Pediatric ME/CFS Research Update

CFSAC June 20, 2018

Peter C. Rowe, M.D.

Professor of Pediatrics

Sunshine Natural Wellbeing Foundation Professor of Chronic Fatigue and Related Disorders

Division of General Pediatrics and Adolescent Medicine

Johns Hopkins University School of Medicine

Disclosure

- I have no relevant financial relationship with the manufacturer of any commercial product or provider of commercial services discussed in this talk.

Pediatric ME/CFS Research Update

Selected highlights of the published literature, 2015-2018:

1. The Impact of Pediatric ME/CFS
2. Cognitive Difficulties in Pediatric ME/CFS
3. Milk Protein Intolerance as a Contributor to Symptoms

frontiers in Pediatrics

REVIEW
published: 19 June 2017
doi: 10.3389/fped.2017.00121

Check for updates

Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer

Peter C. Rowe[1], Rosemary A. Underhill[2], Kenneth J. Friedman[3], Alan Gurwitt[4], Marvin S. Medow[5], Malcolm S. Schwartz[6], Nigel Speight[7], Julian M. Stewart[8], Rosamund Vallings[9] and Katherine S. Rowe[10]*

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Selected highlights of the published literature, 2015-2018:

1. The Impact of Pediatric ME/CFS
2. Cognitive Difficulties in Pediatric ME/CFS
3. Milk Protein Intolerance as a Contributor to Symptoms

Introduction

- Pediatric CFS is a common cause of prolonged school absence *(*Dowsett EG, Colby J. *J CFS 1997; 3:29-42)*
- Several earlier studies have addressed the overall impact of pediatric CFS on health, but most were relatively small.
- Kennedy and colleagues evaluated 25 children with CFS/ME recruited from support groups in the UK. HRQOL was measured using the CHQ. Only 1 child attended regular classes; 12 others attended part-time.
- Compared to healthy controls, CHQ scores for the CFS/ME group were lowest on global health, physical function, and role/social limitations due to physical problems, and lower than published work on children with asthma or diabetes mellitus. [Kennedy G, et al. *Pediatrics* 2010;125;e1324-30]

Winger *et al. Health and Quality of Life Outcomes* (2015) 13:96
DOI 10.1186/s12955-015-0288-3

HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH ARTICLE Open Access

Health related quality of life in adolescents with chronic fatigue syndrome: a cross-sectional study

Anette Winger[1*], Gunnvald Kvarstein[2], Vegard Bruun Wyller[3,4,5], Mirjam Ekstedt[7,8], Dag Sulheim[4,6], Even Fagermoen[3], Milada Cvancarova Småstuen[1] and Sølvi Helseth[1]

Study objective: to examine HRQOL and depressive symptoms in adolescents with CFS and to compare HRQOL and depressive symptoms with a group of healthy adolescents.

Study hypothesis: that adolescents with CFS would report lower HRQOL and have a higher degree of depressive symptoms.

Methods

Setting: national CFS referral center in Oslo, Norway

Recruitment: pediatric departments in Norwegian hospitals and primary care practitioners were invited to refer adolescents with CFS to the NorCAPITAL study

Design: cross-sectional study of adolescents 12-18 years with CFS, recruited over 2 years.

Healthy controls recruited from local schools.

Methods: CFS eligibility

Broad definition of CFS, i.e., fatigue lasting ≥ 3 months, plus functional disability resulting from fatigue to a degree that prevented normal school attendance

No other disease that would explain fatigue

No chronic use of medications that would interfere with other study measurements

Excluded if supine HR < 50 bpm, BP < 85 mm Hg

Methods: measures

Peds QL, a brief, reliable, valid, 23-item assessment of HRQOL

- Items scored 0 (never a problem) to 5 (a lot of a problem)
- Total score 0 to 100 (higher scores = better HRQOL).
- Subscale domains include:

Physical, School, Social, Emotional, Psychosocial

Mood and Feelings Questionnaire

- 33 items, scored 0-2, range 0-66;
- scores ≥ 20 suggestive of depression

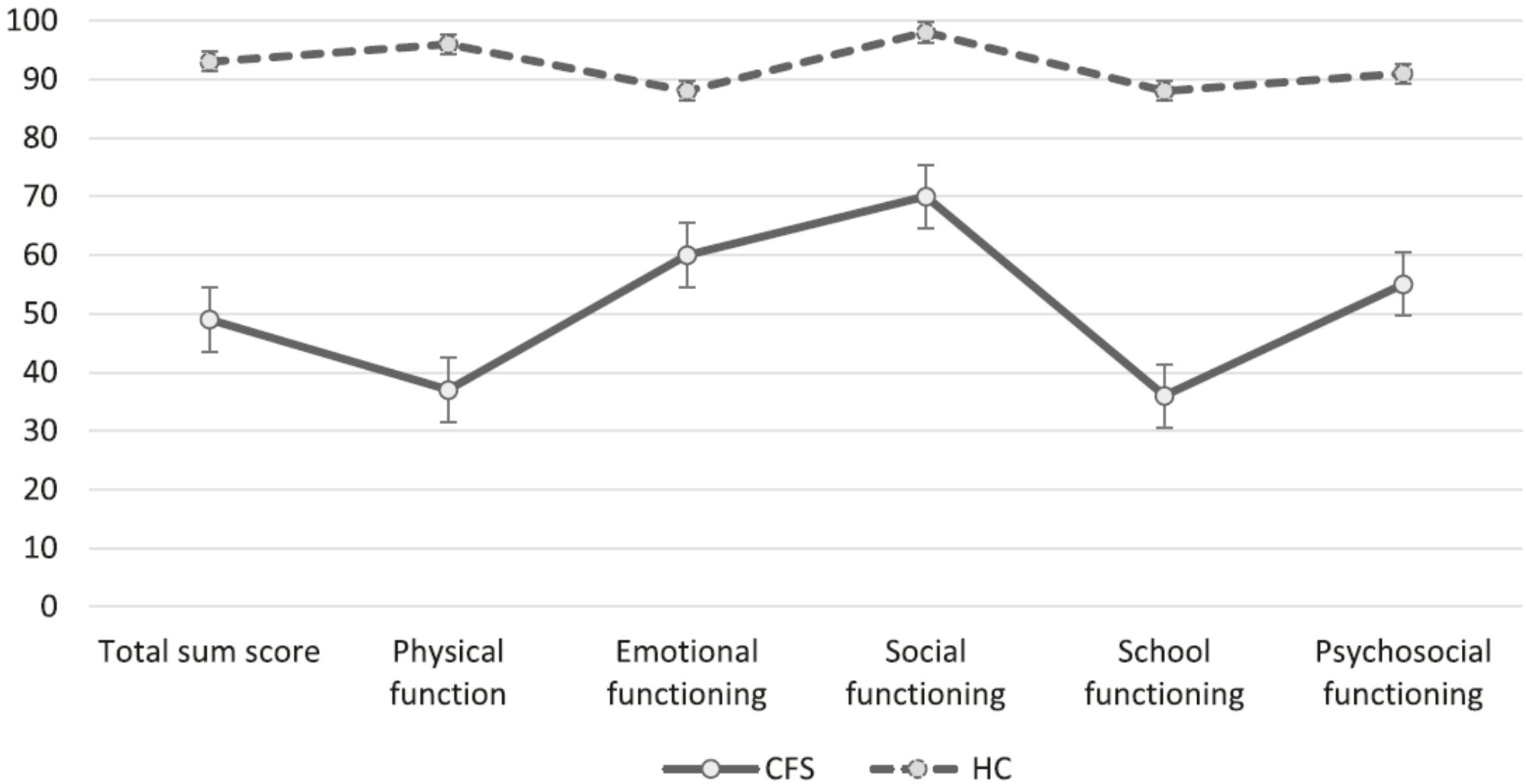
Results:

Variable	CFS N=120	Healthy N=39
Age	15.4 (1.6)	15.2 (1.6)
Female	72%	72%
Disease duration	21.4 (15.2)*	NA
Met Fukuda criteria	74%	NA
School absence %	30	7
MFQ ≥ 20	39%	8%

* Only 2 with illness duration 3-6 months; all others > 6 months

Results:

Variable	CFS N=120	Healthy N=39
Total Peds QL	49 (13)	93 (8)
Physical	37 (17)	96 (8)
Emotional	60 (18)	88 (14)
Social	70 (15)	98 (4)
School	36 (19)	88 (14)
Psychosocial	57 (15)	91 (10)



All comparisons P < 0.001

Results

- Healthy control Peds QL scores in this study were similar to healthy controls in other Norwegian studies
- Girls with CFS had 5 point lower total QOL scores than boys
- There was an 8 times greater risk of depressive symptoms in CFS than HC
- Higher levels of depressive symptoms were inversely associated with higher levels of HRQOL in both CFS and HC
- The lower HRQOL was explained by the illness and not by depressive symptoms

Conclusions

- This large sample of adolescents with CFS confirms previous findings from smaller studies
- CFS is a seriously disabling condition that has a strong impact on HRQOL
- HRQOL was “poorer than we expected”

Discussion

- Limitations include the selection bias, as only those able to travel to Oslo were included, and the results cannot be extrapolated to the most seriously affected with CFS
- Relatively high proportion with depressive symptoms might be due to their lower cut-off value on the MFQ
- Further analysis warranted to explore whether those meeting the Fukuda CFS criteria and the 26% who did not differed on the MFQ or the PedsQL scores
- Other studies now confirm similar Peds QL scores

Comparisons

Variable	Sulheim N=120	Knight* N=42
Total Peds QL	49 (13)	49 (15)
Physical	37 (17)	42 (23)
Emotional	60 (18)	57 (21)
Social	70 (15)	66 (18)
School	36 (19)	31 (17)
Psychosocial	57 (15)	51 (14)

Knight SJ, et al. Measuring quality of life and fatigue in adolescents with chronic fatigue syndrome: estimates of feasibility, internal consistency and parent adolescent agreement of the Peds QL. Fatigue: Biomedicine, Health & Behavior 2015;3: 220-234

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2. Cognitive Difficulties in Pediatric ME/CFS
3. Milk Protein Intolerance as a Contributor to Symptoms

Introduction: From the IOM report, 2015

In study and clinic samples of those with pediatric ME/CFS not selected on the basis of greater difficulty with cognitive tasks, results of baseline neuropsychological testing are similar to those for healthy controls. Abnormalities emerge when participants are selected on the basis of increased difficulty with memory and concentration and when more complex challenges are employed, most notably those combining orthostatic and cognitive stresses

(Haig-Ferguson et al., 2009; Kawatani et al., 2011; Ocon et al., 2012; Stewart et al., 2012; Tomoda et al., 2007; van de Putte et al., 2008).

Introduction:

Studies of cognitive function in pediatric CFS have reported impairment in:

- Attention
- Immediate recall
- Auditory memory
- Spatial working memory
- Motor skills
- Interference control

But, most studies have relatively small samples (N=19-34)

Original article

OPEN ACCESS

Cognitive dysfunction in adolescents with chronic fatigue: a cross-sectional study

Dag Sulheim,[1,2] Even Fagermoen,[3,4] Øyvind Stople Sivertsen,[5] Anette Winger,[6] Vegard Bruun Wyller,[1,7,8] Merete Glenne Øie[9,10]

Arch Dis Child 2015; **100**: 838-844

Study aims:

1°: to characterize cognitive function in a large group of adolescents with CFS and healthy controls
2°: to explore the impact of anxiety traits, depression symptoms, and sleep problems on cognitive function.

Methods:

Design/Patients: From the same NorCAPITAL project

Measures:

Karolinska Sleep Questionnaire

Mood and Feelings Questionnaire,

Behavior Rating Inventory of Executive Function (BRIEF) (completed by parents)

Cognitive battery (40 minutes of testing in clinic)

Table 2 Cognitive tests and assessments

Cognitive function	Test name	Test description
Working memory	WISC-IV Digit span forward and backward	Repeat numbers verbatim or in reverse order as stated by the administrator
Processing speed	D-KEFS CWIT Conditions 1 and 2	Name the colours of different bars (Condition 1) and read written colour names aloud in that colour (Condition 2).
Cognitive inhibition	D-KEFS CWIT Condition 3	Read aloud the colour of the names of colours printed in a different colour
Cognitive flexibility	D-KEFS CWIT Condition 4	Switch between reading colour words and naming dissonant ink colours
Verbal learning	HVLT-R Total recall	The administrator reads 12 words aloud. The examinee repeats as many words as possible in three trials
Verbal delayed memory	HVLT-R Delayed recall	Examinee recalls words after a 20 min delay
Everyday executive function	BRIEF Global executive composite	Parents score 86 statements regarding the daily executive functioning of their child

Cognitive measure	Mean values (SD)			Chronic fatigue group versus healthy controls	
	Chronic fatigue group N=120	CFS (CDC) subgroup N=88	Healthy controls N=39	Difference (95% CI)	p Value
Processing speed					
CWIT condition 1+2 (s)	30.9 (6.3)	31.1 (6.5)	27.5 (5.1)	3.3 (1.1 to 5.5)	0.003
Executive function					
Working memory (sum score)	14.1 (3.4)	13.7 (3.2)	16.5 (3.8)	−2.4 (−3.7 to −1.1)	<0.001
CWIT cognitive inhibition (s)	59.7 (15.2)	60.2 (15.9)	53.5 (14.0)	6.2 (0.8 to 11.7)	0.025
CWIT cognitive inhibition (errors)	2.0 (2.0)	2.0 (2.1)	1.6 (1.8)	0.4 (−0.4 to 1.1)	0.349
CWIT cognitive flexibility (s)	67.2 (15.2)	66.1 (14.1)	62.4 (13.8)	4.8 (−0.8 to 10.4)	0.092
Verbal learning					
HVLT-R total recall (sum score)	27.2 (4.1)	27.3 (3.8)	28.9 (3.7)	−1.7 (−3.2 to −0.3)	0.022
Verbal memory					
HVLT-R delayed recall (sum score)	9.4 (2.1)	9.5 (2.1)	10.1 (1.7)	−0.6 (−1.4 to 0.1)	0.119
BRIEF† GEC	55.1 (9.9)	55.9 (10.1)	43.8 (6.8)	11.2 (8.2 to 14.3)	<0.001

Conclusions

- Adolescents with CF/CFS perform worse than HC on measures of processing speed, working memory, verbal learning, and cognitive inhibition response time
- When controlled for in statistical analyses, sleep problems, depressive symptoms, and anxiety traits do not change the findings
- The subgroup that met Fukuda criteria for CFS did not differ from those meeting the broader definition of chronic fatigue on the cognitive measures.

Discussion

- Unlike earlier studies, this study had the sample size and statistical power to identify clinically important and statistically significant differences between those with CFS and the healthy adolescents.
- The authors speculate that the test conditions might have underestimated cognitive problems in CFS due to the quiet test environment
- Repeated tests, longer tests, tests the day after exertion, or in association with orthostatic challenge all have the potential to accentuate differences between groups.

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Introduction

Allergies and food sensitivities are described with increased frequency among those with CFS.

Most studies of allergy in CFS describe IgE-mediated allergic reactions evaluated using prick skin testing or RAST testing

Little work thus far has focused on delayed or non-IgE mediated reactions in CFS.

In the clinical care of those with CFS, we had informally noted an apparent increased proportion of individuals with signs and symptoms of a delayed reaction to milk protein.

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Cow's milk protein intolerance in adolescents and young adults with chronic fatigue syndrome

Peter C. Rowe (prowe@jhmi.edu)[1], Colleen L. Marden[1], Samantha E. Jasion[1], Erica M. Cranston[1,2], Marissa A. K. Flaherty[1,2], Kevin J. Kelly[3]

Study objective: to examine the prevalence, clinical features, and influence on illness severity of cow's milk protein intolerance in adolescents and young adults with CFS

Methods

Setting: tertiary care CFS referral clinic

Design: comparative study of adolescents and young adults with CFS participating in a 2 year cohort study. All subjects were evaluated, treated, and followed for 2 years.

Eligibility:

- age 10-23 years
- meeting Fukuda criteria
- consecutive subjects referred from 2008-12

Study procedures:

Structured history and physical examination

Questionnaires to measure HRQOL at baseline and every 6 months, including:

- Peds QL

- Peds QL Multidimensional Fatigue Scale (MFS)

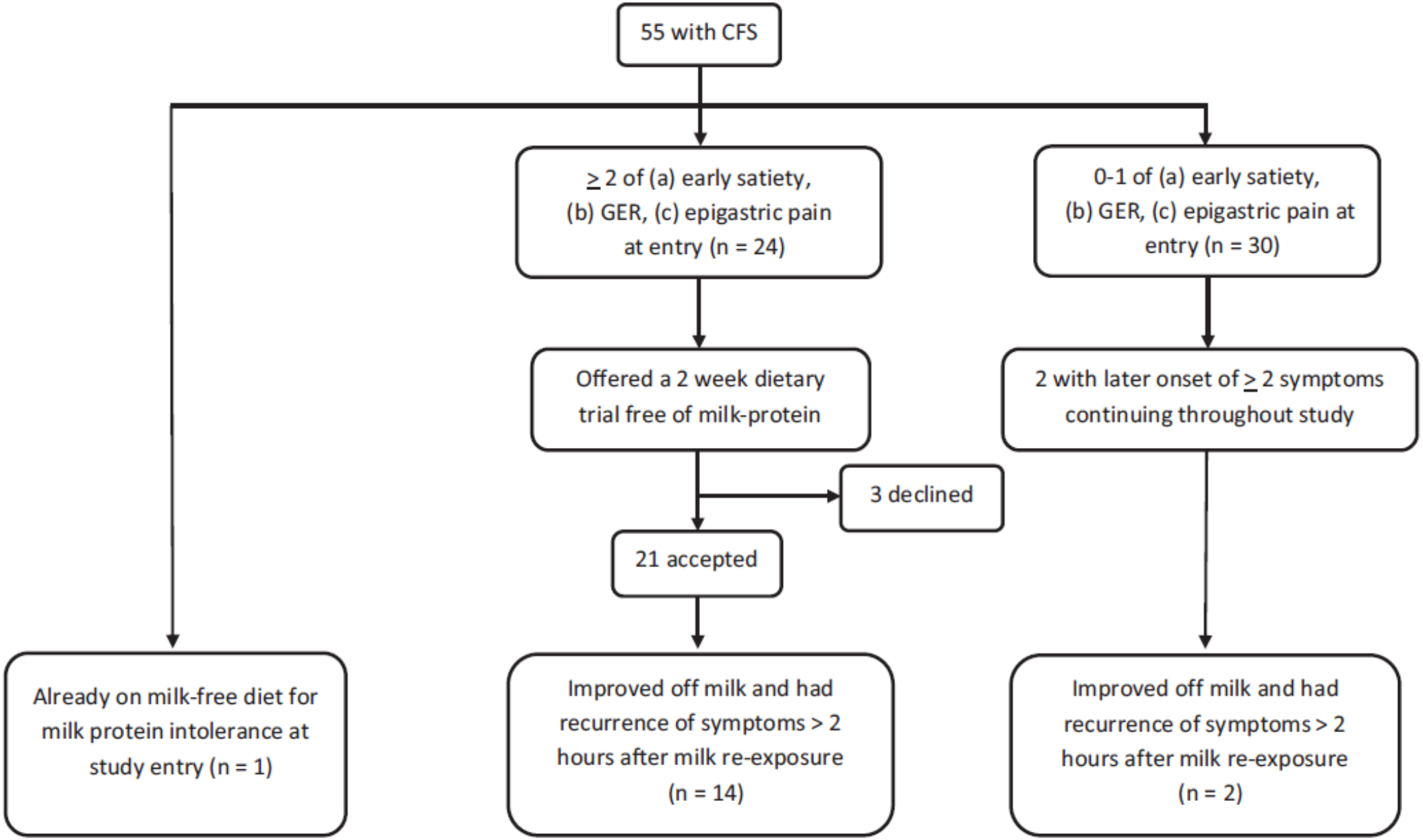
- Functional Disability Inventory FDI

All subjects treated with multi-modal therapy

Those with suspected milk protein intolerance removed milk from their diets

Methods: study definition of suspected milk protein intolerance

1. at least 2 of 3 of the following symptoms:
    a. gastroesophageal reflux (GER)
    b. early satiety
    c. epigastric or abdominal pain
2. improvement in upper GI symptoms on a rigid milk protein elimination diet
3. at least two recurrences of upper GI symptoms following re-exposure to cow's milk protein, and
4. no evidence of immediate/anaphylactic reactions to milk protein


55 with CFS
≥ 2 of (a) early satiety, (b) GER, (c) epigastric pain at entry (n = 24)
0-1 of (a) early satiety, (b) GER, (c) epigastric pain at entry (n = 30)
Offered a 2 week dietary trial free of milk-protein
2 with later onset of ≥ 2 symptoms continuing throughout study
3 declined
21 accepted
Already on milk-free diet for milk protein intolerance at study entry (n = 1)
Improved off milk and had recurrence of symptoms > 2 hours after milk re-exposure (n = 14)
Improved off milk and had recurrence of symptoms > 2 hours after milk re-exposure (n = 2)

Demographic comparisons

	MPI N=17	Not MPI N=38	P
Age, mean (SD)	16.8 (2.3)	16.3 (2.0)	.44
Age at onset of CFS	13.8 (1.9)	13.1 (3.2)	.26
Female	100%	76%	<.05
Type of onset of CFS			<.05
Gradual	3	19	
Abrupt	14	19	

History & Symptom Differences at Study Entry

Feature	MPI	Non-MPI	P
↑ emesis in infancy	47%	13%	<.01
Colic in infancy	35%	18%	.28
Early satiety	69%	26%	<.01
Epigastric pain	75%	26%	<.01
GER	69%	29%	<.01
Aphthous ulcers	56%	8%	<.001

Table 4 Changes in HRQOL from 0 to six months*

HRQOL measures	Milk sensitive (N = 14)	Milk tolerant (N = 38)	p
Peds QL, zero month	47.4 (11.5)	57.9 (15.2)	0.01
Peds QL, six month	65.0 (15.9)	70.1 (18.2)	0.34
MFS, zero month	26.1 (13.1)	44.1 (16.5)	<0.001
MFS, six month	46.2 (17.4)	56.0 (20.1)	0.10
FDI, zero month	25.8 (9.4)	19.0 (10.2)	<0.05
FDI, six month	16.3 (9.5)	13.2 (9.7)	0.32

HRQOL = health-related quality of life.

Conclusions

- Among adolescents and young adults with CFS, 31% with CFS have milk protein intolerance (95% CI, 19-43%)
- 59% with milk protein intolerance were previously unaware that milk was a problem for them
- Those with milk protein intolerance had significantly worse HRQOL at baseline, but not at 6 months (after institution of a milk-free diet).
- Milk protein intolerance is a common but treatable problem in those with CFS

Discussion

Limitations include

- tertiary care setting creates a potential for referral bias
- Absence of skin and RAST testing to exclude IgE-mediated reactions
- Double-blind, placebo-controlled oral food challenges would be the gold standard to confirm the responses to milk protein exposure and evaluate the mechanism

ACKNOWLEDGEMENTS

- Grants from NIAID, DoD, CFIDS Association of America/SMCI
- Sunshine Natural Wellbeing Foundation (endowed Chair)
- Research Coordinator Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma)
- Many families and patients:
  - Special thanks to the following:
    Barnes, Berger, Boies, Bowen, Caldwell, Cornell, Ellen, Kelly, Kiely, Lauver, McFerron, Newbrand, Scheidlinger, Smith, Steffensmeier, and Vogel families.