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Subjective and objective cognitive function in adolescent with chronic fatigue following Epstein-Barr virus infection

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ABSTRACT

Objective: Cognitive difficulties are among the most disruptive and disabling problems reported by chronic fatigue syndrome (CFS) sufferers. Acute Epstein-Barr virus (EBV) infection is a trigger of chronic fatigue (CF) and CFS. The aim of this study was to investigate subjectively reported and objectively measured cognitive functioning in fatigued and non-fatigued adolescents six months after EBV infection.

Methods: A total of 195 adolescents (12–19 years) with acute EBV infection were followed prospectively for six months, after which they were grouped as chronically fatigued (CF^+) and non-fatigued (CF^-) cases based on questionnaire score; the CF^+-group was further subgrouped according to CFS diagnosis. A group of 70 healthy controls was also included. Groups were cross-sectionally compared on objective measures of processing speed, executive functions and memory, and subjective cognitive functioning.

Results: There were no group differences regarding objective cognitive measures, but the CF^+-group reported significantly ($p < 0.001$) more cognitive problems (cognitive symptoms sum score = 9.5) compared to the CF^--group (cognitive symptoms sum score = 5.3) and the healthy control group (cognitive symptoms sum score = 6.4). The CFS subgroup rated symptoms scores even higher but did not differ on cognitive performance tests.

Conclusion: Subjective experiences of cognitive difficulties characterize adolescents with CF and CFS six months after acute EBV infection, whereas objective measures of cognitive impairment are inconspicuous.

1. Introduction

Chronic fatigue (CF) is defined as substantial fatigue lasting for more than six months [1]. If the fatigue is unexplained, persistent, pronounced and disabling with a definite onset, and combined with exhaustion even after the slightest physical or mental exertion, the patient may fulfil diagnostic criteria for Chronic Fatigue Syndrome (CFS) [2,3]. Acute infections, such as Epstein-Barr virus (EBV) infection, are a well-known triggers for acute fatigue, CF and CFS [4].

Most CF/CFS research has focused on adults, but the illness also presents in children and adolescents; prevalence has been reported as high as 3% [5]. CF/CFS in children and adolescents is a major cause of long-term school absence and has profound negative impact on social development, educational achievement, future employment and quality of life [6,7]. About half of children and adolescents with CF/CFS are bedbound at some stage, and on average they miss one academic year of schooling [8].

Both self-reported (subjective) cognitive difficulties and objectively measured cognitive difficulties (cognitive tests) have been reported in adults with CF/CFS, but studies have failed to identify a relationship between them [2,9,10]. Cockshell and Mathias (2010) found that adults with CFS reported more cognitive problems compared to healthy controls, but the two groups did not differ on the objective cognitive tests, and subjective and objective measures were not associated with each other [10]. Rasouli and colleagues (2019) found that CFS patients had problems with psychomotor speed and attention measured by objective cognitive tests [2]. Also, the patients reported a high level of subjective cognitive difficulties which were positively associated with fatigue, pain and depression levels, but not with cognitive test results [2]. Another adult CFS study found that subjective ratings of cognitive difficulties were not linked to objective performance improvements following a 12-week graded-activity program incorporating a cognitive training

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component [9].

In children and adolescents, studies are few and results inconsistent. Van de Putte et al. found reduced cognitive inhibition in adolescents with CFS compared to healthy controls [11]; this finding was replicated by Kawatani et al. [12], who also reported reduced cognitive flexibility. Haig-Ferguson and colleagues found reduced verbal learning, but normal processing speed, working memory and verbal memory in an adolescent CFS group [13]. Another study found reduced processing speed, cognitive inhibition, working memory and reduced verbal learning, but normal verbal memory in adolescents with CF/CFS compared to healthy controls [14]. Finally, a study found reduced processing speed, but normal working memory in adolescent CFS sufferers [15]. Associations between subjective symptoms and objective cognitive test results have hardly been investigated in children and adolescents with CF/CFS; an exception is the study of Haig-Ferguson which did not find such associations [13].

One reason for these inconsistencies may be the heterogeneity of underlying disease mechanisms. Studying chronic fatigue following a common precipitating event may conceivably mitigate this problem. Thus, the aim of the current study was to investigate both subjective and objective cognitive functioning in adolescents with CF/CFS following acute EBV-infection (CF^+) compared with recovered adolescents (CF^-) and healthy controls. We hypothesized both more symptoms of subjective cognitive problems and attenuated performance on objective cognitive tests within in the CF^+-group. Furthermore, we hypothesized more attenuated cognitive functioning in the CF^+-subgroup that adhered to diagnostic definitions of CFS.

2. Methods

2.1. Study design and participants

The current study is a substudy of the research project entitled Chronic Fatigue Following Acute Epstein-Barr Virus Infection in Adolescents (CEBA) (Clinical Trial ID: NCT02335437). The CEBA project has been approved by the Regional Committee for Medical and Health Research Ethics for South-East Norway (ID: 2014/2069). Written informed consent was obtained from all participants and from parents/next-of-kin if required. In CEBA, a total of 195 adolescents (12 to 19 years old) with acute EBV infection (based on their antibody response characteristics) were included and followed prospectively for 6 months. Exclusion criteria were a time limit of six weeks since onset of symptoms, pregnancy, and medical treatment for another disease. Healthy controls ($n = 70$) were recruited among the patients' peers with the equivalent age and demographic conditions as the patients. Additional details of the recruitment, screening and inclusion procedures are described elsewhere [16].

2.2. Procedures

All participants were subjected to the same one-day assessment program at the hospital study center (Dept. of Pediatrics and Adolescent Medicine, Akershus University Hospital, Norway). The time from acute infection to the cognitive assessment was 6 months. Cognitive assessments and questionnaires were performed at 10 am, after breakfast was served (a light meal). The tests and procedures were administered to all participants in the same order. The whole examination program lasted for about three and a half hours including breakfast. All examinations and assessments were performed by the project's two main researchers (MP and TTA), who were supervised on cognitive assessments by a specialist in clinical neuropsychology (MGØ). Each participant received a 200 NOK gift voucher.

2.3. Measures

Participants were tested and interviewed on a large battery of measures (see [16] for details), and only selected data are included in the current study.

2.3.1. Clinical symptoms

The Chalder Fatigue Questionnaire (CFQ) is a validated and widely used self-report questionnaire in CF and CFS research [17,18]. The CFQ has been translated and validated for the Norwegian population [19]. It consists of 11 items scored on a 4-point Likert scale. Each item is either scored zero to three (ordinal) or 0–0–1-1 (binary). In both cases, higher scores reflect greater fatigue. For binary scoring, a total sum score of four or more qualify for fatigue caseness [20]. The participants were grouped as chronically fatigued (CF^+) and non-fatigued (CF^-) cases based on the questionnaire score. The discriminative abilities of the questionnaire seem satisfactory, and the questionnaire has proven to discriminate reliably between clinical and nonclinical conditions [21].

The Hospital Anxiety and Depression Scale (HADS) is a brief self-report questionnaire used to determine the presence of anxiety and depression symptoms [22]. It consists of fourteen items, where seven relate to anxiety seven to depression [23]. Each item is rated zero to three on a Likert scale; higher scores indicate more severe symptoms. The HADS has demonstrated adequate test-retest reliability and factor structure and has been proven to perform satisfactorily when discriminating between adolescents diagnosed with depressive or anxiety disorders and those without these diagnoses [24].

In order to investigate post-exertional malaise (PEM), the following question was set as a single item proxy: “How often do you feel more fatigued the day after an exertion?” This formulation is in line with previously used definitions of post-exertional malaise [25]. Response was given on a five-point Likert scale; a higher score implies more severe symptoms.

2.3.2. Subjective cognitive symptoms

A slightly revised version of the original Centers for Disease Control and Prevention (CDC) Symptom Inventory for CFS was applied to assess subjective experiences of cognitive functioning in the following areas: Concentration, decision making, memory and confusion/disorientation. Perceived frequency of each symptom is graded on a five-point Likert scale, ranging from “never/rarely present” to “present all of the time” [26–28]. Higher scores imply more severe symptoms; a sum score across all items was taken as a global measure of subjective cognitive problems. The original CDC Symptom Inventory for CFS is a self-report questionnaire used to collect information about the presence, frequency and intensity of CFS-related symptoms [27]. The inventory was translated into Norwegian by one of the authors [29], and slight adjusted to fit an adolescent patient group. It has been found useful in several studies and appears to have high face validity [16,26,30–33].

2.3.3. Objective cognitive assessment

2.3.3.1. Processing speed. The Color-Word Interference test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS) includes four different conditions [34,35]. The two baseline conditions assess verbal processing speed, asking the participants to name different color bars on a paper (condition 1) and read out loud the printed word of the color bars (condition 2). Mean completion time (seconds) on the two conditions is recorded; higher completion time implies slower processing speed.

2.3.3.2. Executive functions: working memory, cognitive inhibition, and cognitive flexibility. For assessment of verbal or auditory working memory, the Digit Span test is widely used [36]. The examiner reads aloud strings of random digits (approximately one digit per second). The test starts with two random numbers, increasing with one random number every other string. The digit span forward condition requires the test person to repeat the digits in the same order as heard; for digit span

backward, the test person is required to repeat the digits in reverse order. Each answer is scored 1 (correct) or 0 (incorrect). When both strings in a pair (i.e., two strings of equal length) are answered incorrectly, the test is discontinued. Total scores are the sum of correct answers for both the forward and the backward condition.

The third condition of the CWIT from D-KEFS assesses cognitive inhibition, requiring the participant to name the color of the ink, not the dissonant color-words printed [34]. Higher completion time implies less cognitive inhibition.

The fourth condition in the CWIT from D-KEFS was used as a measure of cognitive flexibility [34]. It requires the participant to switch between naming dissonant ink color and reading color-words of framed words. Higher completion time implies less cognitive flexibility.

2.3.3.3. Verbal learning (immediate recall) and verbal memory (delayed recall). The Hopkins Verbal Learning Test - Revised (HVLT-R) is a test of verbal learning (immediate recall) and verbal memory (delayed recall) [37]. The examiner reads aloud a list of 12 words, and the participant is asked to repeat as many words as possible in three consecutive trials; sum score of remembered words (0–36) in the three trials altogether is as measure of verbal learning. After 20 min, the participant is asked to recall the same 12 words; the number of remembered words (0−12) is a measure of delayed verbal memory. Finally, the examiner reads aloud 24 words, where 12 of these are identical to the previous list of words; the number of correctly recognized and falsely recognized words is recorded separately.

2.3.3.4. Intelligence quotient. Matrix Reasoning and Vocabulary tests from the Wechsler Abbreviated Scale of Intelligence (WASI) [38] were used to estimate Full Scale Intelligence Quotient (FSIQ).

2.4. Statistical analyses

All cases that completed follow-up appointment at 6 months (n = 195) were included in the analyses, and there was no missing data. Statistical analyses were carried out using IMB Statistical Package for Social Sciences (SPSS), version 24. Cross-sectional comparisons were carried out across all three groups ($CF^{+;}$ CF^{-}; Healthy controls) applying one-way ANOVA. Thereafter, differences across the CF^{+} and CF^{-}-groups were assessed using Student t-tests given that the p-values for ANOVA were ≤ 0.1; these comparisons were adjusted for group differences in sex, symptoms of depression and anxiety (HADS) and estimated IQ score (WASI) at baseline, applying multiple linear regression modeling. Generally, a p-value <0.05 was considered statistically significant. As several variables were strongly correlated, Bonferroni adjustment was not carried out.

3. Results

A total of 200 adolescents with acute EBV infection were included at baseline [16] (Fig. 1). Five participants were lost to follow-up during the first 6 months, leaving 195 cases for analyses in the present sub-study; 91 (47%) of them were classified as chronic fatigue cases (CF^{+}), whereas 104 (53%) were classified as non-fatigue cases (CF^{-}). The CF^{+}-group contained more females and had lower estimated IQ and higher HADS and PEM scores than the CF^{-}-group (Table 1). A total of 26 (29%) adhered to the Fukuda-definition of CFS [1], whereas 19 (21%) adhered to the Canada-definition [39]. In addition, 70 healthy controls with similar distribution of sex and age as the EBV group were included.

The performance on all objective cognitive tests were similar across the CF^{+} and the CF^{-}-group, except for one test of working memory (digit span backwards) where the CF^{+}-group performed significantly poorer (means [CIs] 6.1 [5.7–6.4] vs. 6.7 [6.2–7.1], $p = 0.037$); this difference disappeared, however, when controlling for possible confounding factors ($p = 0.445$) (Table 2). Subjective symptoms of cognitive problems

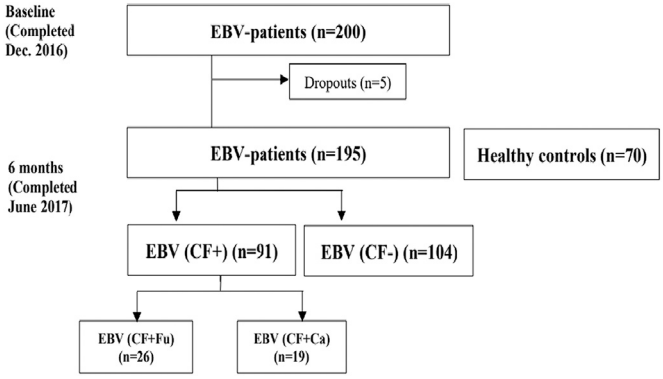

Fig. 1. Patient flow overview. EBV = Ebstein- Barr Viurs. CF = Chronic fatigue. CF^{+} = those who developed chronic fatigue 6 months after acute EBV infection (including a subgroup satisfying diagnostic criteria for Chronic Fatigue Syndrome (CFS)). CF^{-} = those who did not develop chronic fatigue 6 months after acute EBV infection. HC = healthy controls. Fu = Diagnosed CFS according to the Fukuda criteria. Ca = Diagnosed CFS according to the Canada criteria.

were significant more prevalent in the CF^{+}-group (means [CIs] 10.4 [9.5–11.4] vs. 5.9 [5.3–6.4], $p < 0.001$) even after controlling for possible confounding factors ($p < 0.001$) (Table 3). Accordingly, group differences for three of four sub-categories of cognitive symptoms (concentration problems, problems making decisions, memory problems) remained highly significant after p-value adjustment.

CF^{+}-cases adhering to the Fukuda- or Canada-definition of CFS performed similarly to the entire CF^{+}-group on all objective measures of cognitive functioning, except for the verbal learning and delayed recall tests, where the performance was slightly poorer (Supplementary Table 1). However, the subjective symptom scores were higher among CFS-sufferers as compared to the entire CF + -group (Supplementary Table 2).

4. Discussion

The most important findings from the present study are that adolescents with CF after acute EBV-infection are not adversely affected on any of the objective cognitive measures in our study compared to individuals having recovered from EBV-infection and healthy controls. This is contrary to what we expected. Other studies on adolescents with CF/CFS have included participants with longer duration of illness compared to our study. It is possible that reduced cognitive functioning is a consequence of illness duration and chronicity. Adolescents who have had CF/CFS for years, compared to months in our study, have also been physically inactive and absent from school for longer periods of time, which is also likely to affect cognitive functioning [40].

The results confirmed, in line with our hypothesis, that adolescents in the CF^{+}-group reported significantly more subjective cognitive difficulties than the CF^{-}-group and healthy controls. Furthermore, those who were diagnosed with CFS in the CF^{+}-group reported even more cognitive difficulties compared to the total CF^{+}-group. These results are in line with findings in other studies on both adults and children/adolescents with CFS [2,9,41,42], and suggest that CF and CFS exist on a continuum with few, if any qualitative differences related to subjective cognitive functioning.

The discrepancy between objective and subjective measures of cognitive functioning in the present report is in line with other studies on adults with CF and CFS [2,9,10]. This discrepancy is not unique to CF/CFS but has been reported in healthy individuals and other patient groups alike and may indicate that subjective and objective cognitive measures are related to different constructs [43]. Self-report measures typically ask about general cognitive functioning experienced by the individual during everyday tasks, which has the advantage of capturing a broad range of subjective experiences in a realistic setting [41].

Table 1
Background characteristics.

	EBV-group (n = 195), 6 months after acute infection					Healthy controls (n = 70)	
	CF^+ *(n = 91)*		CF^- *(n = 104)*		*p-value**		
Sex - no. (%)							
Male	24	(26)	44	(42)	**0.020**	26	(37)
Female	67	(74)	60	(58)		44	(63)
Age, years - mean (SD)	17.4	(1.5)	17.4	(1.7)	0.780	17.0	(1.8)
BMI, kg/m^2 - mean (SD)	22.1	(2.8)	22.2	(2.5)	0.666	21.5	(3.1)
IQ, estimated - mean (SD)	108.4	(11.7)	112.6	(11.8)	**0.014**	113.4	(8.8)
Steps per day, number - mean (SD)	8710	(3872)	9329	(3019)	0.293	10094	(4149)
Epstein-Barr Virus (EBV) load, copies in blood - no. (%)							
Negative (<160)	44	(51)	38	(37)	0.123	60	(86)
Low (1600 to 2000)	26	(30)	35	(34)		8	(11)
Moderate/high (>2000)	16	(19)	29	(28)		2	(3)
Chalder Fatigue Questionnaire (CFQ), total score - median (IQR)	19.0	(5.0)	11.0	(2.0)	**<0.001**	11.0	(5.0)
Post-exertional malaise, score - mean (SD)	2.9	(1.1)	1.6	(0.6)	**<0.001**	1.7	(0.7)
Hospital anxiety and depression symptoms (HADS), total score - mean (SD)	13.4	(6.3)	8.0	(5.3)	**<0.001**	10.6	(4.6)

In order to estimate the participants IQ, two subtests (Matrix Reasoning and Vocabulary) from the Wechsler Abbreviated Scale of Intelligence (WASI) were applied [38].* Student's t-test or Mann-Whitney *U* test were applied for continuous data, dependent on variable distribution. Pearson's Chi-Square was applied for categorical data.

Table 2
Objective cognitive test performances across all groups.

	CF^+ *(n = 91)*		CF^- *(n = 104)*		*Healthy controls (n = 70)*		*p-value (across all groups)*	*p-value* CF^+ vs CF^-	*Adjusted* p-value* CF^+ vs CF^-
Processing speed									
D-KEFS condition 1, *sec* - mean (SD)	29.7	(5.6)	29.3	(4.7)	30.1	(6.3)	0.591		
Confidence interval	28.5	30.9	28.3	30.2	28.6	31.6			
D-KEFS condition 2, *sec* - mean (SD)	23.3	(5.5)	22.6	(3.6)	22.6	(4.2)	0.515		
Confidence interval	22.1	24.4	21.9	23.3	21.6	23.6			
Sum score, sec - mean (SD)	26.5	(5.0)	25.9	(3.8)	26.4	(5.0)	0.671		
Confidence interval	25.4	27.5	25.2	26.7	25.2	27.6			
Executive function: Working memory									
Digit span forwards, score - mean (SD)	9.3	(1.7)	9.5	(1.8)	9.2	(1.8)	0.580		
Confidence interval	9.0	9.7	9.1	9.8	8.8	9.6			
Digit span backwards, score - mean (SD)	6.1	(1.7)	6.7	(2.2)	6.1	(2.0)	0.076	**0.037**	0.445
Confidence interval	5.7	6.4	6.2	7.1	5.7	6.6			
Digit span, sum score - mean (SD)	15.4	(3.0)	16.1	(3.6)	15.3	(3.2)	0.174		
Confidence interval	14.8	16.0	15.4	16.8	14.5	16.1			
Executive function: Cogntive inhibition									
D-KEFS condition 3, sec - mean (SD)	48.2	(8.9)	48.3	(9.7)	49.8	(11.6)	0.526		
Confidence interval	46.3	50.0	46.4	50.1	47.0	52.5			
Executive function: Cogntive flexibility									
D-KEFS condition 4, sec - mean (SD)	52.7	(10.0)	53.4	(11.1)	59.7	(12.6)	**<0.001**	0.650	
Confidence interval	50.6	54.8	51.2	55.5	56.7	62.7			
Verbal learning and memory									
Verbal learning, sum score - mean (SD)	27.4	(3.7)	27.8	(4.2)	27.5	(3.8)	0.739		
Confidence interval	26.6	28.1	27.0	28.6	26.5	28.4			
Verbal delayed recall, score - mean (SD)	9.7	(1.9)	9.8	(1.8)	9.6	(2.0)	0.831		
Confidence interval	9.3	10.1	9.4	10.1	9.1	10.0			
Verbal correct recognition - no. (%)							0.087	0.666	
10 words	1	(1.1)	2	(1.9)	0	(0.0)			
11 words	16	(17.6)	14	(13.5)	3	(4.3)			
12 words	74	(81.3)	88	(84.6)	67	(95.7)			
Verbal false recognition - no. (%)							0.097	0.308	
0 word	81	(89.0)	98	(94.2)	58	(82.9)			
1 word	9	(9.9)	6	(5.8)	12	(17.1)			
2 words	1	(1.1)	0	(0.0)	0	(0.0)			

* Adjusted for group differences in sex, HADS-score at 6 months, and estimated IQ at baseline applying multiple linear regression modeling. Statistical tests across the CF^+ and CF^- groups (second right column) were only carried out if the p-value across all groups were ≤ 0.1. A total of 17 statistical tests were performed. According to a Bonferroni correction, the level of significance should be set at $p = 0.05/17 \approx 0.003$. SD = standard deviation.

However, everyday life is complex and might not be compatible with tests that measure specific cognitive functions in a controlled and structured test environment [44]. Objective cognitive performance and subjective cognitive functioning in everyday life may also be differently influenced by variables such as fatigue, sleep, depression, and anxiety [9,10,45]. Further, subjective evaluation of cognitive difficulties in both

Table 3
Symptoms of cognitive problems across all groups.

	CF^+ *(n = 91)*		CF^- *(n = 104)*		*Healthy controls (n = 70)*		*p-value (across all groups)*	*p-value* CF^+ vs CF^-	*Adjusted* p-value* CF^+ vs CF^-
Concentration problems, score - mean (SD)	3.5	(1.1)	1.8	(0.9)	2.2	(1.0)	**<0.001**	**<0.001**	**<0.001**
Confidence interval	3.2	3.7	1.6	1.9	1.9	2.4			
Problems making decisions, score - mean (SD)	2.6	(1.3)	1.4	(0.9)	1.9	(0.8)	**<0.001**	**<0.001**	**<0.001**
Confidence interval	2.2	2.9	1.2	1.6	1.7	2.1			
Memory problems, score - mean (SD)	2.5	(1.4)	1.4	(0.8)	1.7	(0.8)	**<0.001**	**<0.001**	**0.001**
Confidence interval	2.2	2.9	1.3	1.6	1.5	1.9			
Feeling confused or desoriented, score - mean (SD)	1.9	(1.1)	1.3	(0.7)	1.3	(0.6)	**<0.001**	**<0.001**	0.154
Confidence interval	1.6	2.1	1.1	1.4	1.1	1.4			
Cognitive symptoms, sum score - mean (SD)	10.4	(4.0)	5.9	(2.5)	7.1	(2.5)	**<0.001**	**<0.001**	**<0.001**
Confidence interval	9.5	11.4	5.3	6.4	6.4	7.7			

*Adjusted for group differences in sex, HADS-score at 6 months, and estimated IQ at baseline applying multiple linear regression modeling. Statistical tests across the CF^+ and CF^- groups (second right column) were only carried out if the p-value across all groups were ≤ 0.1. SD = standard deviation.

healthy and patient populations relates better to personality and psychological factors (e.g., mood), than to objective measures [41,46]. Thus, there is a possibility that objective cognitive tests fail to capture the struggles experienced by adolescents with CF/CFS in situations of everyday life.

It is also possible that CF/CFS patients are more susceptible to the tendency of overestimating their subjective cognitive problems [47]. This might be explained by heightened self-monitoring of cognitive processes and an increase in bodily focus that lead to an over-interpretation of subjective cognitive difficulties [45]. Subjectively perceived cognitive difficulties may be strengthened through mechanisms of conditioning and negative response outcome expectancies that facilitate self-fulfilling prophecies [48,49]. In sum, it is possible that the adolescents with CF/CFS in the current study are guided by cognitive processes that lead them to become more susceptible to overestimate their cognitive difficulties, have higher perceptions of cognitive effort, and develop more negative response outcome expectancies.

4.1. Strengths and limitations

General strengths include a large group of EBV-infected adolescents recruited soon after the onset of EBV infection, and the low number of dropouts and missing data. A possible limitation is that not all adolescents who develop CF/CFS are exposed for a viral trigger such as an acute EBV infection, thereby possibly reducing the generalizability of our results.

5. Conclusion

There are no differences in objective measures of cognitive performance between adolescents with fatigue and adolescents without fatigue 6 month after EBV-infection; also, the subgroup of fatigued patients diagnosed with chronic fatigue syndrome (CFS) did not differ importantly. The fatigued group, however, report more subjective complaints of cognitive dysfunction, and symptom intensity was rated even higher in the CFS subgroup.

Funding

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Ethics approval

The CEBA project has been approved by the Regional Committee for Medical and Health Research Ethics for South-East Norway (ID: 2014/2069) and was performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Authors'contribution

Merete Glenne Øie contributed to the current study design, wrote the second draft and the final draft and supervised MSB and ASBR; Maria Sletten Bølgen (MSB) and Astrid Sofie Buer Rødø (ASBR) conducted the data analyses and wrote the first draft; Maria Pedersen (MP) and Tarjei Tørre Aspursten collected clinical data including cognitive test administration; Vegard Bruun Bratholm Wyller (VBBW) conceived of the study, contributed to study design, participated in data analyses, supervised MSB and ASBR in data analyses and reviewed the drafts. The principal investigator (VBBW) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final manuscript.

Declaration of Competing Interest

None of the authors have conflict of interest or financial relationships relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2022.111063.

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