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Study of Duchenne muscular dystrophy long-term survivors aged 40 years and older living in specialized institutions in Japan

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Abstract

The national muscular dystrophy wards database of Japan lists 118 long-term Duchenne muscular dystrophy (DMD) patients who were at least 40 years old as of October 1, 2013. To elucidate the clinical features of DMD patients aged 40 years and older, we obtained gene analysis and muscle biopsy findings, as well as medical condition information. Ninety-four of the registered patients consented to participate, of whom 55 meeting genetic or biochemical criteria confirming DMD were analyzed. The mean age at the time of the study was 43.6 ± 3.0 years, while at the time of independent ambulation loss it was 10.6 ± 1.5 years and at mechanical ventilation introduction it was 24.1 ± 5.5 years. All were receiving continuous ventilation support, 27 with non-invasive positive pressure ventilation and 28 with tracheal intermittent positive pressure ventilation. Thirty-eight were receiving β-blockers or a renin-angiotensin system inhibitor, while 9 were free from those agents. Forty had maintained oral nutrition. The 55 analyzed patients had survived into their 40s by receiving multidisciplinary intervention. Our findings emphasize the need of future studies to investigate disease modifiers and the mechanism of long-term survival. In addition, establishment of a worldwide care standard with focus on quality of life for adult males with DMD is important.

Keywords: Duchenne muscular dystrophy (DMD); Long-term survivor; Conventional multidisciplinary care

1. Introduction

Duchenne muscular dystrophy (DMD) is a fatal disease caused by a mutation of the *dystrophin* gene [1,2]. Affected individuals slowly and progressively develop consecutive motor dysfunctions, resulting in muscle weakness, respiratory insufficiency, cardiac failure, and nutritional insufficiency. Although non-intervention generally leads to death in adolescence, conventional multidisciplinary care has prolonged the lifespan of individuals affected by this disease throughout the world [1–3].

In Japan, there are 27 national institutions with specialized wards for patients with DMD, other types of muscular dystrophies, or related neuromuscular disorders. The Japan National muscular dystrophy research group has been maintaining a database of inpatients in all of these specialized wards (muscular dystrophy wards database: MDDB) since 1999, with updates recorded on October 1 of each year. The total number of patients registered in the MDDB annually is approximately 2200, among whom the proportion with DMD has gradually decreased from 40.2% in 1999 to 32.2% in 2013 [4,5]. On the other hand, the mean age of those DMD patients gradually increased from 23.6 to 30.1 years from 1999 to 2012

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[5]. In 2012, there were 94 long-term survivors with DMD who were at least 40 years of age and registered in the MDDB.

We were interested in the clinical features of these long-term survivors, including whether their medical management was uniquely customized and whether their diagnosis was correct. Thus, we conducted the present study to collect detailed clinical features of these long-term survivors with DMD and analyzed the findings for use in future investigations of unknown DMD disease modifiers.

2. Subjects and methods

2.1. Muscular dystrophy wards and MDDB

The 27 specialized wards for patients with muscular dystrophies and related neuromuscular disorders in Japan were all established in the 1960s [4,5]. Initially, their main purpose was to provide long-term care beds and school education with support as a sanatorium for boys with DMD. At present, many of the patients stayed for the entirety of their life. In these specialized institutions, experienced care is given based on accumulated knowledge gained by the experience of skillful experts, including appropriate rehabilitation exercises, nutrition support, mechanical ventilation, cardio-protection therapy, psychosocial support, education, family care support, recreation, and participation in society, for well-organized management of DMD patients with the goal of maintaining their physical and mental condition [6–8]. Some reports from these institutions have indicated that patient survival has been improved with appropriate intervention [9–11]. The MDDB is used to collect anonymous data for each patient receiving care at these institutes, such as gender, age, diagnosis, and general condition, with the information verified by attending physicians and annually renewed [4,5].

2.2. Patient information

This was a cross-sectional observation study conducted from August 2013 to December 2013 and the protocol has been registered in the UMIN Clinical Trials Registry (UMIN000017322). Written informed consent was obtained from all analyzed patients.

In 2012, 733 DMD patients were registered in the MDDB [5]. Among them, 118 were 40 years of age or older on July 1, 2013 and receiving care in 21 of the 27 institutions. We sent a questionnaire to the attending physicians of those 118 patients to obtain detailed information, including confirmation of diagnostic evidence of DMD, patient medical condition, and treatments received. The annually renewed dataset contained in the MDDB and findings obtained by our questionnaire survey were combined to determine age at the time of this study, loss of independent ambulation, introduction of mechanical ventilation, present cardio-respiratory status, mental and other physical conditions, body weight, nutrition, corticosteroid use, spinal surgery, and other therapies for analysis. Details regarding those items are shown in Table 1. The criteria for diagnosis of DMD used in this study were as follows.

DMD was confirmed when at least one of the following criteria was met [1].

Table 1
Information available in 2013 version of database, and questionnaire items for attending physicians.

Information available in 2013 MDDB
Present age
Present respiratory status (NPPV, TIV)
Mechanical ventilation (age at introduction, type)
Present nutritional method (oral nutritional supply, gastrostomy, tube feeding)
Present body weight
Questionnaire items for attending physicians
Diagnosis of DMD
Methods and results of gene analysis
Muscle biopsy findings
Age at loss of independent ambulation
Condition and medical treatment
Treatment of cardiomyopathy
Status of cardiomyopathy (ejection fraction in echocardiography findings and plasma BNP)
Corticosteroid therapy (used prior, not used, now using)
Spinal surgery (done, not done)
Central nervous symptoms (mental retardation, autistic disorder, epilepsy)
Other matters worthy of mention

BNP, brain natriuretic peptide; DMD, Duchenne muscular dystrophy; EF, ejection fraction; MDDB, muscular dystrophy wards database; NPPV, non-invasive positive pressure ventilation; TIV, tracheal intermittent ventilation.

1. Genetic findings confirming presence of *dystrophin* gene mutation and loss of independent ambulation by 13 years of age.
2. Immunological confirmation of defect of dystrophin protein in biopsied muscle tissue shown by muscle pathology findings.

2.3. Statistics

Binary and categorical variables were used to calculate frequencies and proportions, while continuous variables we used to calculate mean, standard deviation (SD), and range (minimum to maximum) values. Comparisons of continuous variables between two groups were performed using Student's t-test. Spearman's correlation was used for comparison between age at loss of independent ambulation and introduction of mechanical ventilation. Missing data were excluded from analysis. All data analysis was performed using IBM SPSS software for Windows, version 22.0 (IBM Corp.), and Microsoft Excel 2013.

2.4. Ethical approval

The study protocol was approved by the local ethics committee of Toneyama National Hospital (clinical research number 1312).

3. Results

3.1. Diagnostic evidence of DMD

Of the 118 DMD patients registered in the MDDB, 94 consented to participate in this study. Sixty-six had undergone at least single *dystrophin* gene analysis, while 18 had not received any gene analysis. Ten patients had no information regarding gene analysis findings regardless of whether that had been