Mental Retardation and Lifetime Events of Duchenne Muscular Dystrophy in Japan

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Abstract

Objective  This study investigated the relationship between mental retardation and lifetime events in patients with Duchenne muscular dystrophy (DMD).

Methods  The data on mental retardation and ages of lifetime events (first walking, loss of ambulation, introductions of ventilator support and tube nutrition and death) were collected retrospectively, and the relationships between the factors were analyzed.

Patients  Among 194 DMD patients admitted to our hospital between 1995 and 2007, 74 patients underwent evaluation of their intelligence quotient (IQ).

Results  Twenty-eight patients (38%) demonstrated mental retardation (IQ<70). DMD patients with mental retardation started walking later, required ventilator and tube nutrition support earlier, and died earlier than those without mental retardation.

Conclusions  Since the prognosis of DMD patients with mental retardation was worse than that of those without mental retardation, more careful treatment is necessary for DMD patients with mental retardation.

Key words: Duchenne muscular dystrophy, walking, ventilator, mental retardation, prognosis
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Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease and has the second highest incidence of all inherited diseases, occurring in approximately one in 3,300 live births (1). About 50% of babies with DMD start walking after 18 months (2). Muscle weakness first becomes apparent at 3-4 years of age, walking becomes impossible before 13 years of age (2-4), and death usually occurs before 25 years of age (5, 6). However, the ages of these lifetime events have changed as various new forms of medical support have become available; ventilator support, active rehabilitation, physiotherapy for airway clearance, and so on (7-10).

Behavioral studies have shown that DMD patients demonstrate cognitive impairment and a lower intelligence quotient (IQ, average 80-85) (11, 12). The distribution of IQ in patients with DMD is shifted 1 SD lower, and consequently 30% of patients with DMD have an IQ<70 (11-14). However, the relationship between the level of intelligence and lifetime events in DMD patients has not been clarified.

Here, we analyzed data in the medical records of DMD patients retrospectively and tried to clarify the relationship between mental retardation and lifetime events (first walking, loss of ambulation, the respective introductions of ventilator support and tube nutrition and death).

Patients and Methods

We studied 194 patients with DMD (age, 10-44 years) who were admitted to our hospital for evaluation of their cardiopulmonary or neurological conditions between 1995 and 2007. In all patients, the diagnosis was confirmed by a genetic study (abnormality of dystrophin gene) and/or by muscular biopsy (absence of dystrophin protein). All of the

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patients became wheelchair-bound by the age of 14. On January 1, 2008, 153 of 194 DMD patients were still alive [age, mean (SD), 25.7 (7.3) years] and 41 patients had died [age, 25.2 (4.9) years]. The main causes of deaths were respiratory (20 patients) and cardiac (17 patients) problems.

In 74 DMD patients, intelligence was assessed by the Tanaka-Binet or Suzuki-Binet test (Japanese versions of Binet-Simon Test) between the ages of 6 to 12 years. Here, we focused on these 74 patients in order to investigate the relationship between mental retardation and lifetime events. A review study of 721 DMD patients (11) showed that the mean IQ was 82 with 20% having an IQ below 70, and with 3% an IQ below 50. In this study, DMD patients with an IQ <70 were defined as demonstrating mental retardation as defined in previous reports (11-13). Patient ages at first walking, loss of ambulation, ventilator introduction (any type of ventilator; chest respirator, non-invasive or tracheostomy positive pressure ventilator), permanent tube nutrition introduction (not including transient tube nutrition) and death were collected from medical records. The correlations between mental retardation and lifetime events were analyzed by Kaplan-Meier curves and log-rank test.

**Results**

Evaluations of mental retardation were performed in 74 DMD patients (IQ, mean +/- SD, 76 +/- 19). Twenty-eight patients (38%) demonstrated an IQ of <70 (55 +/- 8) and the other 46 showed an IQ of >/=70 (89 +/- 11). The mean (SD) ages at first walking (n=67) and loss of ambulation (n=74) were 18.6 (6.3) months and 10.2 (1.8) years. Of 74 patients, 53 patients needed ventilator support and the average age at ventilator introduction was 19.9 (4.5) years, whereas the other 21 patients did not need ventilator support as of January 1, 2008. Of 74 patients, 13 patients needed tube nutrition support and the average age at tube nutrition introduction was 24.5 (7.0) years. Eleven patients had died and the average age at death was 25.0 (7.1) years.

Figure 1 shows Kaplan-Meier curves for age at first walking (A), loss of ambulation (B), introductions of ventilator
support (C) and tube nutrition (D) and death (E) in DMD patients with and without mental retardation. In DMD patients with mental retardation, the age at first walking was higher than that in those without mental retardation. The DMD patients with mental retardation required ventilator and tube nutrition significantly earlier, and died significantly earlier than those without mental retardation.

### Discussion

The ages at first walking and loss of ambulation in this study were consistent with past reports (2, 3, 15, 16). The ages at ventilator and tube nutrition introductions and death were similar to those reported in recent studies (3, 10, 17, 18). The conspicuous points in this study were the following two points. 1) In DMD patients with mental retardation, the age at first walking was higher than in those without mental retardation. 2) DMD patients with mental retardation needed ventilator and tube nutrition support earlier, and died earlier than those without mental retardation.

Patients with DMD usually start walking at around 18 months (15). Serum creatine kinase activities in DMD patients are 50-100 times higher than the upper normal limit and this abnormality can be detected shortly after birth (19). Therefore, muscle strength in DMD babies must be weaker than in unaffected babies. In this study, DMD patients without mental retardation began walking at 15.8 +/- 2.5 months (mean +/- SD, n=41), which is clearly later than in unaffected babies (around 12 months) (20). However, DMD patients with mental retardation began walking at 23.1 +/- 7.8 months (n=26), which is significantly later than that in DMD patients without mental retardation. In DMD patients with mental retardation, the age at first walking might be delayed by not only muscle weakness but also brain dysfunction.

The earlier ages at introductions of ventilator support and tube nutrition and death in DMD patients with mental retardation would not simply be caused by worse prognoses for both muscle and brain, since there was no significant correlation between mental retardation and the age at loss of ambulation. Here we could not clarify the reason, but the most likely explanation would be as follows: Dystrophin has been found to be absent in the brain (cerebral cortex, hippocampus, and cerebellum) of DMD patients (13, 21), and the lack of dystrophin in the cerebral cortex would relate to mental retardation. Since both respiration and swallowing are modulated by not only the brainstem but also the cerebral cortex and cerebellum (22-24), the lack of dystrophin in cerebral cortex and cerebellum must relate to the dysfunction of respiration and swallowing. Then, both mental retardation and the dysfunctions of respiration and swallowing would be caused by the same mechanism; brain dysfunction is caused by lack of dystrophin. Thus, we concluded that the level of mental retardation would parallel the level of dysfunctions of respiration and swallowing. In conclusion since DMD patients with mental retardation needed ventilator or tube nutrition support earlier and died earlier than those without mental retardation, more careful monitoring of medications is necessary for patients with mental retardation.

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### References


