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Kumamoto University
Cognitive dysfunction correlates of mental fatigue induced in childhood chronic fatigue syndrome - A six-month follow-up study

Junko Kawatani, MD*, Kei Mizuno**, Miyuki Takano, PhD ***, Takako Joudoi, MD*, Sanae Fukuda****, *Akemi Tomoda, MD*

*Department of Child Development*, Faculty of Life Medical and Pharmaceutical Sciences, Kumamoto University; **Molecular Probe Dynamics Laboratory, RIKEN Center for Molecular Imaging Science; ***Kusyu Lutheran College, Kumamoto; and ****Department of Medical Science on Fatigue, Osaka City University Graduate School of Medicine, Japan

Correspondence address: Akemi Tomoda, MD, PhD
Department of Child Development, Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8566, Japan.
Tel: +81-96-373-5197; Fax: 81-96-373-5200
E-mail: tomo@kumamoto-u.ac.jp

ABSTRACT

Objectives: The aim of this study was to investigate cognitive functions such as allocation and information processing in patients with childhood type chronic fatigue syndrome (CCFS) using modified advanced trail making test (mATMT).

To examine cognitive function in chronic fatigue syndrome. The first aim of the present study was to test whether PCFS showed cognitive dysfunction. The second aim of the study was to cognitive function may be a reversible that can improve with therapy after 6 months, if PCFS
showed cognitive dysfunction at baseline.

Methods: 25 healthy children as controls and 19 patients with CCFS participated in this study. The subjects were 19 patients with chronic fatigue syndrome and 25 healthy controls (grades 7 to 9). Both patients and controls had (i) modified advanced trail making test (mATMT; ) which is computerized cognitive test (TaskA,B,C,D,E) and were instructed to indicate (ii) Chalder’s fatigue scale to evaluate their fatigue state using Chalder’s fatigue scale before and 6 months after therapy. CCFS patients were assessed at follow-up (i.e. therapy).

Results: We calculated differences in reaction time as total reaction times on task A, B, C, or E subtracted by that on task D in the mATMT. The results indicate that 4 tasks from mATMT can discriminate CCFS patients from the control group by 70.5% accuracy. Especially, the average reaction time of the Task E contributes to the identification of CCFS. The amount of reaction time in Task E improved and the amount of mental fatigues score and total fatigue score improved within the past 6 months are correlated. The improvement of their cognitive symptoms and improvement of set shifting function (??) correlated with an overall index of visual memory ($r = .353, P = .032$ and $r = .448, P = .005$).

Conclusions: It shows that there is a relationship between improvement of cognitive symptoms caused by mental fatigue and improvement of set shifting function. Present findings indicate that

**Key words:** Modified advanced trail making test (mATMT); Childhood type chronic fatigue syndrome (CCFS); Cognitive function; Alternative attention.

1. Introduction

Chronic fatigue syndrome (CFS) is a critical problem for children and adolescents, which can cause grave impairment in physical condition, educational achievement, and social development. CFS is a relatively common condition, affecting between 0.1% and 2% of children aged under 18 years. Chronic fatigue occurring in previously healthy children and adolescents is a vexing problem encountered by pediatric practitioners (1-6) and the impact of fatigue in youngsters should not be underestimated (7). In the ME/CFS pediatric case definition which was published the International Association of Chronic fatigue Syndrome, the symptom categories included fatigue, post-exertional malaise, unrefreshing sleep or disturbance of sleep quantity, pain (myofacial, joint, abdominal and/or head pain), two or more neurocognitive manifestations, and at least one symptom from two of the following three categories: autonomic manifestations, neuroendocrine manifestations, or immune manifestations and these symptoms were maintained 3 months or longer duration.
Particularly cognitive dysfunction— including impaired attention/concentration, memory deficits, difficulty in learning new material, problems with abstract thinking, and slowed thinking— are most commonly symptoms with sleep disturbance and headache equally.\textsuperscript{10-13} In the preliminary study, memory and concentration problems affect over 80% of children and young people with CFS.\textsuperscript{14} However, the standard cognitive tests for measuring the deteriorated cognitive functions of the patients with CCFS are not still established.

Recently, modified advanced trail making test (mATMT) is a mental function test developed for the purpose of evaluating the abilities of motor skill, selective and alternative attention and spatial working memory with little effect of the subject’s intelligence quotient or experience in children and adolescents (Ref. 24). In addition, since no learning effect of the mATMT was confirmed, the mATMT can continuously evaluate the same subject's abilities of these cognitive functions. Development of alternative attention is of crucial importance in the transitional period from elementary to junior high school (Ref. 24). In addition, a decrease in ability of alternative attention is positively correlated with the prevalence of fatigue in the junior high school students (Ref. 33), suggesting that the mATMT help the education community to develop screening procedures to identify those at high risk of fatigue, and to conduct early interventions to achieve lower incidences of fatigue in the junior high school students. However, it is unclear that whether the mATMT is useful for evaluating deteriorated cognitive functions and improved cognitive functions by treatments in the CCFS patients.

Although there is pharmacological or nonpharmacological treatment for CFS, there are no established treatment recommendations. Many pharmacological therapies have been used for treating CFS including anti-depressants, NSAIDs, anxiolytic drugs, anti-allergy drugs and anti-hypotensive drugs. However, they are not universally beneficial.\textsuperscript{15} Response to selective serotonin reuptake inhibitors has been minimal, probably because of the serotonergic hypersensitivity demonstrated in CFS.\textsuperscript{16-17}

Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) remain the most common non-pharmacological therapy, these programs have been reported to improve the status of CFS patients.\textsuperscript{18-21}

In this study we determined objective fatigue and cognitive performance in CCFS patients both before and after therapy. We hypothesized that CCFS patients would show a impairment in fatigue score and reaction speed of cognitive task compared to healthy controls before therapy, and an improvement in fatigue score and reaction speed of cognitive task following therapy. Moreover, we hypothesized that their fatigue improvement would be related to the behavioral improvement in cognitive task.

In our study, we used the “Brain Science and Education” cohort study, a
2-and-a-half-year trial funded by the Research Institute of Science and Technology for Society/Japan Science and Technology Agency, whose goal is to prevent fatigue and enhance the efficacy of learning. The goal of the present study was to explore the hypothesis that improvement of fatigue in school children would be related to the behavioral improvement in cognitive task.

2Materials and methods

2.1.Subjects

The study was approved by the Committee of Life Ethics, Graduate School of Medicine, Kumamoto University. All subjects’ parents or guardians gave written informed consent before the experiment. Participants in this study consisted of 25 healthy children as controls (7 boys and 12 girls) and 19 CCFS patients (13 boys and 12 girls) who met the inclusion criteria and satisfied the exclusion criteria described below.

The subjects were asked about the symptoms of chronic fatigue, including the diagnostic criteria of chronic fatigue syndrome (CFS) developed by the US Centers for Disease Control and Prevention {Fukuda, 1994 #859}. Symptoms that lasted for more than 6 months were scored as 2 points; symptoms lasting for more than 1 month were scored as 1 point; and no symptoms were scored as zero points. Responses to the following items were sought: “impossibility of getting up in time to go to school”; “disturbance of falling sleep”; “easily awakened during the night”; “daytime sleepiness”; “difficulty in learning new things, loss of motivation, and difficulty in concentrating on one’s studies”; “becoming very tired with just a small amount of effort, and not feeling refreshed even after one day’s rest”; “getting headaches and feeling heavy-headed”; “getting a sore throat”; “stomach ache and feeling nauseous and sick to my stomach”; “getting swollen lymph nodes”; “having a mild fever”; “recent muscle pain”; “dizziness”; “muscular weakness”; “having sore joints”; “becoming dizzy when there is bright light”; “a portion of what is in front of my eyes disappears at times”; “forgetting things at times”; “easily excited”; “head-spinning”; “feeling less able to think”; “a decline in my ability to concentrate”; and “feeling depressed”. The subjects were also asked whether they were tired for more than 1 month and whether they refused to go to school due to fatigue. To determine the CCFS performance status, subjects were asked whether they felt bad and could not go to school and needed to rest at home; subjects who answered this question in the affirmative fulfilled the first criterion of CCFS. A subscale of sleep disorder was created using the following sleep-related factors: “impossibility of getting up in time to go to school”; “disturbance in falling asleep”; “easily awakened during the night”; and “daytime sleepiness”. Thirty subjects
did not answer all of the sleep disorder items.

Patients were recruited from 9 to 18 years patients who visited Kumamoto University Hospital between April 2007 and December 2008 (baseline) because of CFS-like symptoms. Of the 127 patients who had agreed to participate, 49 patients withdrew for personal reasons (7 patients have moved far away, 5 patients have never visited hospital, 37 patients have rejected examination again) and 28 were excluded because of other diagnoses. After 6 months (follow-up) leaving 50 patients, although all patients fulfilled the diagnostic criteria for CCFS\textsuperscript{11} as assessed by three pediatricians by the Structured Clinical Interview, only 37 patients aged 13 to 15 years (in the 7\textsuperscript{th} to 9\textsuperscript{th} grade) were selected for this study. Not all the tests were completed for each patient, finally 19 patients follow-up completely (Figure 1). The age of the participant was limited to deduct a difference of the ability by the age. Previous findings provide evidence that cognitive functions such as spatial and non-spatial working memory, alternative and divided attention, and semantic fluency improve from elementary to junior high school. In addition, alternative and divided attention were specifically improved during the transitional period from elementary to junior high school, indicating that cognitive flexibility improves in this period.\textsuperscript{24}

And 25 healthy students aged 13 to 15 years (in the 7\textsuperscript{th} to 9\textsuperscript{th} grade) were included this study as control. Characteristics of patients and healthy controls are shown in Table 1. Both patients and controls completed a questionnaire including demographic variables (e.g., grade, sex, height, and weight), and fatigue score.

The present study was approved by the Institutional Review Board, Independent Ethics Committee of the Graduate School of Medicine, Kumamoto University. Written informed consent to give permission to participate in the survey was obtained from the guardians of subjects, and assent form was obtained from the participants because subjects were under the age of 20.

2.2 Questionnaires

The severity degree of a patient’s self-reported fatigue was measured with Chalder’s fatigue scale, which consists of two components: physical fatigue and mental fatigue.\textsuperscript{12} This scale was developed by Chalder et al. to measure the severity of fatigue \{Chalder, 1993 \#1202; Davies, 2008 \#1074\}. It consists of 14 questions and has been found to have reliability and validity, as well as a high degree of internal consistency \{Tanaka, 2008 \#1111\}. A higher score reflects a higher level of fatigue.

The fatigue scale consists of 14 questions, scored on a four-level scale, with higher
scores instead of greater fatigue. Participants were instructed to answer to how they felt during the past two weeks. Although Chalder’s fatigue scale was developed by Chalder et al. (1993) to assess adult chronic fatigue, Patel et al. (2003) reported results of an assessment of an adolescent population using this scale.

2.3 Cognitive function tests

The computerized cognitive function task, participants performed a modified advanced trail making test (mATMT), which consisted of tasks A, B, C, D, and E. For the ATMT, subjects performed visual search trials. In this test, circles numbered from 1 to 25 were randomly located on the display of a personal computer, and subjects were required to use their finger of dominant hand to touch these circles in sequence, starting with circle number 1. When the subjects touched the 25th target, the task was finished. In task A, when the subject touched a target circle, it remained in the same position and its color changed from black to yellow. The positions of the other circles remained the same. In task B, when the subjects touched the first target circle, it disappeared and a circle number 26 appeared on the screen. The positions of the other circles remained the same. Then touching circles 2, 3, and 4 sequentially, for example, resulted in their disappearance and the addition of circles 27, 28, and 29 to the screen. The number of circles seen on the screen always remained at 25. In tasks A and B, required spatial working memory. In task C, the procedure was the same as in task B except that the locations of the other circles randomly changed each time subjects touched target circle. In task C, no memorization was required, suggesting that this task required selective attention alone. In task D, circles numbered from 1 to 25 were regularly and sequentially located on the screen, and subjects were required to no memorization and no visual search, required motor processing alone. In task E, circles numbered from 1 to 13 and 12 KANA letters (Japanese phonograms) were randomly located on the screen, and subjects were required to their finger of dominant hand to alternately touch numbers and KANA letters; this task thus required alternative attention. In order to assess spatial working memory, selective attention, and alternative attention, excluding effects of motor processing, we calculated differences in reaction time as total reaction times on task A, B, C, or E subtracted by that on task D in the mATMT.

2.4 Experimental design

Both patients and controls completed a questionnaire including demographic variables (e.g., grade, sex, height, and weight), and fatigue score, and performed mATMT. (baseline) Only CCFS patients were follow-up for about 6 months, with pharmacotherapy and/or Cognitive behavioural therapy (CBT) with graded exercise therapy (GET). After 6 months patient assessed
questionnaire, fatigue scale, and mATMT again. (follow-up)

Six of 19 patients (31.6%) were treated at one antidepressant, of which four received a selective serotonin reuptake inhibitor (SSRI) only and one received both a sulpiride and SSRI, another received both a Midodrine hydrochloride and SSRI. Five received midodrine hydrochloride only. Four received other medicine and four received no medication.

All patients engaged in cognitive behavioural therapy (CBT) with graded exercise therapy (GET) for 6 months. CBT and GET remain the most common non-pharmacological therapy, to improve the health status of CFS patients. CBT is a psychological approach to addresses thoughts and beliefs about CFS which may impair recovery, and GET is a rehabilitative approach of a graded increase in activity. CBT with GET was used to gain insights into the effects that particular activities have on their physical functioning and ability to tailor their activities to their capabilities. It is expected that CBT with GET reduce perpetuate factors of CFS, as low physical activity and a low sense of control over the symptoms (Bleijenberg et al., 2003). It is shown that CBT teaches patients with CFS how to acquire control over symptoms (Prins et al., 2006).

To exclude a learning effect, another healthy control group-in hyogo prefecture was conducted mATMT two times - the first time and 6 months after. In this group, on account of the facilities, the task on ATMT using computer mouse in substitution for touch panel.

2.5. Statistical analysis

An independent samples t-test was conducted to compare the fatigue scores for healthy control group and CCFS group at base line. Differences between means in patients base line and follow up (before therapy and after therapy) were assessed with Student’s paired t-test.

Discriminant function analysis was used to predict a total reaction time on four tasks(TaskA, B, C, E) as dependent variable by mATMT, and the variables used to predict group membership on base-line.

When statistically no significant effects for timing of data collection × task interaction were found by repeated two-way ANOVA, Tukey-HSD(contrast analysis) was used to evaluate the significance difference of total reaction time each task(TaskA, B, C, E) between baseline and follow-up.

The relationship between improvement of fatigue scores and improvement of total reaction time of tasks by mATMT was investigated using spearman correlation coefficient. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS 17.0 software package (SPSS, Chicago, IL).
3. Results

In CCFS group, the Chalder’s fatigue score was significantly higher than in control students, physical fatigue (14.7±4.8 vs 9.2±6.0; p=0.002), mental fatigue (9.6±4.4 vs 7.6±4.1; p=0.013), and total fatigue score (24.1±8.4 vs 15.6±8.4; p=0.002) in baseline. (Table2) In Follow-up (after 6 months) physical fatigue, mental fatigue and total fatigue score were showed no changes in CCFS group. (Table3)

The results of the mATMT in healthy control groupe and CCFS groupe are shown in Table4. Although average total reaction time on tasks A, B, C, D and E did not differ between the 2 groups. In order to assess spatial working memory, selective attention, and alternative attention, excluding effects of motor processing, we calculated differences in reaction time as total reaction times on task A, B, C, or E subtracted by that on task D in the mATMT. Differences in reaction time on the mATMT in the both groups are shown in Table5.

Findings of the discriminant function analysis showed that the combined differences in reaction time for tasks A, B, C and E on mATMT correctly classified 70.05% participants into healthy control or CCFS group membership ($\Lambda=0.707$, $\chi^2=13.951$, df=4, p<.01, two-tailed test). Table6. Especially, the differences in reaction time of the Task E contributes to the identification of CCFS ($\Lambda=0.901$, p<.05, standardization canonical coefficient=1.076).

The differences in reaction time on tasks A ($\Lambda=0.984$, p>.05, standardization canonical coefficient=-0.331), B ($\Lambda=1.00$, p>.05, standardization canonical coefficient=-1.574) and C ($\Lambda=0.946$, p>.05, standardization canonical coefficient=1.358) did not differ between the two groups.

The differences in reaction time of the Task E among the CCFS group was significantly improved at 6 month follow-up as compared to that of the baseline.

Importantly, the change in mental fatigue score was correlated with the change in differences in reaction time of Task E in mATMT ($r=0.639$, p=0.002), a larger improvement in mental fatigue score was related to a larger behavioural improvement in differences in reaction time of Task E in mATMT following therapy.

Patient’s differences in reaction time of task A, B, C in mATMT did not change, and there was no correlation between the change in mental fatigue score and the change in differences in reaction time of these task in mATMT.

Further, to exclude a learning effect, another healthy control group-in hyogo prefecture conducted mATMT two times - the first time and 6 months after. The differences in reaction time of the Task A, B, C and E among the another healthy control group was not improved at 6 month after as compared to that of the baseline. Table7
Discussion

The main findings of this study were indicating cognitive dysfunction particularly alternative attention in CCFS patients and it improved related to the improvement in mental fatigue.

As expected, the CCFS patients’ the Chalder’s fatigue score was significantly higher than in control students. There was no relation, between severity fatigue scores and their differences in reaction time on mATMT in both groups.

The combined differences in reaction time for tasks A, B, C and E on mATMT correctly classified 70.05% participants into healthy control or CCFS group membership. Especially, the differences in reaction time of the Task E contributes to the identification of CCFS. The CCFS patients showed poor performance on alternative attention involve response inhibition and cognitive flexibility.

Following 6 months, in CCFS group, the Chalder’s fatigue score and differences in reaction time of task A, B, C except Task E on mATMT did not change. The CCFS patients’ the differences in reaction time of task E was significantly improved as compared with baseline. Although learning effect was demonstrated in Task A, it was demonstrated that no learning effect in another healthy control group on mATMT. It was no correlation between severity fatigue scores and their differences in reaction time on mATMT in follow up. Although it was no correlation between the change in fatigue score and the change in differences in reaction time of these task A, B, and C, correlation between the change in fatigue score and the change in differences in reaction time of task E in mATMT.

Previously Neuroimaging studies have reported the neural substrates associated with numerous cognitive function tests. It is known recruitment of the dorsolateral prefrontal cortex during tasks designed to engage central executive functions, such as working memory, maintenance of information, response inhibition, and cognitive flexibility (Baddeley, 1992; D’Esposito et al., 1999; Salmon et al., 1996). It has been reported that, while performing part B of the trail making test (TMT), which is similar to task E in the mATMT, activation in the left prefrontal cortex including the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex was observed (Moll et al., 2002; Zakzanis, Mraz, & Graham, 2005). Associated with Part B are the added demands of “set shifting”, “cognitive flexibility”, and “2 general attention component”. (Zakzanis, Mraz, & Graham, 2005) Previously report, TMT attempting to discriminate patients with chronic toxic encephalopathy (CET) from healthy participants on the basis of TMT performance, found that healthy individuals were identified correctly, but that the
ability to identify CTE correctly was low. (Nilson et al., 1999) Similarly, in our results, on the mATMT performance, found that healthy individuals were identified correctly, but that the ability to identify CCFS correctly was low. The clinical value of the TMT does not contribute to diagnostic decisions, rather than ability provide insight into the subject’s neuropsychological difficulties. (Lezak, Howieson, Loring, 2004) The differences in reaction time of the Task A and B, which directly tests spatial working memory, is not significantly different from normative data. This could be because the Task A, B only requires the children to do one thing continually; locate a target within a 25 circles, whereas the test for switching attention requires the children to do two things continually; count one way until encountering an arrow then count the opposite way.

Other previous study assessment of differences in gray matter volume (GMV) of, CCFS dorsolateral prefrontal cortex patients had significantly lower GMV than controls, and there was an increase in GMV in the CFS group such that the initial between-group difference in GMV decreased following CBT. (Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome Floris P. de Lange, Brain 2008 131 2172-2180)

Among children aged from 10 to 15, a high CCFS prevalence rate group, this region of the brain is still under development and not yet matured. (Mizuno et al.) The dysfunction of dorsolateral prefrontal cortex with CCFS, it was thought same condition in adult CFS, and it was suggested that the reversible function recovery was capable by treatment. The brain is still immature of adolescents a high CCFS prevalence rate group, so it is important that prevent children and adolescents from chronic fatigue, if they contract CCFS early treatment is necessity.

The present study has limitations. We performed this study with a limited number of subjects. To generalize our results, studies involving a large number of subjects are essential.

In addition, not all patients benefited from therapy, and it is unclear that the behavioural effects are likely to be the result of CBT and GET or the result of pharmacotherapy, or other unspecific factors.

**Conclusion**

Our findings indicate that have cognitive dysfunction particularly alternative attention associated with CCFS and it reversed to the improvement in mental fatigue. The cognitive dysfunction with CCFS, it was thought same condition in adult CFS, and it was suggested that the reversible function recovery was capable by treatment. The brain function is still immature of adolescents a high CCFS prevalence rate group, so it is important that prevent children and
adolescents from chronic fatigue; if they contract CCFS early treatment is necessity.

Acknowledgements

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15. (Afari and Buchwald, 2003)