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Health-related quality of life in adolescents with CFS/ME, a cross-sectional population based Norwegian study.

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Abstract

Purpose The primary aim was to measure health related quality of life (HRQoL) in a Norwegian cohort of adolescents with Chronic Fatigue Syndrome (CFS/ME). A secondary aim was to identify factors initial to diagnosis, at time of diagnosis and at follow-up that were associated with HRQoL.

Methods In this cross-sectional population-based study, HRQoL was measured by PedsQL Generic Core scale (PedsQL4.0) in 63 adolescents with CFS/ME. In addition, fatigue was measured by PedsQL Multidimentional Fatigue scale (PedsQL-MFS), depressive symptoms were measured by the Short Mood and Feelings Questionnaire (SMFQ), and disruption in school activities was measured by The De Paul Pediatric Health Questionnaire (DPHQ-N). Data were also collected from patient journals and patient interviews.

Results Age at diagnosis was 15 (2) years (mean (SD)), and four out of five participants were female. Time from diagnosis to reply was 39 (22) months. Adolescents with CFS/ME reported PedsQL4.0 score 50 (17), and boys reported a better score than girls (64 vs 47, CI (-27;-6)). There were positive associations between overall HRQoL and follow-up by school teacher, school attendance or participation in leisure activities. There were negative associations between overall HRQoL and delayed school progression, having been to rehabilitation stay and depressive symptoms.

Conclusion HRQoL in adolescents diagnosed with CFS/ME was low compared to healthy adolescents. The associations between HRQoL, healthcare provided, teacher follow-up, school attendance and participation in leisure activity may provide information of value when developing refined strategies for follow-up of adolescents with CFS/ME. Possible causal relationships must however be explored in future longitudinal studies.

Declarations

Ethics approval and consent to participate: All procedures performed were in accordance with the ethical standards of the national research committee (The Regional Ethical Comittee for medical and health profession research in Norway, REK 2017/749). Informed consent was obtained from all individual participants included in the study.

Consent for publication: Informed consent obtained from all individual participants included consent for publication of anonymized data.

Avaliability of data and materials: The dataset generated and analysed during the current study is not public available due to ethical standards for treatment of patientdata.

Competing interests: The authors declare that there are no competing interest.

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Authors`contribution: WAS collected, analyzed and interpreted the patient data. TBR supervised the project, analyses and interpretation of data. VH supervised the project, analyses and interpretation of data. IBH facilitated and superviced datacollection from Oslo University Hospital. CS superviced the project and collected data from journals. HE collected data from journals. All authors read and approved the final manuscript.

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Introduction

Chronic fatigue syndrome (CFS) is characterized by overwhelming and severe disabling fatigue, and loss of physical and mental endurance [1]. The condition is also cited as Myalgic Encephalomyelitis (ME) to conseptualise a specific neuroimmunological condition [2]. A main characteristic of the disease is post exertional malaise (PEM). Other symptoms include orthostatic intolerance and other signs of autonomic dysfunctions, cognitive impairment, unrefreshing sleep, sore throat, headache, dizziness, heat and cold intolerance, muscular and abdominal pain, nausea, vomiting and mood disturbances [3-6]. CFS/ME occurs more frequently in the age groups 11-19 and 30-39, and is 3-4 times more common in girls than boys. In Norway 0,1-1,0 % adolescents are affected [1, 7, 8]. Adolescents CFS/ME starts with an acute or gradual, infectious or non - infectious onset. Establishment of the diagnosis is frequently delayed, with the period from start of symptoms to diagnosis varying from 5 to 17 months [3, 9]. The CFS/ME disease course is often measured in years, and it is common to experience recurring improvement and relapses [1]. Among adolescents, CFS/ME is the most common cause of long term absence from school [4, 10-13].

Previous studies has shown that CFS/ME severely impact health-related quality of life (HRQoL) [1]. Typically, adolescents with CFS/ME report lower HRQoL than adolescents diagnosed with other chronic health conditions like ADHD, cancer or cerebral palsy [14-17]. In an earlier Norwegian study of HRQoL among adolescents with CFS/ME, patients scored 49 whereas healthy controls scored 93 on a 0-100 generic HRQoL scale based on PedsQL 4.0 [16].

CFS/ME patients require follow-up by primary health care and by schools. Because of the complexity and severity of the illness, specialized care from personnel experienced with CFS/ME is often warranted, but frequently not available [1]. Despite substantial efforts from health care and schools, we are still in lack of knowledge about effective strategies to improve disease outcome and HRQoL. The main aim of this study was to measure HRQoL in adolescents with CFS/ME, and motivated by the need for more knowledge to indentify effective strategies a secondary aim was to identify factors at diagnosis and follow-up

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Methods

Study design

A cross-sectional, population-based follow-up study of HRQoL in adolescents diagnosed with CFS/ME.

Study population

CFS/ME adolescent patients

Adolescents diagnosed with CFS/ME at St. Olavs or Oslo University Hospitals in Norway with age 12-18 at the time of diagnosis were invited by mail to participate. Participants were asked to fill out a questionnaire and to attend an interview. Invitation was sent between August 2017 and January 2018, and time since diagnosis varied from 1-118 months. Of 168 invited, 86 (51,2%) agreed to participate, and 63 (37,5%) sent completed questionnaires in return. All participants were diagnosed with G 93.3 CFS/ME according to Jason diagnostic criteria [5], and the diagnosis was verified by an independent evaluation of patient journals. Exclusion criteriae were not being able to read Norwegian or reply to questionnaires or participate in interview. No one was excluded according to these criteria. Data collection from questionnaires, interviews and journals finished in June 2018.

Measures

PedsQL Generic Core scale

The Norwegian version of Pediatric Quality of Life Generic Core scale (PedsQL4.0) was used to measure HRQoL. PedsQL4.0 is a 23-item generic questionnaire developed to measure HRQoL in both healthy and acute or chronic ill children and adolescents [18]. A young adult version was used for ages 18 -22. The PedsQL4.0 provides a generic sum score and subscale scores; Physical functioning (8 items) and Psychosocial functioning as total of: Emotional functioning (5 items), Social functioning (5 items) and School functioning (5 items). Participants were asked to rate each item during the last month on a Likert scale from 0 (never a problem) to 4 (almost always a problem). The items were reversely scored and linearly transformed on a scale ranging from 0-100 (0=100, 1=75, 2=50, 3=25, 4 = 0). Higher scores indicate better HRQoL [18, 19].

PedsQL Multidimensional Fatigue scale

The PedsQL Multidimensional Fatigue scale (PedsQL-MFS) was used to measure fatigue severity [20]. PedsQL-MFS is a generic scale with 18 items, and with subscale scores for three domains; general fatigue (6 items), fatigue related to sleep/rest (6 items) and cognitive fatigue (6 items). The response scale is the same as for PedsQL4.0. Higher scores indicate less fatigue.

Short Mood and Feelings Questionnaire

The Short Mood and Feelings Questionnaire (SMFQ) is a self-report-form measuring depressive symptoms in children and adolescents. Thirteen items collectively describe depressive symptoms, covering for symptoms specific for major depression in DSM-IV [21, 22]. The SMFQ items have three reply options; “True”=2, “Sometimes”=1, “Not true”=0 referring to the last two weeks [23, 24] with a sum score from 0-26. A sum score of 11 or higher indicates depressive symptoms which possibly require treatment.

De Paul Pediatric Health Questionnaire – Norwegian version

De Paul Pediatric Health Questionnaire (DPHQ-N) for children and adolescents was translated to Norwegian by The Norwegian National Advisory Unit on CFS/ME. Translation and re-translation was performed according to EORTC [25], re-translated by one and accepted by original author.This is a self-report questionnaire for children ages 10-17 in three parts; 1) demographic data, 2) a list of CFS/ME-related symptoms from the current CFS/ME criteria according to Jason, with symptoms rated in frequency (0=never, 1=almost never, 2= half the time, 3 = almost always, 4 = always), and in severity (0 = no problem, 1= small problem, 2 = moderate problem, 3 = big problem, 4 = very big problem), and 3) experience of disruption in school activities or performance due to fatigue or cognitive difficulties [5, 26-28].

Data from patient journals and additional interviews with patients

Data from patient journals was collected using a semi-structured guide developed by the research group. One pediatrician from each hospital and one psychiatrist from St. Olavs hospital used the same guide when collecting data from diagnostic evaluation in patient journals. Supplementary data from follow-up in primary health care and schools were collected directly from the participants via a six to seven minute telephone interview using an interviewguide with the same questions for all participants.

Statistical analyses

Continous data (age, duration of fatigue, HRQoL, fatigue severity and depressive symptom scores) are presented as mean (SD), Median (Q1-Q3), and 95% confidence intervals (CI) where appropriate. Correlations between HRQoL, fatigue severity and depressive symptoms are presented as Pearson`s correlation coefficients. Categorical data (gender, recovered/not recovered, delayed school progression and participation in leisure activities) are presented as numbers and percentages.

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A wide spectrum of factors related to the period initial to diagnostic evaluation, the period of diagnostic evaluation and the subsequent follow-up were examined in relation to HRQoL (PedsQL 4.0). For these dichotomous factors two-sided independent sample t-test were used to assess differences. Complete results are presented in Supplemental Tables 1-6, while statistically significant variables (5% level) are presented in Table 3. Generic HRQoL scores are presented as mean (SD) plus 95% confidence intervals (CI) for differences. For dimension scores only difference and CI is reported. It was not corrected for multiple testing in these analyses.

Table 3: Selected factors present initially to, during or after diagnosis related to HRQoL as determined by PedsQL generic scale score and subscale scores.

		Factors present							
	N	Yes	No	Overall HRQoL	Physical functioning	Emotional functioning	Social functioning	School functioning	Psychosocial functioning
	(Yes/No)	Mean (SD)	Mean (SD)	*Diff (CI)*	*Diff (CI)*	*Diff (CI)*	*Diff (CI)*	*Diff (CI)*	*Diff (CI)*
Factors initial to diagnosis									
School attendance initial to diagnosis < 50%	39/9	50 (18)	61 (21)	Ns	Ns	Ns	Ns	22 *(-39; -6)*	13 *(-26; -1)*
Using medications initial to diagnosis	17/30	45 (20)	56 (17)	Ns	Ns	Ns	13 *(-22; -3)*	Ns	10 *(-20; -1)*
Factors during diagnosis									
Occupational therapist engaged in diagnostic evaluation	31/18	53 (18)	49 (20)	Ns	Ns	-12 *(2 – 24)*	Ns	Ns	Ns
Physical therapist engaged in diagnostic evaluation	34/15	54 (17)	47 (22)	Ns	Ns	-14 *(3 – 26)*	Ns	Ns	Ns
Nutritionist engaged in diagnostic evaluation	5/44	61 (8)	51 (19)	Ns	Ns	-19 *(1 – 37)*	Ns	Ns	Ns
Factors at follow-up									
Follow-up from school teacher	42/7	55 (17)	41 (17)	-14 *(1 – 29)*	Ns	-19 *(4 – 35)*	Ns	Ns	-15 *(2 – 28)*
Follow-up from physical therapist	27/22	50 (17)	57 (19)	Ns	Ns	Ns	Ns	14 (-27; -1)	Ns
Been to rehabilitation stay	14/35	43 (15)	57 (17)	14 *(-24; -3)*	Ns	23 *(-34; -11)*	14 *(-22; -6)*	Ns	14 *(-24; -5)*
Participation in leisure activity	21/41	59 (17)	46 (16)	-13 *(4 –22)*	-18 *(6-31)*	Ns	-13 *(5 – 21)*	-15 *(4 – 26)*	-10 *(2 – 19)*
Delayed school progression	37/12	49 (16)	65 (18)	16 *(-27; -4)*	18 *(-35; -2)*	Ns	14 *(-23; -6)*	21 *(-35; -7)*	14 *(-24; -4)*
SMFQ Sum score 11 or higher (cut of, depression symptoms)	17/46	37 (12)	55 (16)	18 *(-27; -10)*	14 *(-28; -1)*	28 *(-37; -20)*	21 *(-28; -14)*	13 *(-25; -1)*	21 *(-29; -14)*

Two-sided Independent Samples T-test. Overall HRQoL reported as mean (SD), and differences in overall HRQoL and subscale scores reported with 95% Confidence Interval or Ns if not statistically significant

Independent variables significantly associated with HRQoL were further examined as predictor variables in a multiple linear regression model, controlling for gender. The model included all participants with replies to dichotomous variables. Dependent variable was tested for normal distribution and outliers. Predictor variables were tested for multicollinearity. Unstandardized Beta coefficients with confidence intervals (CI), Adjusted R^2, model significance (ANOVA), F-values, β-values and p-values for each predictor were reported. A difference of 10 in primary outcome (HRQoL) was predetermined as clinical relevant.

Among 63 participants, 48 answered all questions from follow-up. All statistical analyses were performed using SPSS version 23.

Ethics

The study was approved by The Regional Ethical Comittee for medical and health profession research in Norway (REK 2017/749). All participants signed an informed conscent, and the study was performed according to the declaration of Helsinki . The participants were offered a consultation to explore the need for further health care.

Results

Study population characteristics

63 adolescents with CFS/ME were included in the study, with a female:male ratio of 4,2:1 and mean age18 years (Table 1). The number of participants from Oslo University Hospital and from St. Olavs Hospital was 41 and 22, respectively. The distributions of gender and age were not significantly different between the two hospitals (data not shown). Duration of fatigue initial to diagnostic evaluation was 15 months (10-33) (median (Q1-Q3)), and at the time of study enrollment 52 months (36-67) (median (Q1-Q3)). 37 (76%) of the adolescents had a delayed school progression defined as not having completed all compulsory subjects in school at their level. Furthermore, a majority of the adolescents (66%) reported no participation in leisure activities. Four adolescents had recovered after 6, 12 and 36 months, respectively (one unknown) (Table 2).

Generic PedsQL4.0 score for all participants in this study was 50 (17) (mean (SD)) (Table 1). The subscale scores were lowest for the domain school functioning and highest for social functioning. Overall PedsQL-MFS score was 36 (19). The domain general fatigue had the lowest score. There was a strong correlation between generic PedsQL4.0 and overall PedsQL-MFS scores (Pearson`s r =.861, p<.001). The SMFQ sum score was 7 (5) (mean (SD)), whereas 27 % of the participants scored 11 or higher, suggesting a possible treatment-requiring depression. The correlation between SMFQ and generic PedsQL4.0 score showed moderate to strong negative correlation (r = -.544, p < .001).

There were no correlation between duration of fatigue at time of study enrolment and overall score of HRQoL, fatigue level or depressive symptoms (Fig. 1). Adolescents recovered from CFS/ME reported higher HRQoL than those who had not recovered (83 vs. 48, p <.001) (Table 2).

Table 1. Patient characteristics and overall results from PedsQL 4.0, PedsQL-MFS and SMFQ.

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	N	%	Mean (SD)	Median (Q1-Q3)
Gender (Female / Male / Undetermined)	50/12/1	79/19/2		
Age at time of enrolment	63		18 (2)	
Duration of fatigue initial to diagnostic evaluation (months) **a)**	48			15 (10-33)
Duration of fatigue at time of enrolment (months)	59			52 (36-67)
Recovered from CFS/ME (yes/no)	4/58	6/94		
Delayed school progression (yes/no)	37/12	76/24		
Participation in leisure activities (yes/no)	21/41	34/66		
PedsQL4.0:				
Overall HRQoL score **(b)(c)**	63		50 (17)	
Sub scale scores: Social functioning	63		67 (16)	
Emotional functioning	63		56 (20)	
Physical functioning	63		42 (25)	
School functioning	58		41 (21)	
Psychosocial functioning	63		55 (16)	
PedsQL-MFS:				
Overall Fatigue score **(b)**	62		36 (19)	
Sub scale scores : Cognitive fatigue	62		41 (25)	
Fatigue related to sleep/rest	62		36 (19)	
General fatigue	62		32 (23)	
SMFQ (13 items) Sum score **(c)**	63		7 (5)	
Score <11 / 11 or higher	46/17	73/27		

a)Not available data from 15 participants, b) Pearson sc or $relation = .861, p < .001 between \geq \neq ric PedsQL 4.0$ and $overall PedsQL\text{-}MFS, c) Pearson$s correlation = -.544, p<.001between generic PedsQL 4.0 and SMFQ sum score.

HRQoL, fatigue and depressive symptoms versus study population characteristics

There was a significant gender difference in generic PedsQL4.0 score where girls scored significantly lower than boys (47 vs 64, p=.003). In subscale scores, girls scored lower than boys for all dimensions (data not shown). There was also a significant gender difference in PedsQL-MFS score where girls scored lower than boys, and a similar result was found in the SMFQ score (Table 2).

Fig. 1. HRQoL-, Fatigue- and SMFQ- scores in relation to Duration of fatigue, n=59. For PedsQL4.0 and PedsQL-MFS high score is better, for SMFQ low score is better.

School attendance, delayed school progression or participation in leisure activities were not statistically significant associated with SMFQ scores (Table 2). However, both generic PedsQL4.0 and overall PedsQL-MFS scores differed between adolescents having or not having participated in leisure activities or delayed school progression, with higher scores for the adolescents who were able to participate in leisure activities and adolescents with a normal school progression. School attendance initial to diagnostic evaluation showed a similar trend when setting the cut-off at 50% school attendance, although not attaining statistical significance.

Table 2. PedsQL generic and multidimensional fatigue scales and SMFQ sum score related to patient characteristics.

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		PedsQL Generic scale (23 items)			*PedsQL Multidimentional Fatigue scale (18 items)*			*SMFQ sum score (13 items)*		
		N	**Mean (SD)**	**95%CI for diff**	**N**	**Mean (SD)**	**95%CI for diff**	**N**	**Mean (SD)**	**95%CI for diff**
Gender:	Girls	50	47 (16)	*(-27; -6)*	49	33 (16)	*(-30; -7)*	50	8 (5)	*(2 – 6)*
Boys		12	64 (20)		12	51 (24)		12	4 (3)	
Age:										
<16		10	57 (17)	*(-4 – 20)*	10	46 (13)	*(-2; -24)*	10	6 (3)	*(-4 – 0)*
16+		53	49 (17)		52	34 (20)		53	8 (6)	
Status at response time:										
Not recovered from CFS/ME		58	48 (16)	*(19 – 51)*	57	33 (16)	*(-61; -28)*	58	8 (5)	*(0 – 10)*
Recovered from CFS/ME		4	83 (13)		4	78 (15)		4	3 (4)	
Is your school progression delayed:										
Yes		37	49 (16)	*(-27; -4)*	37	34 (19)	*(-31; -6)*	37	8 (5)	*(-1 – 6)*
No		12	65 (18)		12	52 (21)		12	5 (6)	
School attendance initial to diagnosis:										
<50%		39	50 (18)	*(-25 – 2)*	38	36 (19)	*(-29 – 1)*	39	8 (5)	*(-2 – 6)*
50% or more		9	61 (21)		9	50 (25)		9	6 (5)	
Do you participate in leisure activity:		21	59 (17)	*(4 – 22)*	21	46 (19)	*(5 – 24)*	21	6 (4)	*(-5 – 0)*
Yes		41	46 (16)		40	31 (18)		41	9 (5)	
No										

Two-sided Independent Samples T-test. Difference in N is due to one undetermined which gender, and that participation with questionnaire was higher than participation in interview.

HRQoL versus selected factors initial to diagnosis, by the time of diagnosis or at follow-up

To further explore factors positively or negatively associated with HRQoL, 34 variables collected from patients and patient journals were selected and divided into three groups; *initial to diagnosis, by the time of diagnosis and at follow-up period.* Factors significantly associated with generic PedsQL4.0 or subscale scores are shown in Table 3.

Looking at the possible association between HRQoL and factors being present initial to the diagnose CFS/ME, we found that school attendance < 50% or using medications were associated with lower HRQoL in PedsQL subscales, but not with generic PedsQL4.0.

All adolescents had a physician involved in diagnostic evaluation. Beyond that, there were differences regarding the type of health personell involved. Our analysis show that when either an occupational therapist, a physical therapist or a clinical nutritionist were involved, this was positively assossiated with the PedsQL4.0 subscale emotional functioning, but not with other subscales or generic score.

For the follow-up period, we found four factors associated with HRQoL. Teacher follow-up at school was positively associated with generic PedsQL 4.0 (55 vs 41, CI (0.08 – 29)), and with the subscale scores for emotional and psychosocial functioning. Participation in leisure activity was positively associated with generic PedsQL4.0 (59 vs 46, CI (4 – 22)) and with the subscale scores for physical, social, school and psychosocial functioning. Been to rehabilitation stay was negatively associated with generic PedsQL4.0 (43 vs 57, CI (-24;-3)) and with subscale scores for emotional, social and psychosocial functioning. Delayed school progression was negatively associated with generic PedsQL4.0 (49 vs 65, CI (-27;-4)) and with subscale scores for physical, social, school and psychosocial functioning. We also found that possible clinical significant depression (SMFQ score equal to or greater than 11) was negatively associated with generic HRQoL (CI (-27;-10)) and with all dimensions.

(insert Table 3 approximately here)

Multivariate analysis: HRQoL versus selected factors in a regression model

Multiple linear regression analysis was performed to predict HRQoL based on the four variables from follow-up, identified from bivariate analyses and with the most significant positive or negative association. Dependent variable generic PedsQL 4.0 was normally distributed. 48 participants had responded to all predictor variables. Predictor variables correlated with HRQoL (Pearson`s r > .300 except from follow up from teacher r .290) (Table 4).

Table 4: Multiple Linear regression - predictors to HRQoL in adolescents diagnosed with CFS/ME

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N=48	Beta coefficient	(95%CI)	β	*p*
Constant	50	(34 – 66)		.000
Gender (a)	10	(-1 – 21)	.230	.079
Follow-up from teacher (b)(c)	10	(-3 – 23)	.200	.121
Delayed school progression (d)	-10	(-21 – 1)	-.249	.051
Participation in leisure activity (e)	8	(-2 – 18)	.211	.114
Been to rehabilitation stay (f)	-8	(-18 – 2)	-.212	.104

1. **a)** female =0, male =1), **b)** follow-up from teacher no =0, yes =1, **c)** follow-up from teacher,

correlation coefficient to HRQoL .290 (<.3). **d)** school delay no=0, yes =, 1, **e)** participate in

leisure activity no=0, yes =1, **f) b**een to rehabilitation stay no=0, yes =1.

Model summary: Adj R² .319, F Change 5.399, Sig (ANOVA) p = .001.

The results from the multiple regression analysis confirmed the assossiations from bivariate analyses. The regression model was significant at the level p = .001, explaining 32 % of the variance. Follow-up from teacher and participation in leisure activities were positively associated with HRQoL, while negative associations came from delayed school progression, and having been to a rehabilitation stay. The regression coefficient for delayed school progression was -10 (β -.249), and for follow-up from school teacher 10 (β .200), indicating clinical relevance. We also looked at the multiple linear regression analyses without the four participants who reported recovery. The predictors was distributed similarly in the regression model, and with similar results.

Based on the difference in bivariate analyses between participants with and without depressive symptoms, we looked at the multiple regression analysis if excluding the group of ten participants with depressive symptoms. With n=38 participants the distribution of the predictors was still the same, but with regression coefficient for delayed school progression at -14 (β -.378), and follow-up from teacher 10 (β .162). Participation in leisure activity, β .260, and been to rehabilitation stay, β -.143. Hence the model explained 23 % of the variance (p = .019).

Discussion

This cross-sectional study of HRQoL in 63 Norwegian adolescents with CFS/ME confirmed findings from previous studies in patients with CFS/ME. Interestingly the study also identified new and possibly important factors associated with HRQoL in this patient group, especially regarding positive associations from teacher follow-up and participation in leisure activities, but also regarding occupational therapist, physical therapist and clinical nutritionist engaged in diagnostic evaluation. On the other hand, school absence higher than 50% initial to diagnostic evaluation, delayed school progression and having been to a rehabilitation stay were negatively associated with HRQoL.

A strength to our study is that we explore the relationship between HRQoL and a large number of factors especially in the period after diagnosis, and that the mean duration of fatigue was close to four years giving a long disease period. This is relevant since long duration is one of the hallmarks of the disease. The diagnosis was verified according to the Jason criteria, and the diagnostic evaluation and follow-up at the two hospitalts participating in this study are relatively uniform. Limitations to our study is that the sample size was small, giving a possibility to miss significant associations between HRQoL and factors initial to or by the time of diagnosis and in follow-up. A further limitation is that the CFS/ME patients often have reduced cognitive function, and it may be difficult to remember exactly what occurred early in the disease course. Importantly, given our cross-sectional study design, it is also impossible to conclude definitely on which factors have a causal significance to HRQoL.

HRQoL in adolescents living with CFS/ME was low compared to healthy adolescents in other studies who typically score 83 or higher, and adolescents with other chronic diseases with scores from 66 to 77 [14-17]. Importantly, girls scored lower than boys in both generic and dimentional PedsQL4.0 and PedsQL-MFS. Similar results, also regarding gender differences, was earlier found in a Norwegian study from 2015 [16], and internationally [29].

An important finding in our study was that follow-up from school teachers was associated with higher HRQoL, and school delay was associated with lower HRQoL. Maintaining contact with school or encouraging the hope for return to school have also in previous studies shown to be important [30, 31]. To meet responsive and caring teachers, get assistance from sympathetic school counselors, and the possibility to have flexible schedules, might be just as important as follow-up from health care professionals [1]. CFS/ME symptoms and the subsequent reduction in activities, socializing and school delay may lead to anxity, depressive mood and increased tension. The positive association between teacher follow-up and emotional functioning may be associated with prevention of depressive symptoms. The importance of meeting in small groups with peers, and cooperation between health care professionals and schools is earlier also described as helpful [32].

As was the case for teacher and school involvement, participation in leisure activities was associated with higher HRQoL. This is an important finding which perhaps deserve more attention: This may decrease stigmatisation of adolescents with CFS/ME when they chose to participate in leisure activities, even if they don`t manage to participate in obligatoric school activity in line with healthy adolescents. Adolescents with less fatigue are most likely the ones who participate in leisure activities in our study. The significance of participation in leisure activities should neverthless be further studied throughout the course of

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We found no correlation between duration of fatigue at time of enrolment and HRQoL, fatigue severity or depressive symptoms. The duration of fatigue initial to diagnosis and the demanding diagnostic process, lack of medical understanding and lack of positive information given around prognosis, might though provoke anxiety since the adolescents perceive their CFS/ME as being permanent and threatening to their future hopes and dreams [6, 10]. Previous studies emphasize how important it is that professionals involved in the diagnostic evaluation and in follow-up of CFS/ME patients agree about treatment, and that there is close communication between professionals involved [33]. According to Rowe [1]"Management of CFS/ME require careful attention..", and to avoid increased symptoms and relapses, there is a need of a long-term follow-up plan with regularly mapping of symptoms, guidance on activity, and regularly adjustments to symptoms severity or improvement. Our findings support an individualized long-term follow-up plan.

Rehabilitation programmes with exercise, mobilization and body awareness typically delivered from physical therapists, are earlier described as effective in redusing medium and long term fatigue severity in CFS/ME patients [34]. These findings seemingly conflicts with our findings, i.e. that physical therapy or rehabilitation stay are associated with lower HRQoL. We know that CFS/ME patients often experience PEM and relapses after physical as well as cognitive activities. The lack of knowledge and disagreement about strategies to improve HRQoL in these patients might contribute to disruption in important therapeutic alliances with patients and parents, and to distrust in health care personell [33, 35, 36]. Our finding, that having been to a rehabilitation stay have negative association with HRQoL, may indicate a greater need of an individualized follow-up plan. A long term follow-up plan with regular mapping of symptoms as earlier mentioned, could be helpful for health care personnel when planning individualized rehabilitation stays.

According to an earlier finding of no statistical evidence between depressive symptoms and low HRQoL in adolescents with CFS/ME [16], and that there is a lack of depression found in diagnostic evaluation of the patient group, it is tempting to assume that depressive symptoms may develope as result of living with CFS/ME. Adolescents with CFS/ME are not able to do the things they want to, and they suffer from loss, disruption and coping barriers [1, 31, 32, 37]. Living with CFS/ME in adolescense require that the surroundings are aware and supportive in order to give the adolescents a potential to prevent depressive symptoms and gain hopes of an active and productive future [1]. Hence, our results from PedsQL subscore analyses, where follow-up from school teacher, and occupational therapist, physical therapist and nutritionist engaged in diagnostic evaluation were positively associated with emotional functioning, are interesting.

Today we still lack effective treatment of the fatigue in CFS/ME patients, and despite effort from health-services and schools, HRQoL in adolescents with CFS/ME is low (Fig. 2). A focus on strategies to maintain psychosocial aspects, especially in relation to school contact, during diagnostic evaluation and in follow-up might contribute to higher HRQoL. A long-term follow-up plan with regularly mapping of symptoms from early stages of the disease might reveal data with importance to prevent the significant reduction of HRQoL, regarding both physical, social and emotional aspects [1]. Cooperation between schools, primary health care and hospitals in follow-up seems to be most important.

Fig. 2: Factors found with association to HRQoL in adolescents living with CFS/ME.

For patients with chronic health conditions, the goal of health care should be to restore them to the fullest health possible by improving symptom management, treatment adherence, and their ability to cope with the impact of the condition. For this reason, HRQoL may be just as important as biomedical measures when assessing patients with chronic health conditions like CFS/ME. The PedsQL4.0 has evolved from the Worlds Health Organization`s definition of health and is a valid instrument for this purpose [38, 39].

Conclusions

In this study we found that HRQoL in adolescents living with CFS/ME was significantly lower compared to healthy adolescents and adolescents living with other chronic diseases. When exploring factors initial to diagnosis, at the time of diagnosis or in follow-up possibly associated with HRQoL, we found that school attendance, participation in leisure activity and follow-up from school teacher were associated with higher HRQoL. Delayed school progression, having been to a rehabilitation stay and depressive symptoms were associated with lower HRQoL. We also found associations to higher emotional functioning as one dimension of HRQoL, when certain health-care personnel were involved in diagnostic evaluation. Early diagnosis, mapping of symptoms severity and HRQoL, maintaining school contact and early action to prevent depressive symptoms might be important to maintaine or improve HRQoL in this patient group. Limitations to our study design imply that future interventional studies are needed to confirm whether the factors we identified can be used to improve HRQoL in adolescents with CFS/ME.

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Abbreviations

CFS/ME Chronic fatigue syndrome/myalgic encephalomyelitis
PEM Post exertional malaise
HRQoL Health related quality of life
PedsQL Pediatric Quality of Life Inventory
PedsQ4.0 PedsQL Generic Core scale
PedsQL-MFS PedQL Multidimentional Fatigue scale
SMFQ Short Mood and Feelings Questionnaire
DPHQ-N De Paul Pediatric Health Questionnaire –Norwegian version

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