersel, 1991). In contrast, children and adolescents with ME/CFS would experience symptoms not only at school, but in other settings. Furthermore, with school phobia, symptoms are typically present only on school days, not weekends or holidays. Similarly, familial disturbance and dysfunction should be closely examined during the diagnostic process. In cases where a child's symptoms are clearly the result of such dysfunction (e.g., the child's illness holding an unstable marriage together), a diagnosis of ME/CFS would be inappropriate. However, it is just as likely that a child may be truly ill with ME/CFS and be part of an unhealthy family system.

CLARIFICATION OF DIAGNOSTIC CRITERIA

The criterion that the fatigue not be the result of ongoing exertion (Criterion 1A) has been criticized as too vague. For the purposes of clarification and consistency, in the case of a child who is active (e.g., participates in extracurricular activities, sports, outings with friends) but exhausted yet recovers quickly when activity is decreased, the fatigue would be considered to be the result of ongoing exertion or activity and, thus, would exclude a ME/CFS diagnosis. However, a child who participates in very little activity (possibly to minimize ME/CFS symptoms) when compared to his or her same-age peers, and becomes exhausted upon minimal exertion would not be excluded from a ME/CFS diagnosis due to the ongoing exertion clause. Inquiring about hobbies and leisure activities will reveal abandonment of their hobbies and leisure activities. In summary, normal fatigue is not activity limiting, whereas the fatigue present in ME/CFS limits the individual's activity to varying degrees.

Similarly, the provision that the fatigue is not substantially alleviated by rest (Criterion 1B) requires clarification. Although a child with ME/CFS may feel better after rest, he or she may get sick again quickly upon minimal activity or exertion. Thus, in this case, the rest does not completely eliminate the syndrome, although it may provide some relief, and this symptom pattern should not exclude a ME/CFS diagnosis. The

duration of the post-exertional fatigue is important. It can last for a considerable time and be accompanied by other symptoms such as cognitive downturn, muscle fatigability, as well as resurgence of other CFS symptoms. Another symptom that frequently occurs is social withdrawal to minimize ME/CFS symptoms. Previously extraverted, easy-going and happy children become introvert and quiet. Their parents talk about the perceived desire of their children to withdraw from social interactions and become less noticeable.

The criterion that the illness results in a substantial reduction in level of academic, social, or personal functioning (Criterion 1C) requires some clinical judgment. It may be difficult to determine changes from previous level of functioning in very young children who may not be able to recall, nor may their parents be able to recall, their previous activity levels. School personnel school reports can provide an estimate of the premorbid intellectual capacities of the ME/CFS child. It is possible to assess premorbid functioning by reviewing teacher reports before and after the onset of the symptoms. Clinical practice indicates that ME/CFS patients had good premorbid functioning and were considered as easy-going and motivated students. With onset of the illness, this level of functioning decreases and it is reflected in the school reports.

In these cases, it is appropriate to compare the child's daily functioning with what would be expected of a same-age peer. For example, inability to attend school, difficulty attending to activities of daily living (e.g., bathing, dressing, or feeding), or lack of participation in social activities due to illness or symptoms such as dizziness should be considered when making the diagnosis. Where possible, there should be validation of decreased activity level and other symptoms by outside sources, such as teachers or school nurses who are familiar with ME/CFS. The AYME Functional Ability Scale (2005) is a promising way of differentiating patients' functional abilities.

PSYCHOLOGICAL INSTRUMENTS

To assess comorbid neuropsychiatric conditions, instruments such as the Diagnostic Interview for Children and Adolescents-Revised (DICA; Herjanic & Reich, 1982) or the Structured Clinical Interview for the DSM-IV for Children (KID-SCID; Hein) may be used to determine diagnoses. Instruments such as the Children's Depression Inventory (CDI; Kovacs, 1992) or the Schedule for Affective Disorders and Schizophrenia-Children's Version (K-SADS; Chambers et al., 1985) may be used

to assess level of depression. Minimal work has been done in the area of assessment of children's fatigue. Walford, Nelson, and McCluskey (1992) report the satisfactory adaptation of the fatigue questionnaire by Wessely and Powell (1989), later revised by Chalder et al. (1993), for use with children. However, no psychometric data are available for this scale in relation to the pediatric population. As Stouten (2005) recently pointed out, many frequently used fatigue scales do not accurately represent the severe fatigue that is characteristics of CFS (although this problem is avoided with the Profile of Fatigue-Related Symptoms, Ray et al., 1992).

Sleep disturbances can be assessed by using the *Pittsburgh Sleep Quality Index* (Buysse, 1989), which has been effectively used in elementary school age samples (Tan, 2004). This Index measures sleep disruptions and sleep quality. The McGill Pain Questionnaire is well validated, is available in a short form (Melzack, 1975), and has been reliably used with pediatric samples (O'Rourke, 2004). Finally, children's functional status may be assessed using the Children's Health Questionnaire (Landgraf, Abetz, & Ware, 1996), an instrument that will assess physical and psychosocial well-being. The 12 concepts measured by both forms of the CHQ include physical functioning, bodily pain, general health perceptions, and self-esteem. As mentioned in the manual, the Changed GHQ-score is most appropriate in chronic conditions as children will incorporate their symptoms in their own 'conceptual frame.' The scale 'no more than usual' is included in the changed GHQ scoring procedure.

INTERVENTIONS TO INCREASE QUALITY OF LIFE

In the case of children, day-to-day management of a chronic disease and its psychological consequences becomes a family affair with parents in particular having a key role to play. Thus, it is not surprising that the role of interventions in facilitating adaptation to the challenges of chronic disease has received growing recognition. Information presented to the child, parents and other primary caregivers should make them equipped to play an active role in the daily management of their illness. A number of interventions are drawn on theoretical concepts such as self-efficacy and empowerment. At the individual level, key elements of empowerment include access to information, ability to make choices, effective change in one's life, assertiveness and self-esteem (Rogers et al., 1997). Similarly, self-efficacy has been posited as a cen-

tral, mediating mechanism in human agency (Bandura, 1988), whereby perceptions of capabilities to carry out the courses of action necessary to meet situational demands influence choice of actions pursued, level of motivation, thought pattern and emotional reactions experienced. There is evidence of effectiveness for interventions incorporating cognitive-behavioral techniques on variables such as self-efficacy, self-management of disease, family functioning, psychosocial well-being, reduced isolation and social competence. Overall, psycho-educational interventions can take many forms including simple provision of information via written materials, computer programs or the Internet.

Psycho-educational interventions for children and their families, however, need to take account of developmental age as well as disease progression. Glasgow and colleagues (1999) suggest that problems with self-care typically emerge during the first few years after diagnosis or during early adolescence (13-15 years). Thus, educational and skills training approaches may be particularly important for both child and family at the time of diagnosis and for adolescents who are assuming responsibility for self-care. In CFS/ME area with pediatric samples, there have been only a few implemented non-pharmacologic interventions, and few had appropriate controls or long-term follow-up (Whiting et al., 2001; Barlow & Ellard, 2004).

SUGGESTIONS FOR FUTURE RESEARCH ON PEDIATRIC ME/CFS

The definition proposed here is provided as a starting point for facilitating consistent research on pediatric ME/CFS. This definition should be subjected to rigorous scientific study to determine its efficacy. In particular, reliability studies should be conducted to determine if the definition facilitates consistent diagnosis (Jason et al., 1997). Rowe and Rowe (2002) used 24 key symptoms and found one underlying syndrome factor, suggesting that the syndrome complex can be legitimately designated as a syndrome. In addition, Komaroff and colleagues (1996) compared symptoms and fatigue characteristics of a large sample of adult ME/CFS patients with three other groups (healthy controls, depressed subjects, and patients with multiple sclerosis) to determine the validity of each symptom and its contribution to differential diagnosis. Similar techniques would be useful in validating the pediatric definition.

Future research on pediatric ME/CFS should carefully word questions aimed at identifying children's level of fatigue, and the developmental context of the children and adolescents being assessed should be taken into account. As children may present as irritable rather than complain of fatigue, questions that focus on school problems (e.g., learning or memory problems) or other consequences of fatigue may need to be asked in addition to questions regarding fatigue. In addition, as there may be discrepancies between caregiver's reports of the child's functioning and the child's own assessment, a comparison of these two descriptions of symptomatology should be made.

Fukuda et al. (1994) recommended subgrouping adult ME/CFS patients and similar efforts would be appropriate in the study of pediatric ME/CFS. In addition, it is clear that the current cohort of individuals diagnosed with ME/CFS is a diverse group with varying disease course and disability patterns, offering limited understanding of the etiology or pathology of the illness and its components when considered together (Jason et al., 2005). Patterns of illness course and duration are difficult to decipher when using the current diagnostic criteria to identify individuals with this illness. Similar to disorders such as cancer, it is highly likely that a number of distinct types of ME/CFS exist and that the current method of grouping all individuals who meet diagnostic criteria together complicates the identification of biological markers in these subgroups.

The arguments against articulating a definition of ME/CFS specifically for pediatric patients revolve primarily around the harm of an inaccurate diagnosis. These arguments include the uncertainty in diagnosing children due to difficulty in obtaining an accurate self-report from young children. In addition, premature diagnosis may prevent recognition of a treatable condition. Finally, some researchers and clinicians doubt that ME/CFS exists as a clinical entity in children, particularly young ones. However, a consistent case definition is needed to facilitate research on pediatric ME/CFS and to assist in the identification of homogenous groups. While some researchers have suggested that children and adolescents have a higher rate of recovery from ME/CFS when compared to adults, there is still a subgroup of pediatric cases whose illness persists for extended periods of time (Arav-Boger & Spirer, 1995; Smith & Carter, 2003). A consistent case definition would facilitate longitudinal investigations into the prognosis of CFS and help identify risk factors which may predict poorer prognosis, so that these higher risk children and adolescents receive earlier intervention.

The summary of symptoms in Table 1 could be referenced by pediatricians, school nurses, and even school teachers and staff responsible for Individual Education Plan development and implementation. In addition, the criteria list could be useful to the young person, parents or others advocating for the youth with ME/CFS in need of accommodations since it would give legitimacy to the child's symptoms. The rapid, accurate identification of cases of ME/CFS followed by comprehensive and appropriate support and treatment might increases chances of recovery for all children and adolescents with this debilitating illness.

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NOTE

1. The acronym ME/CFS refers to Myalgic Encephalomyelitis and Chronic Fatigue Syndrome, according to the Canadian Case Definition. The patient community has felt that the term chronic fatigue syndrome trivializes the seriousness of this illness, as the illness is typified by many severe symptoms in addition to fatigue, and fatigue is generally regarded as a common symptom experienced by many otherwise healthy individuals in the general population. The term Myalgic Encephalomyelitis had been used prior to the use of the term chronic fatigue syndrome (Acheson, 1959). Some individuals have preferred to use the term Myalgic Encephalopathy rather than Myalgic Encephalomyelitis, as the former term does not suggest brain inflammation.

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