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Post-Infectious Fatigue in Adolescents: The Role of Physical Activity

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Abstract

Objectives—To compare adolescents who do and do not recover from acute infectious mononucleosis in terms of fatigue severity and activity levels before, during, and in the two years following infection.

Design—Prospective case-control study.

Setting—The baseline, 12- and 24-month evaluations occurred in the subjects' homes. The six-month outpatient visit occurred at Children's Memorial Hospital in Chicago, Illinois.

Participants—301 adolescents (12-18 years old) with acute infectious mononucleosis.

Main Exposures—All participants were evaluated at baseline (during active infection). Six months following infection, 39 of them met criteria for chronic fatigue syndrome. These subjects were matched by sex and tanner stage to 39 randomly selected screened-negative subjects. Both groups were re-evaluated at 12- and 24-month follow-ups.

Main Outcome Measures—The Fatigue Severity Scale and the Modifiable Activity Questionnaire.

Results—For both groups, physical activity levels declined and sleep increased as a result of having mononucleosis. Compared with their matched controls, adolescents with chronic fatigue syndrome reported significantly higher levels of fatigue at all time points and spent significantly more time sleeping during the day six- and 12- months following infection. The two groups did not differ significantly in terms of physical activity levels before, during, and after infection. There was a consistent trend for decreased physical activity in the chronic fatigue syndrome group.

Conclusions—Adolescents with chronic fatigue syndrome appear to be pushing themselves in an attempt to maintain similar activity levels as their peers, but paying for it in terms of fatigue severity and an increased need for sleep, particularly during the day.

Keywords

Chronic Fatigue Syndrome; mononucleosis infection; physical activity; sleep

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Introduction

Chronic fatigue syndrome (CFS) represents a significant public health concern, possibly affecting as many as 800,000 individuals (primarily adolescents and adults) within the United States [1, 2]. It is a debilitating disorder, characterized by persistent fatigue lasting for more than 6 months. The symptoms are not improved by bed rest and are typically exacerbated by physical and mental activity [3, 4].

In adolescents, CFS accounts for marked functional impairment and educational disruption [5]. Research suggests that infectious mononucleosis may be one disease process that leads to symptom complexes involving severe fatigue and associated physical and cognitive symptoms[6, 7, 8]. In some cases, these symptom complexes endure for six or more months and cohere with international case criteria for CFS [4, 7, 8].

Studies indicate that many individuals with CFS recall a sudden, infectious onset characterized by fever, pharyngitis, and lymphadenopathy[9, 10,11,12,13]. This observation appears particularly frequent in adolescent samples[14, 15]. In retrospective studies, rates of acute, mononucleosis-like illness preceding chronic fatigue have been documented in 73-78% of adolescents, with 46.7% recalling an active mononucleosis infection at onset [12, 13, 16]. A recent, prospective investigation by our team found that 13% of adolescents presenting with acute mononucleosis infection failed to recover and met criteria for CFS 6 months later [17]. Seven percent continued to meet CFS criteria 12 months later and four percent still met criteria 24 months later. Most individuals recovered with time, but those whose symptoms were consistent with CFS remained quite disabled. Questions remain as to what, in addition to the original mononucleosis infection, led to recovery failure in this subgroup of adolescents.

In addition to the role of infectious disease, evidence also points to the role of activity levels[18] as risk or perpetuating factors for CFS. Some studies suggest that high “action-proneness’” or over activity prior to CFS onset may serve as a risk factor for CFS[18,19,20,21] MacDonald and associates found that a great number of individuals with CFS exercised more regularly, and for a longer period of time, in the year before illness onset compared with controls.

On the other hand, underactivity, deconditioning, activity avoidance, and poor physical fitness have all been cited as potential perpetuating factors once a patient is ill with CFS[22, 23]. Bed rest has also been implicated once a patient has contracted mononucleosis and has subsequently developed CFS[24]. Van der Werf and associates measured and classified the actual physical activity levels over a 12-day period and found that the CFS sample had less intense and shorter activity peaks, while the average rest periods that followed these peaks were longer than those of the control group.

White and associates[25] found that number of days in bed and low physical fitness predicted CFS 6 months after mononucleosis onset. They argued that characteristics of the infection and its consequent immune reaction may play a more significant role earlier in the post–infectious process, but physical deconditioning may lead to delayed recovery over time. Meanwhile, Fulcher and colleagues reported that patients with CFS were physically weaker, had a significantly reduced exercise capacity, and perceived greater effort during exercise, when compared with sedentary controls. Low exercise capacity in patients with CFS that was related to quadriceps muscle weakness, low physical fitness, and a high body mass index, implied that physical deconditioning helped to maintain physical disability in CFS [23].

Similarly, Bazelmans et al. did not find any significant differences in physical fitness between CFS patients and controls, but found that more CFS patients failed to achieve a

physiological limitation at maximal exercise. Physical fitness levels were highly correlated with participants' reports of daily physical activity[26].

With few exceptions findings from adult studies are largely retrospective and mixed regarding the role of physical activity in the development and perpetuation of CFS[25]. Moreover, little is known about the role of physical activity in the development of CFS in an adolescent sample. This study focused on a narrowly-defined subgroup of adolescents with CFS and a group of matched controls, all of whom shared a common infectious onset. We tracked physical activity levels before, during, and after infection to shed more light on the role of activity in the onset and course of CFS over time. Our central objective was to compare adolescents who did and did not recover from acute infectious mononucleosis in terms of fatigue severity and activity levels before, during, and in the two years following infection. We therefore sought to determine whether:

- **I.** Adolescents with CFS would report higher fatigue severity compared with controls at all time points.
- **II.** In the year before mononucleosis onset, adolescents who later developed CFS would have been *more* physically active than controls that experienced a normal recovery from infection.
- **III.** During mononucleosis, adolescents who later developed CFS would have been *less* physically active than controls that experienced a normal recovery from infection.
- **IV.** Adolescents with CFS would demonstrate decreased activity levels and increased sleep as compared with controls at all follow-up time points (6-, 12-, and 24-months after infection).

Method

Design

This was a prospective case-control cohort study that involved retrospective measurement of activity in the year before mononucleosis and prospective measurement of activity and fatigue at baseline and at 6-, 12-, and 24-months following infection. The study was approved by the institutional review boards of Children's Memorial Hospital and the University of Illinois at Chicago. Additional methodological information about the larger study from which this paper was derived may be found in an earlier publication by Katz et al. [17]

Participants

A total of 301 adolescents diagnosed with acute infectious mononucleosis were enrolled. The adolescents were referred to the study by school nurses, emergency rooms, the virology laboratory of Children's Memorial Hospital, and through pediatric and family practices, including the Pediatric Practice Research Group, a referral network of Children's Memorial Hospital. Six months following their initial diagnosis, all participants underwent a telephone screening interview to determine their recovery status. Following complete physical and psychiatric examinations with laboratory work, intensive medical history interviewing, and a review of past-year medical records, 39 participants met international case criteria for chronic fatigue syndrome [4,27]. Thirty-nine screened negative controls who had fully recovered from mononucleosis at the six month time point were randomly selected from the remaining pool of subjects and matched one-to-one with the CFS subjects in terms of sex and tanner stage. Sociodemographic characteristics of the sample at six months are presented in Table 1.

Procedures

The original diagnosis of mononucleosis was confirmed by a review of laboratory records (monospot positive for acute infectious mononucleosis) and clinical records (i.e., signs and symptoms of fever, pharyngitis, and lymphadenopathy). In cases where a diagnosis was unclear or when we could not retrieve the original records, we performed additional laboratory testing for active Epstein-Barr Virus infection within our own facility, as documented by a positive IgM anti-viral capsid antigen and low avidity IgG anti-viral capsid antigen in baseline sample. Upon enrollment and during active infection, all subjects participated in an extensive in-person interview and assessment battery, which included measures of fatigue severity and physical activity at baseline. Classification as being either recovered or not recovered from mononucleosis was based on results from a telephone screening interview, which occurred six months after the initial infection.

Screened positive subjects and a group of screened negative controls were invited to Children's Memorial Hospital for a more comprehensive evaluation that included complete physical and psychiatric examinations and additional laboratory work. These examinations were conducted to rule out exclusionary conditions and other alternative explanations for the subjects' enduring symptoms and disability. At the six-month follow up appointment, subjects were also administered the same in-person interview and assessment battery that they received at baseline. A provisional diagnosis of CFS was made by the examining physician. Final classification as having CFS was determined through a blind panel of independent chart reviewers following the clinical evaluations. This classification was made according to Jason and colleagues' [27] revision of the criteria originally described by Fukuda et al. [4]

The 39 participants with CFS and 39 matched controls were invited for re-evaluation at the 12- and 24-month follow-up time points. Both re-evaluations involved the same assessment battery, laboratory work, and chart review procedures that were administered at the other time points. Thirty six of the 39 diagnosed as having CFS underwent a reevaluation at 12 months (three were lost to attrition), 11 had recovered and 3 were re-classified as having an alternative explanation for their symptoms (CF-explained), leaving 22 subjects classified as CFS (7% of the original sample, all female) and their 22 matched controls.

At the 24 month follow-up, 3 more subjects with CFS were lost to attrition. Six had recovered and two were re-classified as CF-explained. One subject who did not meet severity criteria for CFS at 12-months developed more severe symptoms again at 24 months and was re-classified as having CFS at that time. Additionally, one subject originally classified as CFS at six months but had an explanation for her enduring symptoms at the 12-month time point (pregnancy and miscarriage) no longer had this explanation at 24 months and was again classified as CFS. This left 13 subjects (all female, 4% of the original sample, all female) with CFS and their 13 matched controls 24 months after initial infection. More information about this sample may be found in Katz et al[17].

Measures

CFS Screening Questionnaire—The *Chronic Fatigue Syndrome Screening Questionnaire*[28] was used to assess sociodemographic characteristics and to evaluate the presence versus absence of CFS symptoms. The questionnaire assessed interviewees' sociodemographic characteristics and supported preliminary classification into screened positive (non-recovered/possible CFS) versus screened negative (recovered/control) groups. Basic demographic data included age, ethnicity, socioeconomic status, marital status, and sex. The revised scoring rules for Hollingshead's (1975) scale, developed and validated by Wasser[29], were used to classify socioeconomic status. This screening scale has

demonstrated high discriminant validity and excellent test-retest and inter-rater reliability 28.

Fatigue Severity Scale (Krupp et al., 1989)—The *Fatigue Severity Scale*30 is a valid fatigue/function measure comprised of nine items that are rated according to a Likert-type rating scale from 1 to 7, where 1 indicates no impairment and 7 indicates severe impairment. The items were initially selected to identify common features of fatigue in both multiple sclerosis (MS) and systemic lupus erythematosis (SLE). In the initial validation study[29] individuals with MS and SLE were compared with non-disabled, healthy adults. Internal consistency for the Fatigue Severity Scale was high for both illness groups. The scale clearly distinguished between patients and controls, and was moderately correlated with a single-item visual analogue scale of fatigue intensity (r = .68), and with depression scores in the MS, SLE, and control groups.

Modifiable Activity Questionnaire—The Modifiable activity Questionnaire (MAQ) was designed for easy modification to maximize the ability to assess physical activity in a variety of populations. It assessed current (past- year and past-week) occupational and leisure activities, as well as extreme levels of inactivity due to disability[31]. The interview was found to be reliable and valid with eighth and eleventh graders and across sex and ethnicity 32.

Using the MAQ, we collected information on time spent on physical activity, sedentary activity, napping, and sleep. Two MAQ questions scaled from one (none) to five (nine or more days) measured the degree to which participants engaged in hard and light exercise within the past 14 days. A third question also scaled from one (none) to five (six or more hours) measured the degree to which participants engaged in sedentary activities having to do with television and computer devices. Three additional, open-ended questions asked participants to report the number of hours spent on a “typical” day sleeping, napping, and doing other sedentary activities, such as reading, writing, and studying.

Statistical Analysis

Chi-square tests and paired samples t-tests were used to compare the CFS subjects with their matched controls in terms of sociodemographic characteristics. Comparisons of fatigue severity and activity levels were made using t-tests. Means and standard deviations were provided for all continuous variables and frequencies and percentage values were provided for all categorical variables. To reduce the risk of Type I error emanating from multiple comparisons, statistical significance was set conservatively at $p \leq .01$.

Results

Sociodemographic Characteristics of the Sample

There were no significant differences in gender, family socioeconomic status, body mass index (BMI), age and work or/and study status between the CFS subjects and one-to-one matched controls.

Fatigue Severity

We hypothesized that adolescents with CFS would report higher fatigue severity compared with controls during mononucleosis and at all follow-up time points. Results of a series of t-tests supported this hypothesis (Table 2).

Activity Levels Before and During Mononucleosis

We hypothesized that, in the year before mononucleosis onset, adolescents who later developed CFS would have been *more* physically active than controls that experience a normal recovery from infection. This hypothesis was not supported. Findings from t-tests revealed that adolescents who later developed CFS did not differ significantly from controls in their physical activity levels 12-months before mononucleosis onset (Table 3).

Alternatively, we hypothesized that, during active infection with mononucleosis, adolescents who later developed CFS would have been *less* physically active than controls that experience a normal recovery from infection. Findings from t-tests did not support this hypothesis. Adolescents who later developed CFS did not differ from controls in their activity levels during the time of mononucleosis infection (Table 3).

Activity Levels at 6-, 12-, and 24-month Follow-ups

We hypothesized that adolescents with CFS would demonstrate decreased activity levels and increased sleep as compared with controls at all follow-up time points. This hypothesis was only partially supported. At the six-month time point, the only significant differences between the adolescents with CFS and the controls involved napping during the day (Table 4). Adolescents with CFS spent significantly more time napping during the day than controls.

This finding was replicated at the 12-month time point.

At the 24-month time point, there were no significant differences in sleep or activity between the adolescents with CFS and their matched controls (Table 6).

Although no other activity-related findings were significant, the descriptive data in Tables 4 – 6 suggest there were subtle trends for reduced activity in the CFS group, particularly with regard to light and hard exercise at the 12-month follow-up.

Discussion

Historically, findings regarding the role of activity in chronic fatigue syndrome have been mixed and somewhat discordant. Some studies point to the role of over-activity as a risk or perpetuating factor, while other studies point to the roles of under-activity and deconditiong[19,21,23,26]. Findings from this study show no differences in activity levels between adolescents with and without post-infectious fatigue. Although there were trends for reduced activity in the CFS group, the differences did not reach statistical significance and were not sustained at the 24-month follow-up. Despite non-significance, however, these trends, coupled by findings for increased daytime napping within the CFS group, may support the possibility that adolescents in the CFS group were struggling to “keep up” with their peers in order to maintain their usual activity levels. This possibility would have to be investigated in future studies.

One potential explanation for our lack of significant differences between the two groups may, in part, involve the way in which activity was conceptualized and measured in this study. For example, Van Houdenhove and colleagues[21] found that “action-proneness” and an associated “overactive” lifestyle played predisposing, initiating, and perpetuating roles in CFS. They used a validated Dutch questionnaire[33] that defined “action-proneness” and “over activity” as involving psychological, as well as physiological aspects. The questionnaire mainly assessed attitudes toward everyday activities, rather than engagement in actual physical activity. For example, the questionnaire included items such as: “I do not like to postpone things,” and “I love making a supreme effort,” which were quantified as

"correct" or "incorrect". Instead, we measured time spent and intensity of very specific sedentary and non-sedentary activities, with most of our emphasis on physical exercise and sports.

Rijk and colleagues sought to clarify the relationship between external stimulation and fatigue and described two clear dimensions: experienced overload and attractiveness of external stimulation. Both of these aspects of external stimulation contributed significantly to the prediction of fatigue: —experienced overload consistently predicted increased fatigue, while attractiveness of external stimulation consistently predicted decreased fatigue[19]. Similar to the study by Van Houdenhove and colleagues, this study appeared to be measuring attitudes toward different life activities and events, rather than engagement in actual physical activity[21].

Another explanation for our unique findings may involve the age and duration of illness of the subjects with CFS in this study. Comorbid and secondary medical and psychiatric conditions, such as obesity and orthopedic problems, tend to be more prevalent with increasing age and with sustained disability. We studied adolescents newly diagnosed with CFS, who had endured the syndrome for anywhere between six months and two years. Population-based studies of adults point to an average duration of CFS of five years [34], with the upper limit reaching decades in some cases. One could argue that the longer an individual is disabled by CFS, the more likely it is that his or her physical activity levels will be affected. Additionally, adolescents in this study were diagnosed as having CFS only if they did not have any other medical or psychiatric conditions that would explain their fatigue and symptoms. Compared with adults, it is possible that youth, combined with an absence of other non-exclusionary but comorbid conditions, may have served as a resiliency factor for sustained activity.

Other psychosocial variables, including social and environmental demands for adolescents to continue performing their daily activities, may also serve to explain why we did not find more significant activity reductions. The adolescents may have felt some pressure within themselves or from parents, peers, educators, or even their physicians, to continue attending school and participating in sports and other activities to the best of their ability. The fact that we found significant differences in fatigue severity between the two groups suggests that the adolescents with CFS were feeling the effects of their lifestyles but may have been pushing themselves to sustain activity. It is possible that the sustained activity led not only to increased fatigue severity but also to an increased need for sleep, particularly during the day.

Limitations

Our study, like all studies, has certain limitations. First, we did not corroborate subjects' self-reported activity levels and sleep behavior with physiological measures of physical fitness and sleep. Therefore, it is possible that, despite no significant differences in BMI between the two groups, undetected differences in physical fitness levels between the two groups could have played a role in extinguishing any differences that could have been observed. Secondly, there is the risk for Type II error. Our sample size was reduced at the 12- and 24-month time points due to a combination of adolescents recovering from CFS, changing diagnostic categories, and some minimal attrition. Some of the statistical trends toward physical activity reduction in the CFS group, particularly at the 12-month time point, may have been statistically significant had we tested a larger sample.

Conclusion

Findings from this study suggest that the onset or perpetuation of CFS was not linked to differences in the levels of physical activity. Before, during, and following infection,

adolescents with CFS appear to be engaging in similar levels of activity as their recovered peers, but they seem to be "paying for it" in terms of increased fatigue severity and an increased need for sleep, particularly during the day. The consistent, yet non-significant trend for slightly reduced activity in the CFS group may further support the possibility that adolescents in the CFS group were struggling to maintain their activity levels. One might imagine that, whatever the controls were doing during the time that the adolescents with CFS were napping would have to be more active (mentally, physically, or both) than napping. Further investigation of the role of sleep dysfunction in the development and perpetuation of CFS following mononucleosis in adolescents will be necessary to shed light on these important findings.

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Table 1

Sociodemographic Characteristics of Participants With CFS and Matched Controls

	CFS Participants (n=39)	Matched Controls(n=39)
	f (%)	**f (%)**
School/Work Activity		
Full-time students, not working	24(61.54)	21(53.85)
Full-time students, Part-time working	14(35.90)	18(46.15)
Part-time students, not working	1(2.56)	0(0.00)
Gender		
Female	35(89.74)	35(89.74)
Male	4(10.25)	4(10.25)
Ethnicity		
African American	3(7.70)	1(2.56)
Caucasian	34(87.18)	36(92.31)
Multi-raced	12(5.13)	1(2.56)
Others(not Latino)	0(0.00)	0(0.00)
	M(sd)	M(sd)
Age	16.08(1.40)	16.31(1.32)
Body Mass Index	22.10(3.50)	21.37(3.01)
Family Socioeconomic Status		
SES SCORE	59.41(23.78)	64.69(22.49)

f = frequency

M = mean

sd = standard deviation

Table 2

Krupp Fatigue Severity Scale Score at 6-,12-,24-Month Follow-ups

	CFS		Control		N	t	p
Krupp Fatigue Severity Scale Score	**Mean**	**SD**	**Mean**	**SD**			
Baseline *	39.13	11.84	30.21	9.40	39	3.70	<.001
6 month *	37.05	7.90	21.64	9.72	39	7.62	<.001
12 month *	40.20	10.38	19.91	9.84	22	6.50	<.001
24 month *	36.77	19.27	25.23	13.36	13	2.56	.01

*Indicates a significant difference at $p \leq 0.01$

Table 3

General Physical Activities of CFS Diagnosed Adolescents and Matched Controls Before and During Mononucleosis (MONO) Infection (N=39)

		CFS		Control			
MAQ Activity Scale		**Mean**	**SD**	**Mean**	**SD**	**t**	**p**
20min hard exercise	before MONO	3.15	1.44	3.69	1.36	−1.696	.09
	during MONO	2.05	1.17	2.46	1.55	−1.318	.19
20min light exercise	before MONO	3.95	1.21	3.87	1.26	.275	.78
	during MONO	3.46	1.25	3.05	1.43	1.346	.18
TV/Video/Computer	before MONO	2.72	.92	2.82	.82	−.520	.61
	during MONO	3.00	.83	2.87	.80	.695	.49
Sleep	before MONO	6.86	2.26	6.97	1.53	−.264	.79
	during MONO	9.33	2.61	8.08	2.40	.927	.36
Napping	before MONO	.474	.95	.19	.37	1.750	.08
	during MONO	1.64	1.28	1.17	1.03	1.780	.36
Other Sedentary Activity	before MONO	2.23	1.88	2.36	1.87	−.347	.73
	during MONO	2.50	1.54	2.24	1.83	.688	.49

MONO = mononucleosis

Table 4

Physical Activities of CFS-Diagnosed Adolescents and Matched Controls at 6-month Follow-up (N=39)

	CFS		Control			
MAQ Activity Scale	**Mean**	**SD**	**Mean**	**SD**	**t**	**p**
20min hard exercise in the past 14 days	2.87	1.32	3.36	1.46	−1.55	.13
20min light exercise in the past 14 days	3.76	1.08	3.72	1.28	0.17	.87
TV/Video/Computer	2.87	0.99	2.90	0.68	−0.15	.88
Sleep	8.35	1.89	7.45	1.58	2.28	.03
Napping *	1.68	1.92	0.45	0.62	3.71	<.01
Other Sedentary Activity	2.54	1.73	2.57	1.98	−0.07	.95
Total Activity in Hours per Week	5.90	4.73	7.60	5.86	−1.34	.18

* Indicates a significant difference at $p \leq 0.01$

Table 5

Physical Activities of CFS-Diagnosed Adolescents and Matched Controls at 12-month Follow-up (N=22)

	CFS		Control			
MAQ Activity Scale	**Mean**	**SD**	**Mean**	**SD**	**t**	**P**
20min hard exercise in the past 14 days	2.85	1.31	3.59	1.30	−1.841	.07
20min light exercise in the past 14 days	3.30	1.34	4.09	1.11	−2.090	.04
TV/Video/Computer	3.10	.852	3.05	.950	.195	.85
Sleep	8.13	1.72	7.45	1.19	1.432	.16
Napping *	3.85	1.14	2.39	1.91	4.083	<.01
Other Sedentary Activity	2.68	3.14	2.23	1.29	.617	.54
Total Activity in Hours per Week	6.16	4.70	8.69	7.06	−1.30	.20

* Indicates a significant difference at $p \leq 0.01$

Table 6

Physical Activities of CFS-Diagnosed Adolescents and Matched Controls at 24 month Follow-up (N=13)

	CFS		Control			
MAQ Activity Scale	**Mean**	**SD**	**Mean**	**SD**	**t**	**p**
20min hard exercise in the past 14 days	2.85	1.21	3.46	1.27	−1.27	.22
20min light exercise in the past 14 days	3.62	1.26	3.38	1.71	0.39	.70
TV/Video/Computer	2.69	.947	2.69	.630	0.00	.99
Sleep	8.08	1.59	7.08	.838	2.00	.06
Napping	2.04	2.33	.642	.582	2.10	.05
Sedentary Activities	1.92	1.13	1.81	1.47	.225	.82
Total Activity in Hours per Week	4.92	5.17	7.90	5.55	−1.42	.17