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# Cognitive Function and Quality of Life of Muscular Dystrophy

Yukihiko Ueda

## Abstract

Duchenne muscular dystrophy and myotonic dystrophy are genetic, progressive muscle diseases. These muscular dystrophies, which are currently incurable, cause muscle wasting or muscle weakness and decrease patients' quality of life. In addition to muscular impairments, cognitive impairments are also reported in both Duchenne muscular dystrophy and myotonic dystrophy. Cognitive impairments in each type of muscular dystrophy are different and closely related to psychosocial variables and the quality of life of the patients. We reviewed the features of cognitive functions in each type of muscular dystrophy and their correlations with the quality of life of patients. Based on the findings, we have suggested effective interventions for improving the quality of life of muscular dystrophy patients.

**Keywords:** Duchenne muscular dystrophy, myotonic dystrophy, quality of life, cognitive function

## 1. Introduction

Muscular dystrophy is a genetic, progressive disease of the muscles with several clinical forms, all of which have an early onset and are incurable with current medical technology. These diseases severely decrease motor functions and make it difficult to live an independent social life or engage in an occupation. In this decade, the life span of muscular dystrophy patients has improved considerably as a result of improvements to ventilators. Therefore, it has become necessary to help patients maintain their quality of life (QOL) throughout the life span. Furthermore, muscular dystrophy causes not only physical impairments but also cognitive impairments [1]. Such cognitive impairments are associated with difficulties in communicating with medical workers and family members and also affect medical compliance and the QOL.

## 2. QOL of patients with muscular dystrophy

Muscular dystrophy has an early onset, and thereafter body functions decrease progressively beginning with a decrease in motor functions that require the use of a wheelchair to maintain mobility and a decrease in the breathing function that require a ventilator to maintain breathing, which makes the patients bedridden. As a result, the patients' behavior repertoire becomes severely restricted, and they require considerable assistance. Netterlund et al. investigated activities of daily living (ADL) and the QOL of 45 people (mean age 44 years) with muscular

dystrophy [2] and reported that all the sampled patients were living at home. The QOL was assessed by the Sickness Impact Scale (SIP) and the Psychosocial Well-Being Questionnaire, which indicated that their disability and dependence on others increased, whereas ADL decreased during the previous 5 years. Moreover, the patients' QOL and life satisfaction also decreased. Boström and Ahlström investigated 46 people with muscular dystrophy through interviews using a qualitative research approach for 10 years [3]. They reported that nearly all muscular dystrophy patients had decreasing functions such as limited mobility, increasing fatigue, and feebleness, accompanied by psychological distress. Moreover, if there is a difficulty in securing assistance for patients to continue living in their homes, they must live in recuperation wards.

Ueda et al. [4] investigated the QOL of 50 inpatients with muscular dystrophy. The QOL was assessed by the World Health Organization-Quality of Life 26 (WHO-26). Results indicated that the mean QOL score (SD) of patients with muscular dystrophy was 2.96 (0.34), which was significantly lower than the general Japanese population (mean 3.75) or patients with cancer (mean 3.3). The results of the comparison between patients' conditions indicated that those who could move by using a wheelchair had higher QOL scores than those who were bedridden. The QOL score of patients that had throat surgery was higher than those who had no surgery. The comparison between clinical types indicated that the QOL in myotonic dystrophy was significantly lower than limb girdle-type muscular dystrophy or Fukuyama-type congenital muscular dystrophy. They also investigated factors that could affect the QOL of patients with muscular dystrophy, including age, gender, clinical type, duration of the diseases, throat surgery, duration from throat surgery, functional independence (Barthel Index), use of a ventilator, use of a wheelchair, use of a computer, the frequency of family visits, and participation in activities. The results of categorical regression analysis ( $R^2 = 0.671$ ,  $R^2 = 0.400$ ,  $F = 2.479$ ,  $P < 0.05$ ) showed that only the use of a computer influenced the QOL ( $\beta = 0.598$ ). These results suggest that using a computer could be an effective method of maintaining or improving the QOL of muscular dystrophy inpatients, with deteriorated body functions and limited activities due to the progression of the disease.

### **3. Profile of cognitive functions in Duchenne muscular dystrophy**

Duchenne muscular dystrophy (DMD) is a genetic disease of the muscles caused by deficits in the dystrophin-glycoprotein complex (DGC). The loss of dystrophin is associated with a complex set of physiological and anatomical adaptations that are known contributors to the cognitive deficits observed in patients with DMD and related disorders. Some studies have indicated disordered CNS architecture, abnormalities in dendrites, and loss of neurons in boys with DMD [5]. These boys show EEG abnormalities [5], and the prevalence of epilepsy is higher in DMD (6.3%) than the general population [6]. Studies of CT [7] and MRI [8] have indicated brain atrophy in patients with DMD. These studies suggest that functional and morphological abnormalities are affected by the absence of dystrophins.

Several studies have assessed the intellectual functioning of boys with DMD and reported mean IQs that are approximately one standard deviation lower than the general population [9–12]. Also, boys with DMD have lower verbal IQs (VIQ) than performance IQs (PIQ) [10, 13–16]. Furthermore, Hinton et al. [17] indicated that boys with DMD did poorly on Story Recall, Digit Span, and Auditory Comprehension compared to unaffected siblings. They concluded that verbal working memory was impaired selectively. Moreover, sequential processing ability is more impaired than simultaneous processing ability in boys with DMD [14, 18].

Cotton [19] reported that the boys with DMD had a mean full-scale IQ (FIQ) and a PIQ score of approximately 80 based on a meta-analysis of 1224 boys with DMD. However, the mean VIQ scores improved with age, particularly in the verbal subscales: Information, Similarities, Arithmetic, Comprehension, and Digit Span. Moreover, there were less deficits in older age groups in abilities of logical verbal abstract reasoning, language development, and arithmetic. They suggested the need to adopt more specific and directed neuropsychological assessments to further delineate age-related cognitive changes in DMD populations [19].

### 3.1 Cognitive functions in adults with DMD

Ueda et al. [20] conducted a study using a wide range of neuropsychological assessment instruments to investigate whether the cognitive weaknesses remain in adult patients with DMD.

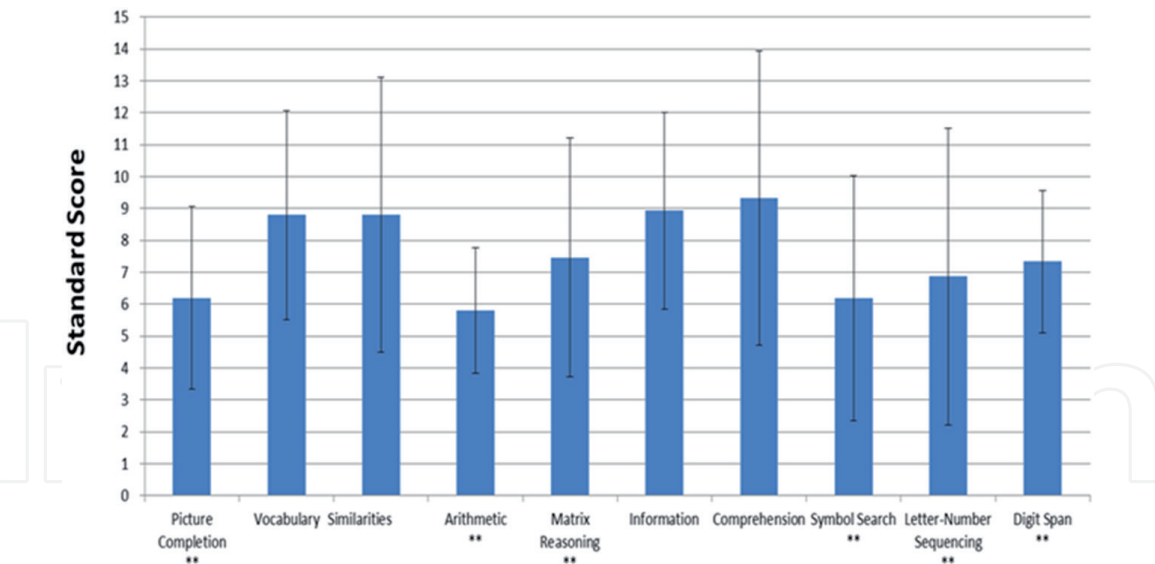
Fifteen inpatients and outpatients with DMD (mean age = 30.4 years, age range = 19–44 years) participated in the study. Twenty-four subscales of the Wechsler Adult Intelligence Scale-III (WAIS-III), the Clinical Assessment for Attention (CAT) [21], and the Wechsler Memory Scale (WMS-R) were used for the assessment. The assessment instruments were:

- Ten WAIS-III subscales: (1) Picture Completion, (2) Vocabulary, (3) Similarities, (4) Arithmetic, (5) Matrix Reasoning, (6) Information, (7) Comprehension, (8) Symbol Search, (9) Letter-Number Sequencing, and (10) Digit Span
- Seven subscales of CAT: (11) Auditory Detection, (12) Symbol Digit Modalities, (13) Memory Updating (3 span), (14) Memory Updating (4 span), (15) Paced Auditory Serial Addition Test (PASAT; 2 sec.), (16) PASAT (1 sec.), and (17) Position Stroop
- Seven subscales of WMS-R: (18) Logical Memory, (19) Visual Paired Association, (20) Verbal Paired Associate, (21) Figural Memory, (22) Delayed Logical Memory, (23) Delayed Visual Paired Association, and (24) Delayed Verbal Paired Associates

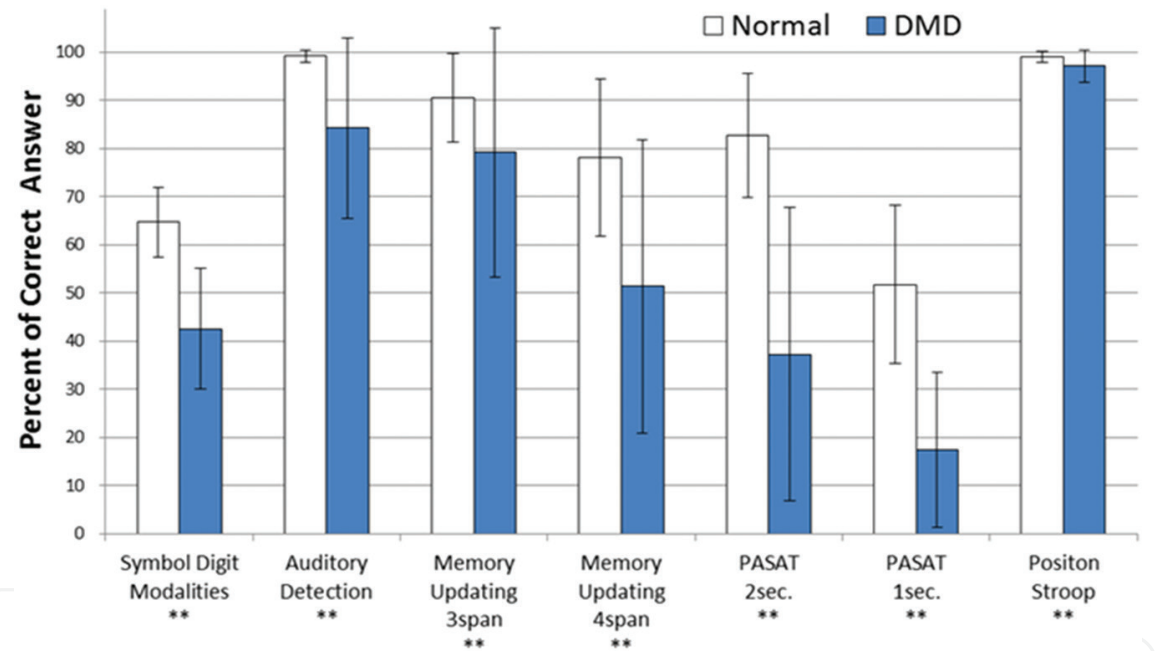
All assessment instruments were standardized for use in Japan. Therefore, the Z test was used to compare the scores of DMD patients on the 24 subscales with the normal population.

The mean and SD of WAIS-III in DMD adults patients (**Figure 1**), Picture Completion (M = 6.20, SD = 2.86), Arithmetic (M = 5.80, SD = 1.97), Matrix Reasoning (M = 7.47, SD = 3.74), Symbol Search (M = 6.20, SD = 3.84), Letter-Number Sequencing (M = 6.97, SD = 4.64), and Digit Span (M = 7.33, SD = 2.23) were significantly deficient ( $p < .01$ ) compared to the normal population (M = 10, SD = 3). However, there were no significant differences in Vocabulary (M = 8.80, SD = 3.28), Similarities (M = 8.80, SD = 4.31), Information (M = 8.93, SD = 3.08), and Comprehension (M = 9.33, SD = 4.61). The mean FIQ of adult patients with DMD was 87.4 (SD = 15.96, range = 61–109), which was estimated by dyadic short forms of WAIS-III [22, 23].

On the CAT, they were significantly deficient in all subscales (**Figure 2**): Symbol Digit Modalities (M = 42.5, SD = 12.5), Auditory Detection (M = 84.2, SD = 18.8), Memory Updating 3 span (M = 79.2, SD = 25.9), Memory Updating (4 span) (M = 51.4, SD = 30.4), PASAT (2 sec.) (M = 37.2, SD = 30.5), PASAT(1 sec.) (M = 17.4, SD = 16.1), and Position Stroop (M = 97.1, SD = 3.3). In addition, the total Response Time for Position Stroop of patients group (M = 163.0, SD = 75.5) was significantly longer than the normal population.



**Figure 1.** Comparison between DMD sample (N = 15) and normal population for WAIS-III. Means and SDs for standard scores are shown. The mean and SD for the normal population are 10 and 3. \*\*p < .01. Ueda et al. [4].

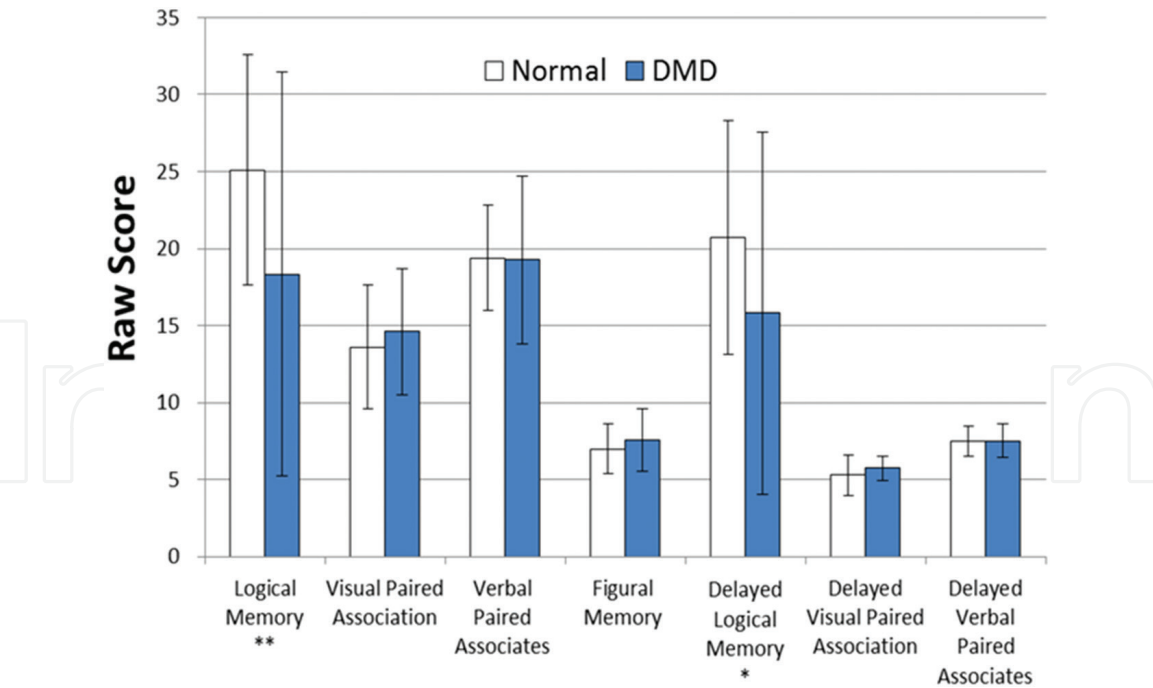


**Figure 2.** Comparison between DMD sample (N = 15) and normal population for CAT. Means and SDs for percentage of correct answers are shown. \*\*p < .01. Ueda et al. [4].

On the WMS-R, Logical Memory (M = 18.3, SD = 13.1) and Delayed Logical Memory (M = 15.8, SD = 11.7, Z = 2.495, p < .01) were significantly lower. However, there were no significant differences between patient group and normal population in other subscales: Visual Paired Association (M = 14.6, SD = 4.1), Verbal Paired Associates (M = 19.3, SD = 5.4), Figural Memory (M = 7.6, SD = 2.0), Delayed Visual Paired Association (M = 5.7, SD = 0.8), and Delayed Verbal Paired Association (M = 7.5, SD = 1.1) (**Figure 3**).

These results indicate that specific cognitive functions of adults with DMD are deficient compared to the normal population. In particular, the ability to sequentially process auditory information was reduced in attention and memory. On the other hand, cognitive abilities that do not require sequential processing were not impaired, suggesting that adults with DMD remain relatively weak in sequential auditory information processing. Moreover, tests of visual information processing showed impairments. These findings suggest that sequential visual information





**Figure 3.** Comparison between DMD sample ( $N = 15$ ) and normal population for WMS-R. Raw means and SDs are shown.  $*p < .05$ ,  $**p < .01$ . Ueda et al. [4].

processing involving alterations of attention and processing speeds were weak in adult patients with DMD. The weaknesses of cognitive functions were maintained without improvement in adults with DMD. It suggests that these deficits are not caused by environmental factors but represent organic impairments.

Taylor et al. [24] reported differences in neuropsychological profiles of DMD patients and then postulated that these differences are caused by the affected number and type of CNS-expressed isoforms. The site of DMD mutation and the extent of the cognitive deficits are related to each other distinctly. The best model for this phenomenon was that mutations affecting exons 45 to 50 are mainly mutations of coding exons. This effect is restricted to Dp260 and Dp427. In the case of mutations that affected the coding regions of the CNS expressing isoforms Dp140pc and Dp71 are clustered together, there was a significant difference in the degree of cognitive disability. Mutations affecting the Dp140 isoforms affected FIQ less than mutations affecting the Dp140 promoter or protein-coding regions [24]. Nevertheless, the relationship between these isoforms and the ability of sequential information processing has not been clarified. Further research is needed to explore the mechanisms underlining cognitive deficits associated with DGC.

Over the past few decades, the prognosis of DMD patients has shown remarkable improvement; however, the improvement of their quality of life still remains as an important task. Compared with ADHD [25], autistic spectrum disorders, and obsessive-compulsive disorders [25, 26], cognitive problems of DMD patients have been discussed. Particularly, the poor facial recognition of DMD patients [27] might have a negative influence on their QOL. A better evaluation of cognitive deficits in DMD patients could improve their relationship with care staff, thereby contributing to better care and improving the QOL.

#### 4. Cognitive functions of myotonic dystrophy type 1

Myotonic dystrophy type 1 (DM1) is a chronic progressive multi-system disorder with autosomal dominant inheritance. This disorder is caused by a cytosine-thymine-guanine (CTG) repeat expansion in the protein kinase (DMPK) gene [28],

resulting in cognitive and psychiatric dysfunctions that have a significant impact on the QOL [29, 30].

Okkersen et al. [31], based on a systematic review and meta-analysis, demonstrated that DM1 patients have significant deficits in all cognitive domains compared to controls. Effect sizes were large ( $-.76$ – $1.01$ ) for global cognition, intelligence, visual memory, visuospatial perception, visuoconstruction, psychomotor speed, and social cognition. Moreover, small to medium effect sizes ( $-.33$ – $.66$ ) were observed for language, executive functioning, overall and verbal memory, as well as attention.

A few studies have examined the relationship between cognitive impairment and the QOL [30, 32, 33]. However, the majority of these studies did not take all the

Cognitive variable	n	Mean	SD	Frequency, %,	Frequency, %,
				(95% CI): 1 SD below	(95% CI): 2 SD below
General cognitive function					
MMSE	60	26.6	3.1		
WAIS-III: Estimated IQ	59	78.8	19.1	63 (51–73)	27 (18–38)
Abstract reasoning					
WAIS-III: Similarities	60	7.7	3.2	52 (40–63)	20 (12–30)
VPTA: Story Telling	57	1.7	2.1	30 (20–41)	7 (2–15)
Attention/working memory					
CAT: Auditory Detection task (%hit)	58	60.4	26.5	79 (69–88)	67 (56–77)
CAT: Auditory Detection task (%correct)	58	82.7	18.9	67 (56–77)	60 (49–71)
CAT: PASAT-2	46	42.2	26	74 (61–84)	41 (29–54)
CAT: Memory Updating 3	57	73.3	22.2	44 (33–56)	30 (20–41)
CAT: Digit Span (backward)	56	4.1	1.2	55 (44–67)	16 (9–26)
CAT: Tapping Span (backward)	57	4.4	1.4	49 (38–61)	9 (4–18)
CAT: Tapping Span (forward)	57	5.7	1.2	26 (17–38)	7 (2–15)
CAT: Digit Span (forward)	56	5.7	1.4	50 (38–62)	5 (1–13)
Executive function					
CAT: Position Stroop test	56	134.3	71.6	86 (76–93)	79 (68–87)
TMT-B	53	220.5	174.5	45 (34–57)	34 (23–46)
FAB	59	15.9	2.0	20 (12–31)	14 (7–23)
WCST: Categories Achieved	55	2.7	2.0	44 (32–56)	11 (5–20)
Phonemic fluency	60	23.7	9.0	40 (29–51)	10 (4–19)
Semantic fluency (animal)	60	17.9	4.6	38 (28–50)	8 (3–17)
Processing speed					
CAT: Visual Cancellation task (Ka)	53	186.6	99.9	96 (89–99)	91 (81–96)
CAT: Symbol Digit Modalities test	56	36.7	14.0	82 (72–90)	54 (42–65)
TMT-A	59	180.9	117.9	66 (55–76)	47 (36–59)
Visuoconstructive ability					
WAIS-III: Block Design	59	4.4	2.5	85 (75–92)	64 (53–75)
VPTA: Copying Figures	56	1.7	1.5	48 (37–60)	48 (37–60)
VPTA: Bisection of Lines	57	1.4	1.5	39 (28–50)	28 (18–39)
VPTA: Copying Flowers	55	2.3	3.3	42 (31–54)	24 (15–35)

**Table 1.**  
*Cognitive function of patients with DM1 (Fujino et al. [34]).*

domains of cognition into consideration, and they used QOL measures insensitive to specific issues related to DM1.

4.1 Assessment of cognitive function of DM1

Fujino et al. [34] conducted a study of the affected cognitive domains and evaluated the relationship between cognitive functions, psychological factors, and the QOL. Participants (N = 60) were recruited from five hospitals of National Hospital Organization in Japan. The general cognitive functions of the participants were evaluated with the Japanese version of the Mini-Mental State Examination (MMSE), and the estimated IQ was calculated from two subsets (Picture Completion and Information) of WAIS-III. Abstract reasoning was evaluated by using the Similarities subset and the Visual Perceptions Test for Agnosia (VTPA) Story Telling subset [35] in WAIS-III. Attention and working memory were evaluated with CAT subsets (Digit Span [forward, backward], Tapping Span [forward, backward], Auditory Detection task, Memory Updating 3, and PASAT-2. Executive function was evaluated with the Wisconsin Card Sorting Test (WCST), the Frontal Assessment Battery (FAB), the Trail Making Test (TMT)-B, the CAT Position Stroop test, and the semantic and phonemic fluency test. For the assessment of processing speed, TMT-A and 2 CAT subtests (Visual Cancellation task and Symbol Digit Modalities test) were used. For the evaluation of visuoconstructive ability, the WAIS-III Block Design and VPTA subtests (Copying Figures and Flowers, Bisection of Lines) were used. The CAT and VPTA are cognitive functional test batteries, which were developed by the Japan Society for Higher Brain Dysfunction.

As in psychological functioning, the five specific domains were assessed: apathy, depression, excessive daytime sleepiness, fatigue, and social responsiveness. The evaluation tools were Apathy Scale [36], Patients Health Questionnaire-9 (PHQ-9) [37], Epworth Sleepiness Scale (ESS) [38], Multidimensional Fatigue Inventory (MFI) [39], and Social Responsiveness Scale (SRS) [40]. The QOL was estimated with the Muscular Dystrophy Quality of Life Scale (MDQoL) [41] that was developed for Japanese patients with muscular dystrophies including DM1. This scale consists of 10 subscales: Psychological Stability, ADL, Environment, Hope, Activity, Health Relationships, Family, Sexuality, Breathing, and Defecation.

Psychological variable	n	Mean	SD	Frequency, %, (95% CI): 1 SD below	Frequency, %, (95% CI): 2 SD below
Apathy					
Apathy Scale	59	18.5	6.4	59 (48–70)	22 (14–33)
Depression					
PHQ-9	60	8	5.5	47 (36–58)	23 (15–34)
Excessive daytime sleepiness					
ESS	59	6.6	4.2	31 (21–42)	5 (1–13)
Fatigue					
MFI	59	64.2	12.0	46 (35–57)	15 (8–25)
Social responsiveness					
SRS	23	56.7	29.7	30 (15–50)	13 (4–30)
QoL (2 factor scores)					
Psychosocial Relationships	57	60.4	17.5		
Physical Functioning and Health	57	62.2	19.0		

Table 2.  
Psychological variables and QOL of patients with DM1 (Fujino et al. [34]).



4.2 Cognitive impairments and QOL of DM1

The mean age of the 60 participants with DM1 (35 men and 25 women) was 47.1 (SD = 10.8), and the mean age at the onset of DM1 was 29.0 (SD = 13.2). Moreover, the mean duration of illness was 17.2 years (SD = 11.4). Also, the mean number of CTG repeats was 1132.2 (SD = 1025.2).

The results indicated that most cognitive functions of DM1 patients were lower than the general population (**Table 1**). In particular, more than half of the patients scored 2 SD lower than the general population for attention and working

Cognitive function	Psychosocial Relationships		Physical Function and Health	
	Correlation coefficient	Adjusted <i>P</i> -value	Correlation coefficient	Adjusted <i>P</i> -value
General cognitive function				
WAIS-III: Estimated IQ	0.27	0.197	0.05	0.850
MMSE	0.16	0.467	0.01	0.975
Abstract reasoning				
WAIS-III: Similarities	0.21	0.313	-0.05	0.857
VPTA: Story Telling	-0.01	0.975	0.02	0.938
Attention/working memory				
CAT: Auditory Detection (%hit)	0.08	0.810	0.03	0.938
CAT: Auditory Detection (%correct)	0.18	0.424	-0.01	0.976
CAT: PASAT-2	0.21	0.389	0.08	0.810
CAT: Tapping Span (backward)	0.30	0.155	0.16	0.467
CAT: Digit Span (backward)	0.29	0.172	0.11	0.606
CAT: Memory Updating 3	0.33	0.081	0.28	0.194
CAT: Digit Span (forward)	0.39*	0.033	0.13	0.589
CAT: Tapping Span (forward)	0.40*	0.030	0.18	0.424
Executive function				
CAT: Position Stroop test	-0.25	0.243	0.08	0.810
TMT-B	-0.27	0.232	-0.15	0.543
FAB	0.20	0.346	0.10	0.654
WCST: Categories Achieved	0.28	0.197	-0.04	0.893
Phonemic fluency	0.14	0.557	-0.16	0.467
Semantic fluency (animal)	0.22	0.306	-0.12	0.589
Processing speed				
CAT: Visual Cancellation task (Ka)	-0.48*	0.006	-0.24	0.275
CAT: Symbol Digit Modalities test	0.22	0.306	0.07	0.810
TMT-A	-0.38*	0.033	-0.06	0.831
Visuoconstructive ability				
WAIS-III: Block Design	0.24	0.243	0.05	0.857
VPTA: Copying Figures	0.03	0.938	0.13	0.589
VPTA: Bisection of Lines	-0.24	0.263	-0.17	0.447
VPTA: Copying lowers	-0.01	0.976	0.07	0.810

\*Significant after adjustment using false discovery rate.

**Table 3.**  
Correlations between cognitive function and QOL (Fujino et al. [34]).

Psychological measure	Psychosocial Relationships		Physical Function and Health	
	Correlation coefficient	Adjusted <i>P</i> -value	Correlation coefficient	Adjusted <i>P</i> -value
Apathy: Apathy Scale	-0.37*	0.035	-0.20	0.343
Depression: PHQ-9	-0.52*	0.001	-0.65*	<0.001
Excessive daytime sleepiness: ESS	-0.13	0.589	-0.11	0.601
Fatigue: MFI	-0.42*	0.014	-0.55*	<0.001
Social responsiveness: SRS	-0.20	0.589	0.10	0.825

\*Significant after adjustment using false discovery rate.

**Table 4.**  
Correlation between psychological variables and QOL (Fujino et al. [34]).

memory (Auditory Detection task, 67% [hit], 60% [correct]), executive function (Position Stroop test, 79%), processing speed (Visual Cancellation task, 91%, Symbol Digit Modalities test, 54%), and visuoconstructive ability (Block Design, 64%). Although patients were markedly impaired on tasks that assessed complex attentional functions (PASAT-2 and Memory Updating 3), they were not severely affected on those assessing simple attentional functions (Digit Span [forward] and Tapping Span [forward]). Certain patients scored 2 SD higher than the general population on psychological factors including apathy (22%), depression (23%), and fatigue (15%) (**Table 2**).

Factor analysis categorized MDQoL results into Psychosocial relationship factor and Physical functioning and Health factor. The Psychosocial relationship factor was associated with Digit Span (forward,  $r = 0.39$ ), Tapping Span (forward,  $r = 0.40$ ), TMT-A ( $r = -0.38$ ), and Visual Cancellation task ( $r = -0.48$ ) (**Table 3**). Additionally, the Psychosocial relationship factor was negatively associated with apathy ( $r = -0.37$ ), depression ( $r = -0.52$ ), and fatigue ( $r = -0.42$ ). Physical Functioning and Health factor was negatively associated with depression ( $r = -0.66$ ) and fatigue ( $r = -0.55$ ). Apathy was associated with the FAB ( $r = -0.47$ ), Visual Cancellation ( $r = 0.46$ ), and Auditory Detection task ( $r = -0.44$ ) (**Table 4**).

These results demonstrated that patients with DM1 have specific cognitive impairments including executive dysfunctions, processing speed impairments, attentional problems, and visuoconstructive problems. Improved cognitive abilities in attention and working memory, as well as processing speed, were associated with higher QOL, whereas higher apathy, depression, and fatigue were associated with lower QOL. It is possible that apathy mediates the influence of cognitive functions on the QOL, which suggest that the reduction of apathy might lead to better cognitive performance or vice versa [42]. Cognitive assessment can provide useful information for patients, allowing them to plan support in their daily lives. Cognitive interventions might also contribute to improving the QOL of patients with DM1 because neuropsychological rehabilitation and cognitive remediation have been effective in other neurological conditions [43–45].

## 5. Psychopathological features and personality of DM1 patients

Some studies pointed that depression and fatigue predict psychological and physical QOL in patients with muscular diseases [46, 47]. Additionally, apathy could promote social inhibition and avoidance of social interactions [48]. All of them, in conjunction with each other, lead to the deterioration of the

QOL. Therefore, the psychological interventions for DM1 should incorporate these factors as potential targets for improving patients' QOL.

Minier et al. [49] conducted a systematic literature review of psychopathological features in DM1 and reported that patients with DM1 present mild psychopathological problems, such as interpersonal difficulties, lack of interest, dysphoria, concern about bodily functioning, and hypersensibility. However, they do not present more psychiatric disorders than the general population, except for personality disorders and depression. Moreover, avoidant personality disorder was the most common of several personality disorders among DM1 patients.

### **5.1 Lack of awareness about the illness**

In clinical practice, DM1 patients commonly showed less awareness of the disease distress and its progression. This is named anosognosia or lack of awareness, which can lead to misattributions of symptoms, delay of diagnostic procedures, and low compliance with treatment. The lack of awareness about their illness often is observed in individuals with brain diseases and neurodegenerative disorders, such as Alzheimer's diseases and acquired brain injury. In these disorders, the lack of awareness can be a direct consequence of the underlying pathological process [50]. Research on brain injuries suggests that the prefrontal cortex plays a crucial role in maintaining awareness [51].

Baldanzi et al. [52] conducted a study to estimate the prevalence of disease awareness in 65 adult patients with DM1. The degree of awareness was evaluated by comparing motor impairments using MIRS, patients' complaints about their symptoms, and by comparing INQOL between caregivers. The results indicated that 51.6% of patients were unaware of the disease, and the lack of awareness was most prominent in Independence (52.4%) and Social Relationship (47.6%) domains. Moreover, the lack of awareness was significantly related to failures in cognitive test performance, specifically in the domains of visuospatial memory, cognitive flexibility, and conceptualization. Baldanzi et al. suggested that gaining a better understanding of anosognosia would be useful for the medical management of patients with DM1 and for providing guidance for occupational and social interventions.

## **6. Interventions**

DM1 leads to substantial physical impairments, which in combination with the neuropsychological effects of the condition results in severely restricted social participation. However, there is little evidence for the efficacy of rehabilitative approaches designed to improve health status. Previous studies have demonstrated that fatigue is a highly prevalent, debilitating symptom of DM1 [53, 54], and cognitive behavioral therapy reduces fatigue and increases objective activity, as well as social participation in patients with facioscapulohumeral muscular disease [55]. Therefore, Okkersen et al. [56] conducted a large randomized trial to determine whether cognitive behavioral therapy plus optional graded exercise improved the health status of patients with DM1 compared to standard care alone.

### **6.1 Cognitive behavioral therapy for the patients with DM1**

The study by Okkersen et al. [56] was a large-scale, multicenter, single-blind, randomized trial conducted at four neuromuscular referral centers located in France, Germany, Netherlands, and the UK, which was known as Observational

Prolonged Trial In Myotonic Dystrophy Type 1 to Improve Quality of Life- Standards, a Target Identification Collaboration (OPTIMISTIC). Participants (N = 255) were aged 18 years and older with a confirmed genetic diagnosis of DM1, who were severely fatigued (CIS-fatigue scale, score  $\geq 35$ ) but able to walk independently. They were randomly assigned to either cognitive behavioral therapy plus standard care and optional graded exercise (n = 128) or standard care alone (n = 127). Cognitive behavioral therapy focused on addressing the reduced initiative in the patients, increasing physical activity, optimizing social interactions, regulating sleep-wake patterns, coping with pain, and beliefs about fatigue and DM1. Cognitive behavioral therapy was delivered over a 10-month period in 10–14 sessions based on a manual, by therapists that had extensive training. It was possible to include a graded exercise module that was individually tailored and incorporated moderate-intensity exercises such as walking, cycling, jogging, or dancing for a minimum of 30 minutes, three times a week.

The active-c score of participants in cognitive behavioral therapy increased from a mean (SD) of 61.22 (17.35) at baseline to 63.92 (17.41) at the 10th month. However, the score decreased from 63.00 (17.35) to 60.79 (18.49) in the standard care group. The mean difference between the groups was 3.27 and significant ( $p = 0.007$ ). As secondary outcomes, the cognitive behavior therapy group showed significant differences in the 6-minute walk test, the fatigue and daytime sleepiness scales, CIS-fatigue, and daily activity levels. Moreover, both groups had decreased scores in the myotonic dystrophy health index and INQOL. However, there was no significant difference between the groups. Also, there were no changes or no differences between the groups on the apathy scale, Stroop-color-word interference, accelerometry for the least active 5 hours, or the Beck Depression Inventory. Based on these results, Okkersen et al. [56] emphasized that cognitive behavioral therapy could increase the capacity for activity and social participation in severely fatigued patients with DM1. This study showed that cognitive behavioral therapy could be one effective intervention for improving the health status of patients with DM1.

## 7. Conclusion

Cognitive impairments are observed in patients with DMD and DM1. These impairments are caused by gene mutations, especially by CNS-expressed isoforms. These impairments, however, do not encompass every aspect of their intellectual ability. Patients with DMD show deficits in sequential information processing and alterations of attention and processing speed. Moreover, patients with DM1 have weaknesses in executive function, processing speed, attention, and visuoconstructive abilities. These cognitive impairments are related to their psychosocial characteristics, social participation, and the QOL. Especially, apathy, depression, and fatigue are the key factors that deteriorate the QOL of patients with DM1. It is suggested that precisely targeted cognitive assessments and cognitive intervention are necessary to provide them with better care and improve their QOL.



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