A Validated Scale for Assessing the Severity of Acute Infectious Mononucleosis

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Objectives To develop a scale for the severity of mononucleosis.

Study design One to 5 percent of college students develop infectious mononucleosis annually, and about 10% meet criteria for chronic fatigue syndrome (CFS) 6 months following infectious mononucleosis. We developed a severity of mononucleosis scale based on a review of the literature. College students were enrolled, generally when they were healthy. When the students developed infectious mononucleosis, an assessment was made as to the severity of their infectious mononucleosis independently by 2 physicians using the severity of mononucleosis scale. This scale was correlated with corticosteroid use and hospitalization. Six months following infectious mononucleosis, an assessment is made for recovery from infectious mononucleosis or meeting 1 or more case definitions of CFS.

Results In total, 126 severity of mononucleosis scales were analyzed. The concordance between the 2 physician reviewers was 95%. All 3 hospitalized subjects had severity of mononucleosis scores ≥2. Subjects with severity of mononucleosis scores of ≥1 were 1.83 times as likely to be given corticosteroids. Students with severity of mononucleosis scores of 0 or 1 were less likely to meet more than 1 case definition of CFS 6 months following infectious mononucleosis.

Conclusions The severity of mononucleosis scale has interobserver, concurrent and predictive validity for hospitalization, corticosteroid use, and meeting criteria for CFS 6 months following infectious mononucleosis. *(J Pediatr 2019;209:130-3)*.

Chronic fatigue syndrome (CFS), or systemic exertion intolerance disease, is a complex condition involving severe fatigue and disabling cognitive and musculoskeletal symptoms.[1-4] Six months following infectious mononucleosis, ~10% of adolescents or young adults meet criteria for CFS.[5-7]

One to 5% of college students develop acute infectious mononucleosis annually.[8] In an attempt to understand why about 10% of young adults meet criteria for CFS following infectious mononucleosis, 2 previous studies related the severity of the acute illness (infectious mononucleosis) to the development of CFS.[9,10] In 1 study, however, the specifics of the severity measurements were not detailed,[9] and in the other, the scale used was not validated for this use.[10] We are aware of 2 other tools that have been used to measure the severity of acute infectious mononucleosis, but these scales also have not been validated either in general or for infectious mononucleosis specifically.[11,12] As part of a study to assess risk factors for the development of CFS following infectious mononucleosis, we developed and then attempted to validate a scale for rating the severity of infectious mononucleosis, by first reviewing the literature available prior to beginning our study for risk factors for the severity of acute infectious mononucleosis.[13-18] We excluded 1 study that involved young Chinese children.[13] Chretien et al showed that gastrointestinal symptoms such as anorexia, nausea or vomiting, and palatal petechiae correlated with prolonged recovery from infectious mononucleosis.[14] Tattevin et al reported on patients hospitalized with acute infectious mononucleosis with severe hepatitis, dysphagia, hemophagocytic lymphohistiocytosis, a painfully enlarged spleen, airway obstruction, meningoencephalitis, myocarditis, hemolytic anemia, or pleural effusion; thus, any of these signs or symptoms that lead to hospitalization were considered a severe manifestation of infectious mononucleosis.[15] Macsween et al have shown a significantly longer duration of fatigue following infectious mononucleosis in female patients who could not walk 100 m at the time that their acute illness was most severe.[16] Jason et al and Katz et al found that days spent in bed since infectious mononucleosis, along with autonomic dysfunction 2 months after the diagnosis, was associated with postinfectious CFS at 6 months.[17,18] We used all these data to develop a scale for the severity of infectious mononucleosis (Table I), in which each item was assigned a score of 1.

CFS	Chronic fatigue syndrome
NUHS	Northwestern University Health Service

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Methods

Our ongoing study to examine risk factors for developing CFS following infectious mononucleosis has 3 stages. In stage 1, we attempt to enroll students who are generally healthy. When the students develop infectious mononucleosis, they enter stage 2 of the study. Six months following infectious mononucleosis, students are assessed for recovery vs nonrecovery (stage 3).

We rated 126 students who developed infectious mononucleosis (stage 2) at the Northwestern University Health Center (NUHS) from December 2013 through March 2017. There were 56 male students and 70 female students, ranging in age from 18 to 23 years. Students enrolled in the study who were diagnosed with infectious mononucleosis were treated by NUHS physicians. The diagnosis of infectious mononucleosis was made either via a positive monospot test, a positive viral capsid antigen IgM test, or a positive viral capsid antigen IgG test in the presence of a negative antibody to Epstein-Barr nuclear antigen. Records of the acute clinic visit(s) were reviewed separately by 2 independent study physicians not involved in the clinical care of the student at the time infectious mononucleosis was diagnosed; each independent study physician separately completed the severity of mononucleosis scale for each of the 126 subjects. All disagreements were resolved by discussions between the 2 physicians.

Six months following infectious mononucleosis, all of the students were contacted by phone and/or email and assessed for recovery vs non-recovery. An approximately 1:1 ratio of those who were still symptomatic vs those who endorsed completely recovery were then brought in for a comprehensive medical evaluation (stage 3). Students were then classified as recovered or meeting 1 or more than 1 case definition of CFS. The 3 case definitions of CFS used were the Fukuda definition,[1] the Canadian Consensus criteria,[2,3] and the Institute of Medicine criteria for systemic exertion intolerance disease.[4] The Fukuda criteria tend to be the least stringent. We characterized those who met >1 set of criteria for CFS as having severe CFS. Serum, plasma, and viable white blood cells are stored on each subject at each visit for future studies (cytokines, metabolomics, and genomics). Plasma and serum are preserved at −80°C, and pelleted viable white blood cells are preserved in liquid nitrogen.

χ^2 analyses were conducted using IBM SPSS v 21 (IBM, Armonk, New York). Fisher exact tests were conducted for analyses where sample sizes of conditions were less than 5. Post-hoc risk ratios were calculated following χ^2 tests.

This study was approved by the Institutional Review Boards of Northwestern University, DePaul University and the Stanley Mann Research Institute of the Ann and Robert H. Lurie Children's Hospital of Chicago. All subjects provided written, informed consent at each stage of the study.

Results

Records pertaining to acute care visits for infectious mononucleosis (n = 126) were blindly reviewed by 2 independent study physicians; concurrence between scorers was 95%, thus, showing the severity of mononucleosis scale to have interobserver reliability. Discrepancies generally were matters of judgment involving over or under interpretation of clinical findings (eg, scoring elevated transaminases without clinical symptoms as hepatitis) or double scoring a single sign or symptom (eg, counting trouble breathing because of a pleural effusion twice). All disagreements were resolved by discussions between the 2 physicians.

Table I. Severity of infectious mononucleosis scale

Severe symptoms*:
Pharyngitis to the point where can't swallow even liquids
Headache so severe as to prompt an LP or neuroimaging
Fever >104°F for >2 wk
Fever >101°F for >5 wk
Not able to leave home during worst symptoms
Reduced walking distance during worst symptoms
Trouble breathing
GI symptoms (anorexia, nausea, vomiting: not diarrhea alone)
Severe Physical Examination findings:
Jaundice
"Bull neck" (prominent, warm, tender bilateral cervical adenopathy with edema)
Painfully enlarged spleen
Painfully enlarged liver
Palatal petechiae
Complications†:
Cardiac (eg, myocarditis)
Hematologic (eg, thrombocytopenia (<150 000/mm^3), neutropenia (<1000/mm^3), lymphopenia (<2000/mm^3), hemolytic anemia, hemophagocytic lymphohistiocytosis)
Neurologic (eg, meningoencephalitis)
Pulmonary (eg, pleural effusion, pneumonitis)

*Each sign, symptom, or complication present scores a 1.
†Do not count the same sign or symptom more than once (eg, if trouble breathing because of pleural effusion, count one or the other but not both).

Of the 8 symptoms of severe infectious mononucleosis identified from the literature (Table I), our subjects endorsed only 3: "Not able to leave home during worst symptoms," "Trouble breathing," and "GI symptoms." No subject had a bull neck or a cardiac or neurologic complication. Of the 9 remaining signs or symptoms of infectious mononucleosis, we grouped together the symptom of "Trouble breathing" and "Pulmonary complications" because of small numbers and likely overlap. All items present in >2 subjects are shown in Table II.

There was a statistically significant association between severity of infectious mononucleosis score and prescription of corticosteroids (χ^2 [3, n = 126] = 11.55, $P < .01$). Of 56 participants endorsing 1 or more risk factors for severe infectious mononucleosis, 31.4% were prescribed corticosteroids, whereas of 70 participants who did not meet any risk factors for severe infectious mononucleosis, 17.2% were prescribed corticosteroids. Those who scored ≥1 on the severity of infectious mononucleosis measure had 1.83 times the risk of being prescribed corticosteroids compared with those who had a score of 0 on the severity of infectious mononucleosis measure.

There was also a significant association between severity of infectious mononucleosis score and hospitalization (χ^2 [3,

Table II. Frequency of severe symptoms/signs by case definition criteria for CFS

Symptoms	Participants who did not meet case definition criteria	Participants diagnosed by 1 criterion	Participants diagnosed by >1 criteria	χ^2(df)	*P*
Gastrointestinal symptoms	26.5% (9)	22.2% (4)	75.0% (6)	8.11 (2)	.01
Hematologic complications	26.5% (9)	16.7% (5)	12.5% (1)	0.90 (2)	.30
Trouble breathing/pulmonary complications	2.9% (1)	11.1% (2)	25.0% (2)	4.32 (2)	.035
Tender, enlarged spleen	2.9% (1)	5.6% (1)	0.0% (0)	0.57 (2)	.50

n = 126] = 9.99, $P < .01$). Patients endorsing 2 or more risk factors for severe infectious mononucleosis (n = 25) had a 12% risk of hospitalization, whereas patients who met 1 or fewer risk factors (n = 101) had no hospitalization. These data provide evidence of concurrent validity for the severity of mononucleosis scale, as the scale was able to identify those more likely to be hospitalized or prescribed corticosteroids, as physicians scoring the severity of mononucleosis scale played no role in the decision to hospitalize or prescribe corticosteroids.

Of the 65 participants evaluated 6 months after infectious mononucleosis diagnosis, 52.3% (n = 34) did not meet any CFS case definition criteria, 27.7% (n = 18) met a single CFS case definition criterion, and 12.3% (n = 8) met the criteria for 2 or more CFS case definitions. An additional 7.7% (n = 5) participants were diagnosed with either lingering symptoms or idiopathic chronic fatigue, and could, therefore, not be classified as either recovered from mononucleosis or as meeting a case definition. There was a statistically significant relationship between severity of mononucleosis score and CFS diagnosis (χ^2 [6, n = 60] = 9.63, $P < .05$, V = .31). A higher severity of mononucleosis score increased the risk of a more severe CFS diagnosis (Table III). At a severity of mononucleosis score of 2 or greater, the risk of meeting more than 1 case definition of CFS was 28.6%. At a severity of mononucleosis score of 1 or less, the risk of meeting more than 1 case criteria of CFS was 8.7%. Participants who had a severity of mononucleosis score of 2 or greater had 3.29 times the risk of meeting more than 1 case definition of CFS compared with participants who had a lower severity of mononucleosis score. A CFS diagnoses also trended toward a relationship with needing hospitalization (χ^2 [2, n = 60] = 3.81, $P < .08$); 7.7% (n = 2) of participants who met 1 or more case definition criteria were hospitalized, whereas no participant who did not meet a case definition criteria were hospitalized. No significant relationship between CFS diagnosis and being prescribed corticosteroids was identified (χ^2 [2, n = 60] = 0.11, $P > .05$). Individual severity items were also examined for their association with case definition criteria (Table II). Of these items, only GI symptoms and breathing difficulties were associated with meeting CFS case definition criteria.

Table III. Association of risk factors scores at diagnosis of infectious mononucleosis and case definition criteria of CFS

CFS Case Definition(s)	≤1 Risk factor (n = 46)	≥2 Risk factors (n = 14)
None	60.9% (28)	42.9 % (6)
1	30.4% (14)	28.6% (4)
>1	8.7% (4)	28.6% (4)

Discussion

We developed a scale to rate symptoms and signs of infectious mononucleosis in college students that is relatively easy to use, has high interobserver reliability and correlates with hospitalization, the likelihood of corticosteroids being prescribed, and development of *severe* CFS (ie, subjects who met >1 set of standard criteria for CFS 6 months following infectious mononucleosis). These findings partially corroborated some[9,10] but not all (eg, Buchwald et al[6]) data from adult studies of CFS following infectious mononucleosis.

Several previous publications have rated the severity of infectious mononucleosis. In 1 report, the details were not given.[9] In others, the scales, which appeared useful, were either not validated[10] or not validated specifically for use in infectious mononucleosis.[11,12] In our study, we developed a validated scale for rating infectious mononucleosis.

Limitations of the present study include heterogeneity in evaluation at the time of diagnosis of infectious mononucleosis because subjects received care by a variety of NUHS physicians who were not part of our study. Also, although the severity of mononucleosis scale correlated with corticosteroid use, hospitalization, and the diagnosis of CFS, corticosteroid use and hospitalization were not statistically significantly associated with a diagnosis of CFS, possibly because of the small sample size. Finally, the percentage of students who met at least 1 set of criteria for CFS 6 months following infectious mononucleosis was higher than generally is reported, perhaps because we were studying college students who often report a high level of background fatigue.

Our validated scale provides a simple, objective, reproducible measure for quantifying the severity of infectious mononucleosis in young adult college students. Hopefully, the severity of mononucleosis scale can be used to guide future attempts at anticipatory guidance and/or prevention of some of the more serious consequences of infectious mononucleosis by identifying individuals who at the time of diagnosis of infectious mononucleosis are at risk for

hospitalization or nonrecovery 6 months following the diagnosis. The score could also be useful in a prospective study of benefit and risk of corticosteroid therapy or other interventions. ■

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