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Examining Criteria to Diagnose ME/CFS in Pediatric Samples

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A Pediatric Case Definition

- Case definition developed for adults
 - Fukuda et al. (1994) might not be appropriate for children & adolescents
- International Association of Chronic Fatigue Syndrome developed a Pediatric ME/CFS case definition
 - (Jason et al., 2006)

Changes From the Adult Fukuda et al. Case Definition

- Incorporated structure of clinical case definition for ME/CFS developed in Canada
 - (Carruthers et al., 2003)
- Requiring certain symptoms provides more specification of critical symptoms for case definition

Developed DePaul Pediatric Health Questionnaire (DPHQ)

- Instrument developed to measure pediatric symptoms
 - Generally recommended that adolescents age 12 & older fill it out themselves
 - parents can assist or fill it out for children 11 & under
- Medical Examination needs to occur

Method

- **54 participants included in this study**
 - 33 children were diagnosed with ME/CFS by a physician experienced in assessing and treating children with this illness
 - 21 were referred as healthy controls
- **Three cooperating physicians conducted medical examinations to screen for exclusionary illnesses**
 - **Parent and/or child completed DPHQ**

All Cases Diagnosed Two Ways

- **Adult Fukuda et al. (1994) criteria**
- **New Pediatric ME/CFS case definition**

New ME/CFS Pediatric Case Definition:

Severe

- **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 had to experience substantial reduction in previous levels of educational, social and personal activities**
- **Participants needed to evidence specific symptoms within the five classic ME/CFS symptom categories, which needed to have persisted or recurred during the past 3 months of illness, but may predate the reported onset of fatigue**

Diagnosis of ME/CFS

- 5 symptom categories:
 - Post-exertional malaise must occur with loss of physical or mental stamina, rapid muscle or cognitive fatigability
 - Unrefreshing sleep or disturbance of sleep quantity or rhythm
 - Myofascial pain, joint pain, abdominal and/or head pain
 - Two or more neurocognitive manifestations
 - At least one symptom from two of three subcategories:
 - Autonomic manifestations
 - Neuroendocrine manifestations
 - Immune manifestations

Rating Criteria for Symptoms

- **They needed to report severity ratings of moderate or severe and frequency ratings of occurs half the time or more**
 - (a rating of 4 or higher, on a scale of 1-7)

Severe ME/CFS

- **According to the Pediatric ME/CFS criteria**
 - 16 participants of the 33 referred to this study met all criteria for having Severe ME/CFS

Moderate Pediatric ME/CFS criteria

- **Needed to meet only four out of the five classic ME/CFS symptoms**
- **For autonomic, neuroendocrine, and immune manifestations**
 - at least one symptom in any of these three categories
- **14 participants of the 33 referred to this study as having ME/CFS were diagnosed as having Moderate Pediatric ME/CFS**

Additional subtypes: Atypical ME/CFS

- **Atypical ME/CFS**
 - defined as 3 or more months of fatigue
 - having two or three of the classic five ME/CFS symptoms, each lasting for 3 or more months.
 - 2 children met the criteria for Atypical ME/CFS illness.

ME/CFS-Like

- Meeting all classic ME/CFS symptom criteria except for the 3 month duration or when one is lacking a medical evaluation
- One participant only experienced fatigue for 2 months but expressing the other major symptom criteria

Remission

- **One child was classified as having ME/CFS in remission**
- **Met full symptom criteria at one time**
- **Not experiencing symptomology at the time of the study**

Classification

- **Pediatric New Case Definition ME/CFS** group included participants who were diagnosed with Severe ME/CFS, Moderate ME/CFS, and atypical ME/CFS
- The participant who was categorized with ME/CFS-like illness and the participant in remission were categorized as not having ME/CFS

Statistical Analyses

- **Fukuda criteria was analyzed in comparison to the Pediatric ME/CFS criteria to determine specificity and sensitivity**
- **Receiver Operating Characteristic (ROC) to evaluate the overall appropriateness of these two criteria**

Results: Fukuda et al. criteria vs MD diagnosis

- the ROC resulted in an area under the curve that was calculated along with its asymptotic standard error
 - (SE=.05, 95% CI, .76 to .95)
- Area under the curve of .88
 - a randomly selected individual from the illness group will have a laboratory test value larger than that for a randomly chosen individual from the non-ill group 88% of the time

Results: New Pediatric Case Definition compared to MD diagnosis

- **ROC resulted in an area under the curve of .99**
 - (95% CI, .90 to 1.00)
- **Means that for 99% of the time**
 - a randomly selected individual from the illness group will have a laboratory test value larger than that for a randomly chosen individual from the non-illness group

Conclusions: Differential Outcomes

- **Of the 33 ME/CFS cases referred by the physicians**
 - only 25 were identified as having ME/CFS with the Fukuda et al. criteria
 - In contrast, the ME/CFS Pediatric criteria identified 32 as having ME/CFS
- **Pediatric ME/CFS criteria are more accurate in correctly distinguishing between the presence and absence of pediatric ME/CFS**

- **The Fukuda et al. criteria evidenced 76% sensitivity and 100% specificity**
 - would miss 24% of patients with ME/CFS
- **Pediatric ME/CFS criteria evidenced 97% sensitivity and 100% specificity**
 - would miss only 3% of patients with ME/CFS
- **In a population with a low illness prevalence, the risk of under diagnosis is a key concern**
- **Important for a diagnostic tool with a low prevalence illness to have high sensitivity and negative predictive value**

Reasons for misclassifications

- **Fukuda et al. (1994) criteria missed cases due to the longer duration requirement**
 - the Fukuda et al. (1994) criteria requires a duration of 6 months.
- **Pediatric ME/CFS criteria requiring a duration of 3 months for fatigue**

- **Fukuda et al. (1994) criteria states that the concurrent symptoms such as sore throat and concentration problems must not predate fatigue**
 - lead to an unnecessary exclusion of children who did in fact have ME/CFS
- **New Pediatric ME/CFS criteria recognizes that in children with an insidious onset, such symptoms may in fact predate fatigue**

Cases Missed by the Fukuda et al. criteria

- 8 participants who received a physician's diagnosis of ME/CFS but did not meet ME/CFS according to the Fukuda et al. criteria (1994)
 - each of these children experienced symptoms from all major categories of the Pediatric ME/CFS criteria
 - Fatigue
 - post-exertional malaise
 - Sleep
 - Pain
 - neurocognitive difficulties
 - and autonomic/neuroendocrine/immune manifestations

Conclusion

- **Fukuda et al. (1994) criteria is the most widely used diagnostic measure to diagnose ME/CFS**
- **Found using these criteria a high rate of underdiagnosing pediatric ME/CFS**
- **New pediatric definition of ME/CFS and a reliable instrument to assess it will lead to more adequate diagnosis of youth with ME/CFS**

Problems with the Fukuda et al. criteria

- **Person can meet criteria without having classic symptoms**
 - 4 out of 8 symptoms needed
 - Person included as a case without memory/concentration or post-exertional malaise
- **Exclude many who really have the illness**
 - Some symptoms predate the illness and therefore symptoms excluded

Research versus Clinical Criteria

- **Research criteria**
 - Select those in the severe Pediatric category
 - Very impaired and homogenous group
- **Clinical criteria**
 - Use those in moderate, atypical Pediatric criteria
 - They are more variable
 - Allows use of the ME/CFS diagnosis for those that have the illness but have less severe or atypical symptoms