DNAを抽出し，*SMN1*遺伝子のexon 7，8の欠失の有無を確認することにより診断する．*SMN1*遺伝子のホモ接合性の欠失はSMA I型，II型では90％以上に認められるが，III，IV型では50％以下となる[3]．

治療と医療管理

- SMAに対する根本的な治療は，いまだ確立していない．*SMN2*遺伝子のexon 7のスプライシングパターンを変えることにより*SMN2*由来の全長mRNAを増やす方法，*SMN*の転写のレベルを全体的に上げる方法，SMNタンパクを安定化させる方法，変性した運動ニューロンを幹細胞によって修復する方法などが研究されている．
- SMAは現在の社会的環境では日常生活の多くの活動を他人に頼らなければならない疾患である一方，患児はしばしば高度な能力を有し，正常の心臓機能を示している．適切な道具や訓練により，社会的に満足のいく生活を送ることが可能である．彼らの能力を発揮できる環境を整備していくことが必要である*33．

呼吸

- SMAのI型，II型の患児の最大の問題は，呼吸器感染や誤嚥に伴う呼吸不全である．
- I型は気管挿管と人工呼吸管理を行わなければ死亡する疾患である．人工呼吸器はコンパクトで便利になり人工呼吸管理を受けつつ病院や在宅にてQOLの向上をめざしているI型の患児も増加している．
- 座位保持が可能なII型の患児は，呼吸不全状態のため気管挿管と人工呼吸管理が必要になっても，永続的な使用とはならないことも多い．肺の低換気を示すII型の患児は，鼻マスクを用いたNPPV（間欠的陽圧換気）の使用により，呼吸不全の治療と予防が可能である．インフルエンザの予防接種など，呼吸器感染の予防も積極的に行うべきである．

理学療法

- I型で人工呼吸管理を受けている患児やII型で車椅子の生活をしている患児は，関節の拘縮に対して予防が必要である．II型では座位の保持が可能であるが，次第に側弯や関節拘縮が著明になるために，III型では起立や歩行が困難になった場合も，リハビリテーションによる拘縮の予防が必要である．
- II型では側弯に対して，手術的治療として脊柱固定術が行われ始めている．
- 呼吸器感染時には，カフマシンの使用や，肺の理学的療法によって排痰ドレナージを行う．

移動

- I型，II型では一人で起立や歩行が不可能であり，車椅子が必要である．上半身の力がないので，手動ではなく電動の車椅子を必要とする．
- 欧米では2～3歳で電動車椅子を安全に動かすことを教えており，家や外で家族や友達と一緒に活動できるようになる．

（斎藤加代子）

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3) 斎藤加代子，伊藤万由里．脊髄性筋萎縮症の遺伝子診断．神経内科 2008；69：528-32.

＊33 患者サポート組織：SMAの人々をとりまく環境を快いものにして，ともに支え合う場をもつことを目的として，1999年10月に「SMA家族の会」が結成され，全国レベルの活動をしている．

13

Database of Wards for Patients with Muscular Dystrophy in Japan

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1. Introduction

Twenty-seven hospitals in Japan specialize in treatment of muscular dystrophy patients, including inpatient care, of which 26 belong to the National Hospital Organization, and the other is the National Center of Neurology and Psychiatry. Since 1999, Japanese muscular dystrophy research groups investigating nervous and mental disorder have been developing a database of cases treated at these 27 institutions. In that regard, we conducted a survey of inpatients with muscular dystrophy and other neuromuscular disorders based on data collected by the National Hospital Organization and National Center of Neurology and Psychiatry. Herein, we examined data obtained between 1999 and 2010 in order to evaluate the medical condition of inpatients with muscular dystrophy in Japan.

2. Subjects and methods

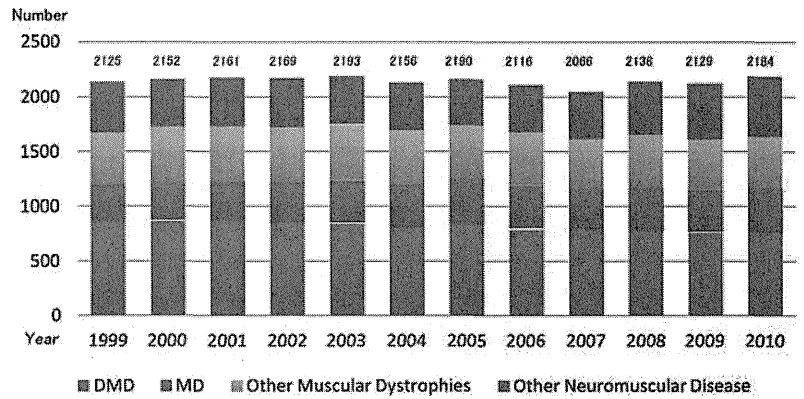
The database includes numbers of inpatients, gender, age, diagnosis, respiratory condition, nutritional state, number of death cases, causes of death, and other relevant findings from data collected annually on October 1 every year since 1999. We examined these data using longitudinal and horizontal analyses.

3. Sequential changes in total numbers of inpatients treated at muscular dystrophy wards of National Hospital Organization and National Center of Neurology and Psychiatry

The total numbers of inpatients treated at the muscular dystrophy wards of the National Hospital Organization and National Center of Neurology and Psychiatry were quite consistent during the examination period. The lowest number of inpatients was 2066 in 2007 and the highest was 2193 in 2003 (Fig. 1).

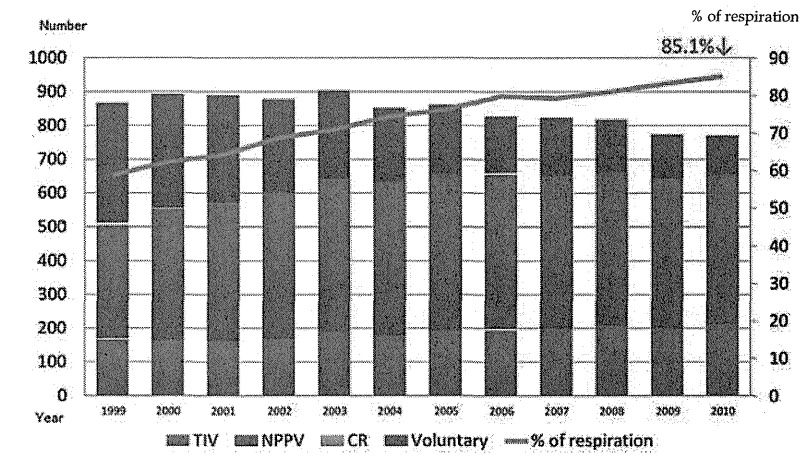
3.1 Details regarding number of inpatients

The number of inpatients with Duchenne muscular dystrophy gradually decreased (882~770) every year (Fig. 2), whereas that of those with myotonic dystrophy gradually increased (327~411) (Fig. 3). The numbers of inpatients with other types of muscular dystrophy, such



"Other muscular dystrophies" includes Becker muscular dystrophy, Fukuyama congenital muscular dystrophy, limb-girdle muscular dystrophy, facio-scapulo-humeral muscular dystrophy, Ullrich muscular dystrophy, and others.
"Other neuromuscular disease" includes amyotrophic lateral sclerosis, spinal muscular atrophy, hereditary sensory motor neuropathy, congenital myopathy, and others.
DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy

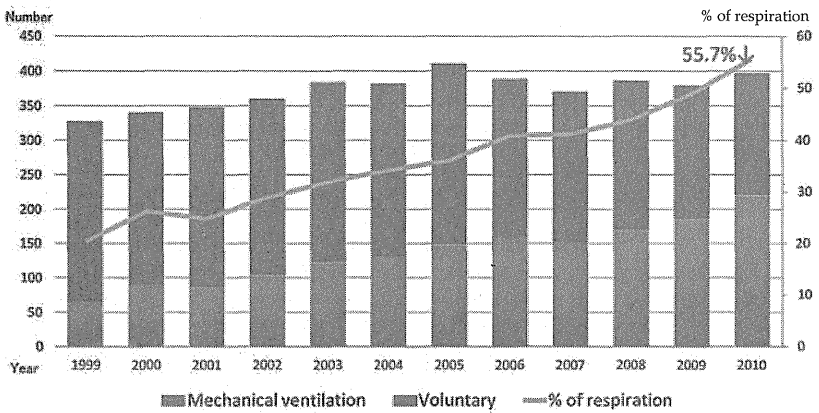
Fig. 1. Total numbers of inpatients in muscular dystrophy wards of National Hospital Organization and National Center of Neurology and Psychiatry.



The number with Duchenne muscular dystrophy has gradually decreased every year.
TIV,tracheostomy intermittent ventilation; NPPV, non-invasive positive pressure ventilation

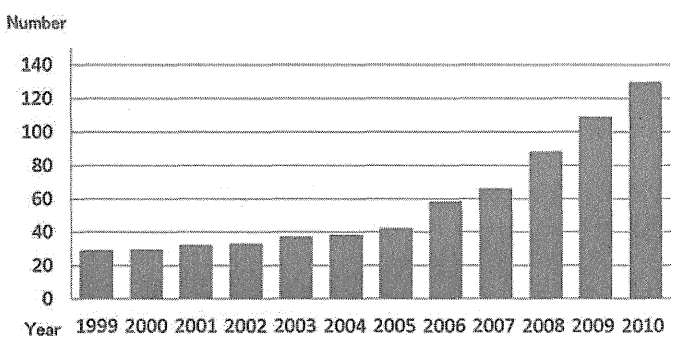
Fig. 2. Sequential changes in number of inpatients with Duchenne muscular dystrophy and rate of mechanical ventilation dependence.

as Becker muscular dystrophy (94~105), Fukuyama congenital muscular dystrophy (50~64), limb-girdle type muscular dystrophy (185~216), and facio-scapulo-humeral muscular dystrophy (64~72) showed some fluctuations. Inpatients with spinal muscular atrophy showed a gradual decreasing tendency from 73 in 1999 to 56 in 2010, while those with amyotrophic lateral sclerosis increased every year from 29 to 132 (Fig. 4). Other diseases encountered in these patients included congenital metabolic disease, mitochondrial disease, various types of myopathy, peripheral nerve disease, bone disease, chromosomal abnormalities, spinocerebellar ataxia, neonatal period disease sequelae, infectious diseases, and others, though their numbers were small and equalled around 10% of all diseases.



The number with myotonic dystrophy has gradually increased every year.

Fig. 3. Sequential changes in number of inpatients with myotonic dystrophy and rate of mechanical ventilation dependence.

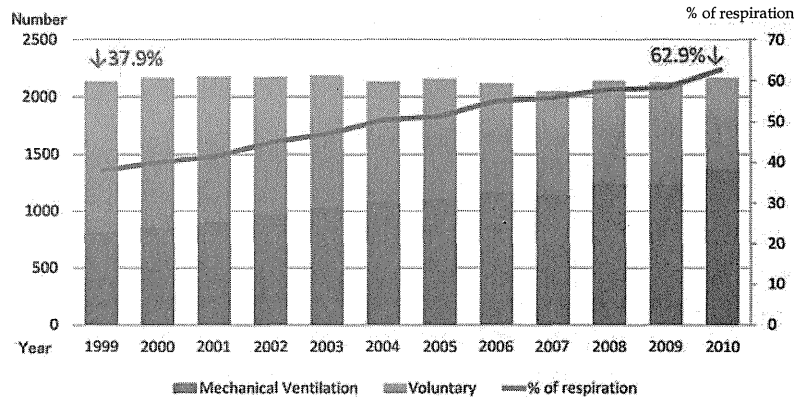


The number with amyotrophic lateral sclerosis has gradually increased every year.

Fig. 4. Sequential changes in number of inpatients with amyotrophic lateral sclerosis.

3.2 Sequential changes in respiratory care for inpatients and rate of mechanical ventilation dependence

The rate of mechanical ventilation use in 1999 was 37.9%, which gradually increased to 62.9% in 2010 (Fig. 5), while that for Duchenne muscular dystrophy patients in 1999 was 58.7% and gradually increased to 85.1% in 2010 (Fig. 2). Although the total number of inpatients with Duchenne muscular dystrophy gradually decreased, cases of non-invasive ventilation gradually increased and tracheostomy cases were also slightly increased. The rate of mechanical ventilation use for myotonic dystrophy patients in 1999 was 20.3%, which gradually increased to 55.7% in 2010 (Fig. 3).



The rate of mechanical ventilation use in 1999 was 37.9%, which gradually increased to 62.9% in 2010.

Fig. 5. Sequential changes in respiratory care for inpatients and rate of mechanical ventilation dependence.

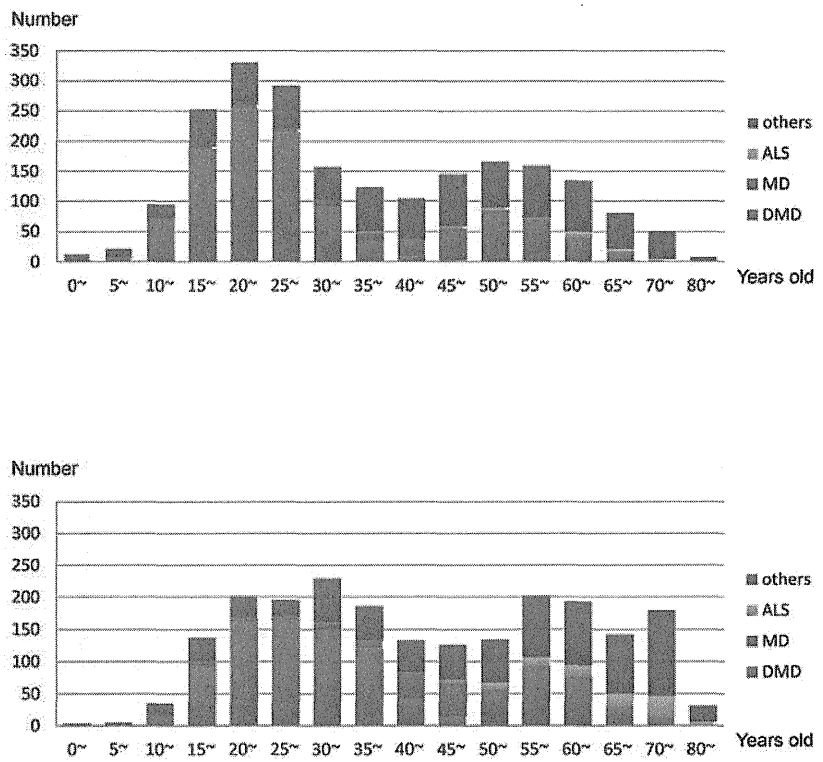
3.3 Analysis of mean age of inpatients

3.3.1 Changes in age distribution of inpatients in muscular dystrophy wards

The age distribution of inpatients in muscular dystrophy wards in 1999 showed 2 peaks. Those with Duchenne muscular dystrophy largely constituted the younger age peak in the 20s, while those with myotonic dystrophy larger constituted the older age peak in the 50s. These age peaks shifted to a higher range and became slightly flattened in 2009 (Fig. 6).

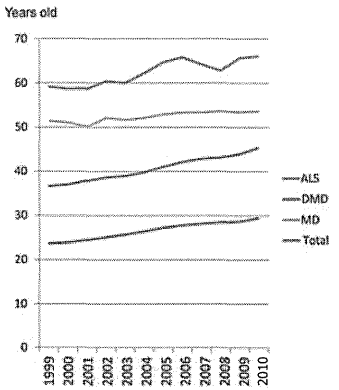
3.3.2 Sequential changes in mean age of inpatients

The mean age of the inpatients in 1999 was 36.6 years old, which gradually increased to 45.3 years old in 2010. That of Duchenne muscular dystrophy patients in 1999 was 23.6 years old, which gradually increased to 29.4 years old in 2010, while that of myotonic dystrophy patients changed only slightly from 51.4 years old in 1999 to 53.6 years old in 2010 (Fig. 7).



Upper: 1999. Lower: 2009. The age distribution of inpatients in muscular dystrophy wards shifted to a higher range over time.

Fig. 6. Changes in age distribution of inpatients in muscular dystrophy wards.



The mean age of the inpatients was gradually increased. DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy; ALS, amyotrophic lateral sclerosis

Fig. 7. Sequential changes in mean age of inpatients.

Gradual changes in age distribution of inpatients with Duchenne muscular dystrophy was observed. The age peak in 1999 shifted to a higher range and became slightly flattened in 2009 (*Fig. 8*).

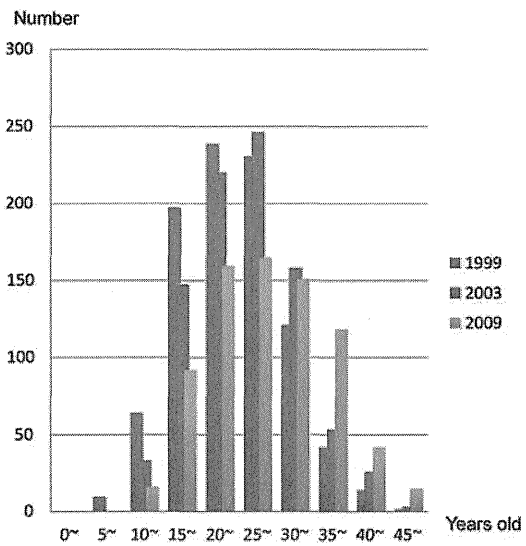
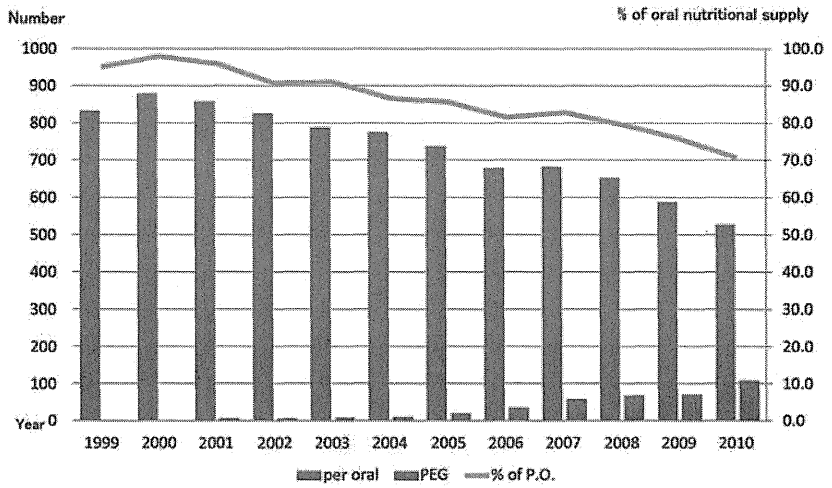


Fig. 8. Changes in age distribution of inpatients with Duchenne muscular dystrophy.

3.4 Sequential changes in numbers of patients receiving oral nutrition and those with Duchenne muscular dystrophy who underwent a percutaneous endoscopic gastrostomy

The proportion of patients with Duchenne muscular dystrophy receiving oral nutrition in 1999 was 95.1%, which gradually decreased to 70.6% in 2010. In contrast, the number who required tube feeding, including a nasal nutrition tube and undergoing a percutaneous endoscopic gastrostomy, gradually increased to 107 in 2010.



PEG, percutaneous endoscopic gastrostomy

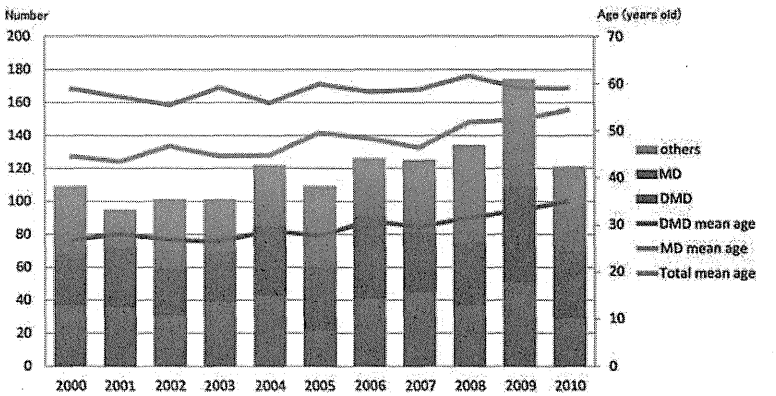
Fig. 9. Sequential changes in numbers of Duchenne muscular dystrophy patients and those who underwent an endoscopic gastrostomy patients receiving oral nutrition.

3.5 Death case analysis

The total number of deaths reported from 2000 to 2010 was 1307, which ranged from 95-174 annually in a variable pattern (Fig. 10). The number of Duchenne muscular dystrophy patients who died was 409, while that of myotonic dystrophy patients was 363.

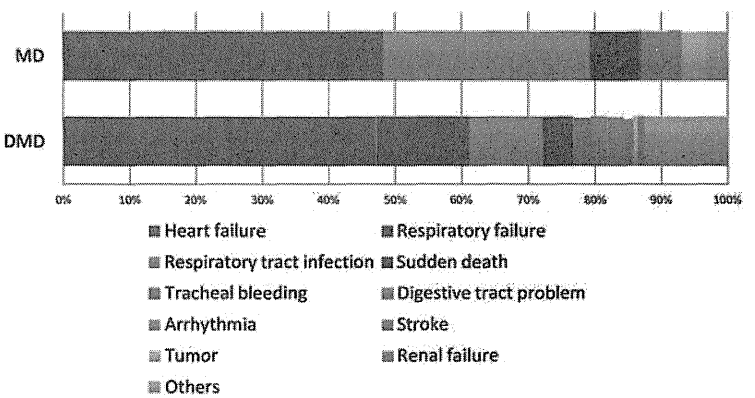
The mean age of death among Duchenne muscular dystrophy patients was 26.7 years old in 2000, which gradually increased to 35.1 years old by 2010. On the other hand, the mean age of death for myotonic dystrophy patients was 59.0 years old in 2000 and 59.1 years old in 2010, which was not significantly different (Fig. 10).

The most frequent cause of death among Duchenne muscular dystrophy patients was heart failure, accounting for 47%. As for myotonic dystrophy patients, the most frequent cause was respiratory disorders, such as respiratory failure and respiratory tract infection, which accounted for 64% (Fig. 11).



DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy

Fig. 10. Sequential numbers of deaths and mean age at death reported to the database.



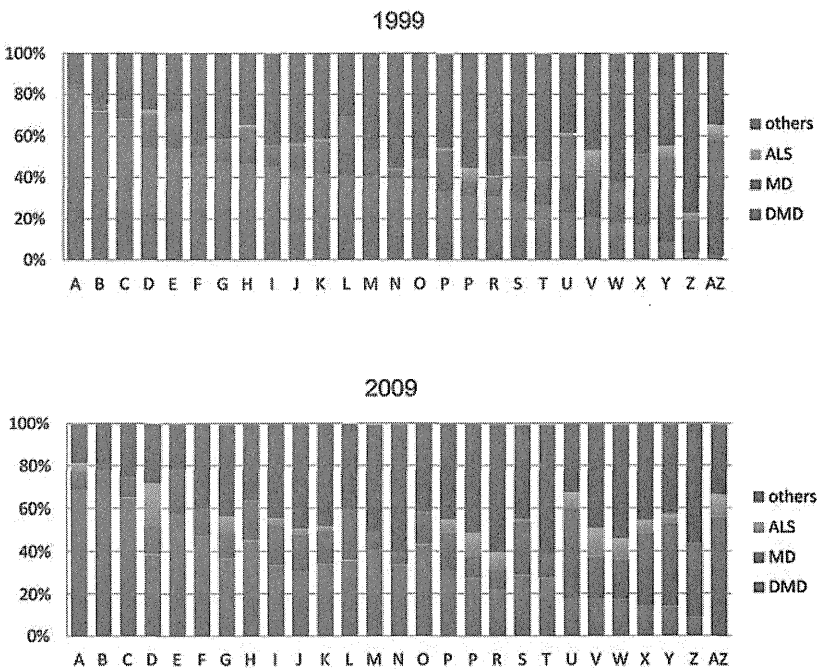
The most frequent cause of death among Duchenne muscular dystrophy patients was heart failure. In contrast, that of myotonic dystrophy patients was respiratory disorder.
DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy

Fig. 11. Causes of death among Duchenne muscular dystrophy and myotonic dystrophy patients (2000~2010).

3.6 Proportional changes in numbers of inpatients in muscular dystrophy wards of each institution

Twenty-seven hospitals in Japan specialize in treatment of muscular dystrophy patients are not same in terms of types of muscular dystrophy of inpatient, disease severity, and actual care. Fig. 12 shows the proportion of inpatients by each institution. The upper figure, which

shows the proportion in 1999, is arranged according to rate of Duchenne muscular dystrophy inpatients. There were significant differences in regard to the proportion of inpatients among the institutions in 1999, which changed over time. In 2009, the proportion of inpatients with amyotrophic lateral sclerosis was notable.



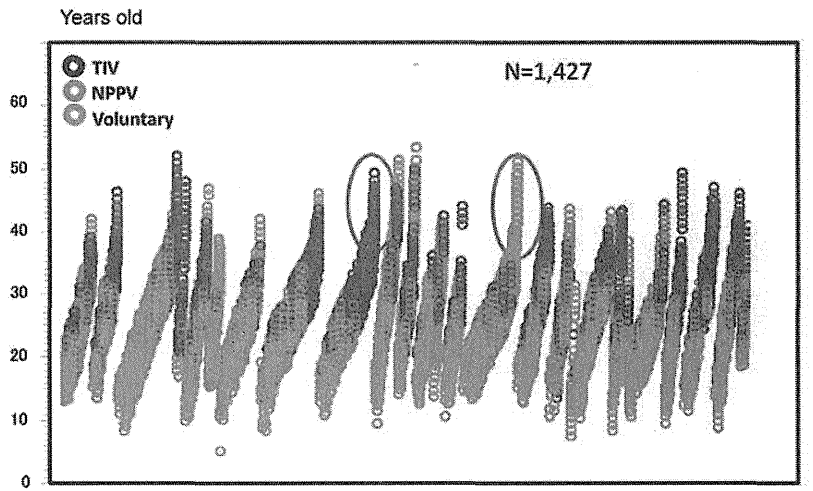
Upper: 1999. Lower: 2009. A~AZ represent the individual institution. Institute AZ, which had lowest rate of DMD patients among institutions in 1999, has no DMD patient in 2009.
DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy; ALS, amyotrophic lateral sclerosis

Fig. 12. Changes in proportions of inpatients in muscular dystrophy wards of each institution

3.7 Sequential changes in respiratory conditions of Duchenne muscular dystrophy patients at each institution (1999~2009).

The total number of Duchenne muscular dystrophy patients treated from 1999 to 2009 was 1427. The changes in motor function of the patients were nearly uniform, whereas the therapeutic respiratory conditions varied among the institutions.

Figure 13 presents the respiratory conditions of the patients for the 11-year period from 1999 to 2009. In the 10s, almost patients keep voluntary respiratory function. In the 20s, various respiratory patterns are observed, which seem not to be different among the institutions. In more than 30s, there were apparent differences among the institutions. Some institutes have no tracheostomy older patients, which generation is generally supposed not to be compensated by non-invasive positive pressure ventilation and use tracheotomy ventilation.



Each cluster indicates a single institution. The vertical axis indicates the course of a single Duchenne muscular dystrophy patient. The respiratory conditions of older patients differed among the institutions. For example, the left oval indicates a tracheostomy case and the right oval a non-invasive positive pressure ventilation case.
TIV,tracheostomy intermittent ventilation; NPPV, non-invasive positive pressure ventilation

Fig. 13. Sequential changes in respiratory conditions of Duchenne muscular dystrophy patients treated at each institution (1999~2009).

4. Conclusion

Wards for patients with muscular dystrophy were originally established in Japan in 1964 and then gradually expanded throughout the country. As a result, approximate 2500 beds are now provided among 27 institutions. In the early days, many of the patients were boys with Duchenne muscular dystrophy, who received education in schools near the hospital where they received care. However, over time, regular public elementary and junior high schools began to accept disabled children, and such patients were then able to receive an education at schools in their home town. Thus, cases of admission for the purpose of education gradually decreased.

On the other hand, progress in therapeutic strategies for respiratory failure (American Thoracic Society Documents, 2004), heart failure (Ishikawa, 1999; Matsumura, 2010) and other complications associated with muscular dystrophy prolonged the life span of affected individuals (Bushby 2010a, b). Now, most inpatients admitted to a muscular dystrophy ward have a severe general condition and many are assisted by mechanical ventilation (Tatara, 2008). In addition, in terms of nutritional control (American Thoracic Society Documents, 2004; Bushby 2010b), the number of percutaneous endoscopic gastrostomy patients with Duchenne muscular dystrophy has gradually increased.

Thus, the age and disease severity of inpatients have been gradually progressed with this changing environment. And social welfare systems related to muscular dystrophy wards in Japan also have been changing during this research. The social role of wards for inpatients with muscular dystrophy has been changing. The gradual increase of number of inpatients with amyotrophic lateral sclerosis means that the ward for patients with muscular dystrophy is no longer only for patients with muscular dystrophy. Present wards have purpose for care and treatment for severe disabilities, not limited to patients with muscular dystrophy.

There are some reports concerned with prognosis of patients with Duchenne muscular dystrophy from single institution belonging to the National Hospital Organization (Ishikawa, 2011; Matsumura, 2011). Just as these reports, we showed the increasing mean age of death among Duchenne muscular dystrophy patients. Although the most frequent cause of death among Duchenne muscular dystrophy patients was heart failure, the progression for cardioprotection therapy to cardiomyopathy (Ishikawa, 1999; Matsumura, 2010) improved the prognosis.

However, the present findings showed that there are apparent differences in regard to the proportion of inpatients and therapeutic conditions among institutions. Hereafter, these differences will be more remarkable. So far almost same therapy has been offered among the National Hospital Organization and National Center of Neurology and Psychiatry. However, these conditions will not continue and may influence the prognosis of patients with muscular dystrophy in Japan.

Social role of wards for patients with muscular dystrophy at establishment, offering patients with muscular dystrophy opportunities of education and treatment, has changed into offering severe disabilities care and treatment. We should consider how to manage these conditions.

5. Acknowledgments

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We are grateful to Dr. Mitsuru Kawai for the kind advice, as well as the members of the FUKUNAGA (1999-2005) and SHINNO (2006-2011) muscular dystrophy research groups of the National Hospital Organization for the data collection.

Institutions specializing in muscular dystrophy treatment in Japan (Fig.14)

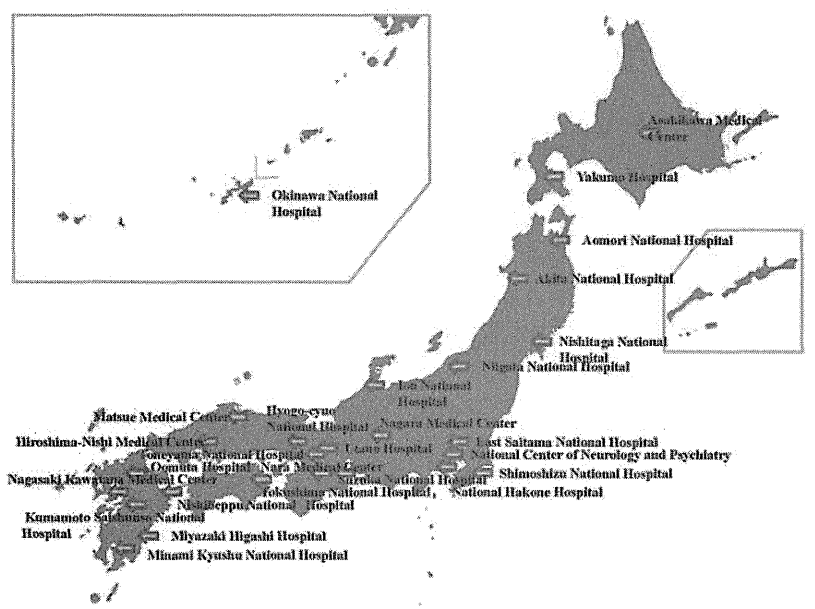

Fig. 14. Institutions specializing in muscular dystrophy treatment in Japan

National Hospital Organization:

- Asahikawa Medical Center, Yakumo Hospital, Aomori National Hospital,
- Akita National Hospital, Nishitaga National Hospital, East Saitama National Hospital,
- Shimoshizu National Hospital, National Hakone Hospital, Niigata National Hospital,
- Iou National Hospital, Nagara Medical Center, Suzuka National Hospital,
- Nara Medical Center, Utano Hospital, Toneyama National Hospital,
- Hyogo-cyuo National Hospital, Hiroshima-Nishi Medical Center, Matsue Medical Center,
- Tokushima National Hospital, Oomuta Hospital, Nagasaki Kawatana Medical Center,
- Kumamoto Saishunso National Hospital, Nishibeppu National Hospital,
- Miyazaki Higashi Hospital, Minami Kyushu National Hospital, Okinawa National Hospital

National Center of Neurology and Psychiatry

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5

Comparison Between Courses of Home and Inpatients Mechanical Ventilation in Patients with Muscular Dystrophy in Japan

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Japan

1. Introduction

In Japan, 27 hospitals specialize in treatment of muscular dystrophy patients, including inpatient care, of which 26 belong to the National Hospital Organization, and the other is the National Center of Neurology and Psychiatry. Since 1999, Japanese muscular dystrophy research groups investigating nervous and mental disorder have been developing a database of cases treated at these 27 institutions. In that regard, we conducted a survey of inpatients and home-mechanical ventilation patients (HMV patients) with muscular dystrophy and other neuromuscular disorders based on data collected by the National Hospital Organization and National Center of Neurology and Psychiatry.

Herein, we examined data obtained in order to evaluate efficacy of mechanical ventilation therapy for HMV patients and mechanical ventilation-dependent inpatients (MV inpatients) with those wards.

2. Subjects and methods

The database includes numbers of inpatients, gender, age, diagnosis, respiratory condition, nutritional state, number of death cases, causes of death, and other relevant findings from data collected annually on October 1 every year since 1999. Additionally we collected the data of HMV patients from 27 institutes for this study.

By using the database and newly collected HMV data, we analyzed the courses of HMV patients group and those of MV inpatients of wards. We compared data of these two groups. Examination points are mechanical ventilation periods, outcome of these two groups, and caregiver for HMV patients.

2.1 Objective diseases

Objective diseases of this study were muscular dystrophy and spinal muscular atrophy, in particular Duchenne muscular dystrophy and myotonic dystrophy. Amyotrophic lateral sclerosis was not included.

2.2 Patients introduced HMV after 1999

The data which we requested 27 institutes specializing muscular dystrophy care was as follows; the number of patients introduced HMV after 1999, diagnosis of disease, gender, age at being introduced HMV, type of mechanical ventilation, such as non-invasive positive pressure ventilation (NPPV) or tracheostomy intermittent ventilation (TIV), present status, death cause for death case, main caregiver, and so on.

2.3 Patients introduced MV in muscular dystrophy wards after 1999

We selected data of newly MV introduced inpatients after 1999 from the database of the muscular dystrophy wards.

3. Results

3.1 Demographic features of HMV patients group and MV inpatients

3.1.1 HMV patients group

HMV patients group included 434 patients from 14 institutes. Gender was male: 356, female: 78. The number of representative disease were as follows; 262 patients with Duchenne muscular dystrophy, 60 myotonic dystrophy, 17 Becker muscular dystrophy, 16 limb-girdle muscular dystrophy, 14 spinal muscular atrophy, and so on (Table 1-1).

Diagnosis	HMV	Inpatient	Total	Death cases
BMD	17	35	52	10
CMD	12	6	18	2
DMD	262	476	738	96
EDMD	2	0	2	
FCMD	16	43	59	13
FSHD	6	33	39	7
LGMD	16	42	58	12
MD	60	222	282	62
MG	1	0	1	
SMA	13	19	32	6
SPMA	0	11	11	4
UCMD	9	1	10	
Mitochondrila disease	0	5	5	1
Distal myopathy	2	3	5	2
Congenital myopathy	8	12	20	
Glycogen storage disease	2	1	3	
Other myopathies	3	1	4	
Other dystrophies	4	5	9	
Unknown	1	0	1	
total	434	915	1349	215

BMD, Becker muscular dystrophy; CMD, congenital muscular dystrophy; DMD, Duchenne muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; FCMD, Fukuyama congenital muscular dystrophy; FSHD, facio-scapulo-humeral muscular dystrophy; LGMD, limb-girdle muscular dystrophy; MD, Myotonic dystrophy; MG, myasthenia gravis; SMA, spinal muscular atrophy; SPMA, spinal progressive muscular atrophy, UCMD, Ullrich congenital muscular dystrophy

Table 1-1. Details of disease (HMV: from 14 institutes)

3.1.2 MV inpatients group

MV inpatients group included 915 inpatients. Gender was male: 718, female: 197. The number of representative disease were as follows; 476 Duchenne muscular dystrophy, 222 myotonic dystrophy, 35 Becker muscular dystrophy, 58 limb-girdle muscular dystrophy, 19 spinal muscular atrophy, and so on (Table 1-1).

3.1.3 Mean age at starting mechanical ventilation and type of ventilation

The range of mechanical ventilation introduction age for HMV patients was 6.3~72.8 years old (mean 25.9), and that of MV inpatients was 0.0~78.0 years old (mean 33.2). The number of NPPV introduction cases of HMV patients was 420, and that of MV inpatients was 517 (Table 1-2). Fifty of NPPV cases of HMV group were switched to tracheostomy during the course.

	HMV	Inpatient	
Age at starting mechanical ventilation (years old)	25.9	33.2	p<0.05
NPPV introduced case	420	517	

Table 1-2. Mean age at starting mechanical ventilation and type of ventilation

3.2 Survival analysis of HMV patients group and MV inpatients

We performed survival analysis of those two groups. The endpoint for HMV patients was death or transition to hospitalization, and that for MV inpatient was death. Kaplan-Meier analysis showed that 75% life time of HMV patients was 1,689 days, while that of inpatients was 2,988 days (Log Rank (Mantel-Cox) p<0.01) (Fig. 1).

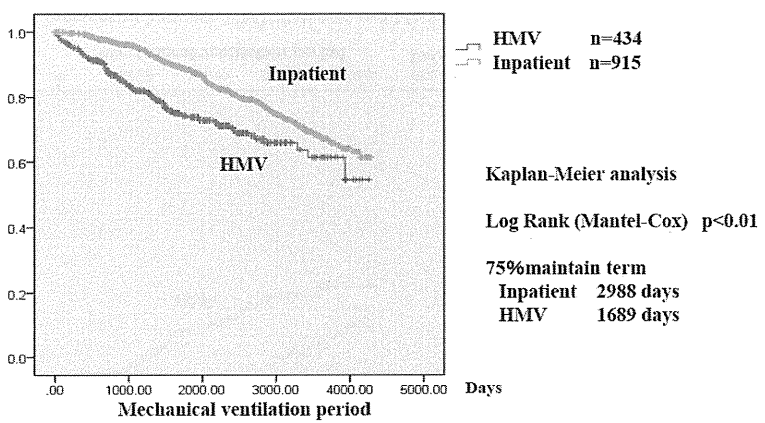

Fig. 1. Comparison between HMV Patients and Mechanical Ventilation Inpatients (Total)
Endpoint for HMV patient: death or transition to hospitalization
Endpoint for MV inpatient: death

3.3 Analysis data of Duchenne muscular dystrophy and myotonic dystrophy

As the number of patients with Duchenne muscular dystrophy and myotonic dystrophy was great in these two groups, we analyzed the data of Duchenne muscular dystrophy and myotonic dystrophy separately.

3.3.1 Mean age at starting mechanical ventilation and type of ventilation of patients with Duchenne muscular dystrophy

Mean age at starting mechanical ventilation of Duchenne muscular dystrophy was 19.8 years old, ranged from 11.5 to 39.9 years old. While that of inpatient with Duchenne muscular dystrophy was 21.5 years old, ranged from 10.0 to 42.0 years old. There was no significant difference. The number of NPPV introduction cases of HMV patients with Duchenne muscular dystrophy was 220, and that of MV inpatients was 338 (Table 2).

	HMV	Inpatient	
Age at starting mechanical ventilation (years old)	19.8	21.5	NS
NPPV	220	338	
TIV	42	138	
total	262	476	

Table 2. Mean age at starting mechanical ventilation and type of mechanical ventilation (Duchenne muscular dystrophy)

3.3.2 Type of nutrition of patients with Duchenne muscular dystrophy

The number of patients who required tube feeding, including a nasal or oral nutrition tube, and undergoing a percutaneous endoscopic gastrostomy (PEG) was apparently greater in MV inpatients group than HMV group (Table 3).

	HMV	Inpatient
Oral nutritional supply	118	314
PEG	11	78
Tube feeding (per nasal or per oral)	3	71
Intravenous hyperamelitaion	0	13
unknown	130	0
total	262	476

Table 3. Type of nutrition (Duchenne muscular dystrophy)

3.3.3 Survival analysis of two Duchenne muscular dystrophy groups

We performed survival analysis of those two Duchenne muscular dystrophy groups. The endpoint for HMV patients was death or transition to hospitalization, and that for MV inpatient was death. Kaplan-Meier analysis showed that 75% life time of HMV patients was 1,562 days, while that of inpatients was 3,739 days (Log Rank (Mantel-Cox) p<0.01) (Fig. 2).

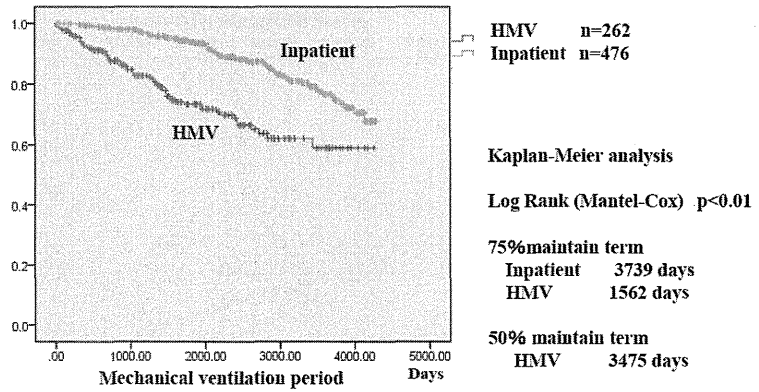

Fig. 2. Comparison between HMV Patients and Mechanical Ventilation Inpatients (Duchenne muscular dystrophy)
Endpoint for HMVpatient: death or transition to hospitalization
Endpoint for MV inpatient: death

3.3.4 Mean age at starting mechanical ventilation and type of ventilation of patients with myotonic dystrophy

Mean age at starting mechanical ventilation of myotonic dystrophy was 46.8 years old, ranged from 15.8 to 72.8 years old. While that of inpatient with myotonic dystrophy was 50.6 years old, ranged from 12.0 to 76.0 years old. There was no significant difference between two groups. The number of NPPV introduction cases of HMV patients with myotonic dystrophy was 55, and that of TIV was 5. The number of NPPV case was greater than TIV. While the number of NPPV introduction cases of MV patients with myotonic dystrophy was 108, and that of TIV was 114. In MV patients with myotonic dystrophy, the number and proportion of NPPV and TIV were almost equal (Table 4).

	HMV	Inpatient	
Age at starting mechanical ventilation (years old)	46.8	50.6	NS
NPPV	55	108	
TIV	5	114	
total	60	222	

Table 4. Mean age at starting mechanical ventilation and type of mechanical ventilation (myotonic dystrophy)

3.3.5 Type of nutrition of patients with myotonic dystrophy

The trend of nutrition was similar to Duchenne muscular dystrophy. The number who required tube feeding in MV inpatients group was apparently greater than HMV group (Table 5).

	HMV	Inpatient
Oral nutritional supply	18	93
PEG	1	69
Tube feeding (per nasal or per oral)	0	50
Intravenous hyperamelitaion	0	10
unknown	41	0
total	60	222

Table 5. Type of nutrition (myotonic dystrophy)

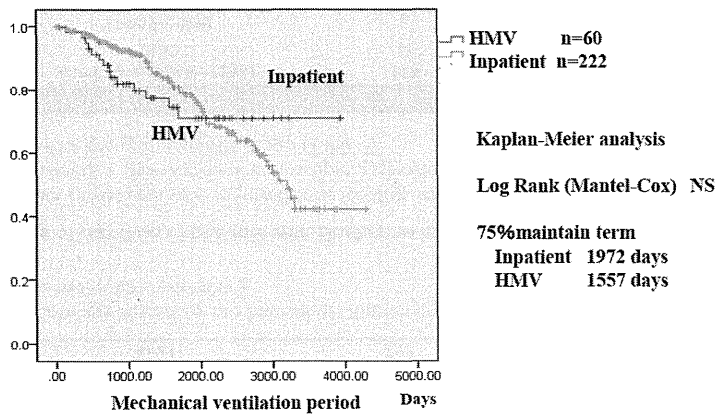

Fig. 3. Comparison between HMV Patients and Mechanical Ventilation Inpatients (myotonic dystrophy)
Endpoint for HMVpatient: death or transition to hospitalization
Endpoint for MV inpatient: death

3.3.6 Survival analysis of two myotonic dystrophy groups

Similarly, we performed survival analysis of those two myotonic dystrophy groups. The endpoint for HMV patients was death or transition to hospitalization, and that for MV inpatient was death. Kaplan-Meier analysis showed that 75% life time of HMV patients was 1,557 days, while that of inpatients was 1,972 days. There was no significance (Fig. 3).

3.4 Death case

The total number of death cases was 215 (Table 1-1). As the number of death case of Duchenne muscular dystrophy and myotonic dystrophy was the majority, we analyzed the data of Duchenne muscular dystrophy and myotonic dystrophy separately.

3.4.1 Cause of death of Duchenne muscular dystrophy

The number of death cases of HMV patients was 29, and that of MV inpatients was 67.

The most frequent cause of death was heart related disorders, such as heart failure and arrhythmia, accounting for 16/29 for HMV group and 33/67 for MV inpatient group. Frequency was not significantly different between two groups. In MV inpatient group, respiratory related disorders, such as respiratory failure and respiratory infection, accounted for 23/67. HMV group included more sudden death cases than MV inpatient, and had an accidental case (Table 6).

	HMV	Inpatient	Total
Heart failure	13	27	40
Arrhythmia	3	6	9
Respiratory failure	2	11	13
Respiratory infection	1	12	13
Tracheal bleeding	1	0	1
Pneumothorax	0	1	1
Renal failure	0	1	1
Infectious disease	2	0	2
Malignancy	1	0	1
Ileus	1	0	1
Sudden death	4	2	6
Power supply accident	1	0	1
Others	0	7	7
total	29	67	96

Table 6. Cause of death (Duchenne muscular dystrophy)

3.4.2 Cause of death of myotonic dystrophy

The majority of death case of myotonic dystrophy was reported from MV inpatient group. The most frequent cause was respiratory related disorders, such as respiratory tract infection and respiratory failure, which accounted for 29/56. Sudden death case was conspicuous in HMV group, accounting for 3/6(Table 7).

	HMV	Inpatient	Total
Respiratory infection	1	19	20
Respiratory failure	2	10	12
Heart failure	0	8	8
DIC	0	1	1
MOF	0	2	2
Cholangitis	0	2	2
Ileus	0	1	1
Choking	0	1	1
Malignancy	0	2	2
Intestinal bleeding	0	1	1
Hepatic failure	0	1	1
Sudden death	3	2	5
Others	0	6	6
total	6	56	62

Table 7. Cause of death (myotonic dystrophy)

3.5 Outcome of HMV patients and MV inpatients with Duchenne muscular dystrophy and myotonic dystrophy

One hundred ninty four cases with Duchenne muscular dystrophy among 262 cases continued HMV, while 46 cases with myotonic dystrophy among 60 cases continued HMV (Table 8). Twenty two cases with Duchenne muscular dystrophy were switched to hospitalization.

	DMD		MD	
	HMV	Inpatient	HMV	Inpatient
Continuing HMV	194	-	46	-
Continuing hospitalization	-	407	-	151
Death	29	67	6	56
Transition to hospitalization	22	-	3	-
Introduction to other institution	10	-	-	-
Withdrawing MV	-	-	3	-
Unknown	7	2	-	-
Others	-	-	2	15
total	262	476	60	222

Table 8. Outcome (Duchenne muscular dystrophy and myotonic dystrophy)

3.6 Caregivers for HMV patients

Caregivers for most of HMV patients with Duchenne muscular dystrophy were patients' families (Table 9). In particular, patients' mothers were playing important role in continuing HMV. Similarly, caregivers for HMV patients with myotonic dystrophy were patients' families. On reflecting their age, some caregivers were patient' spouse (Table 9).

Caregiver	DMD	MD
Mother	94	6
Parents	22	
Father	3	2
Family	3	
Mother/sibling	1	
Mother/uncle	1	
Mother/grandmother	1	
Grandmother	1	
Husband		2
Wife		1
Sister		1
daughter		1
foundation		2
Helper	2	2
(Response)	(134/262)	(17/60)

Table 9. HMV-continuing cases main caregiver (Duchenne muscular dystrophy and myotonic dystrophy)

3.7 Summary of results of Duchenne muscular dystrophy and myotonic dystrophy

Proportion of TIV was higher in MV inpatients group than HMV group. And proportion of tube feeding was also higher in MV inpatients group than HMV group. Namely, respiratory condition and nutritional status were more severe in MV inpatients group than HMV group (both Duchenne muscular dystrophy and myotonic dystrophy).

In Survival analysis, outcome of patients with Duchenne muscular dystrophy of MV inpatients group was better than HMV group. Meanwhile in that of myotonic dystrophy, HMV group was better than inpatient group.

In MV inpatient group of Duchenne muscular dystrophy, respiratory related death was remarkable.

In HMV group, some sudden death cases and accidental death case were conspicuous.

Caregivers of HMV group were constructed by patients' families, centrally mother.

4. Conclusion

Approximate 2500 beds for patients with muscular dystrophy and related disorders are now provided among 27 institutions in Japan. In accordance with progress in therapeutic strategies for respiratory failure (American Thoracic Society Documents, 2004) and heart failure (Ishikawa, 1999; Matsumura, 2010), the life span of patients with muscular dystrophy prolonged (Bushby 2010a, b). Now, most inpatients admitted to muscular dystrophy wards have severe general conditions and many are assisted by mechanical ventilation (Tatara, 2006; 2008), which is accordance with our data of MV patients in this study.

In recent two decades, social welfare systems and home medical care systems in Japan have been changing gradually. HMV has been penetrating into home medical care (Joseph, 2007). The number of HMV patients has been increasing (Tatara, 2006). Stable mechanical ventilated patients have been getting back home.

Our study demonstrated that the course of HMV patients was fairly good, although there was difference between Duchenne muscular dystrophy and myotonic dystrophy in long term outcome. However, the support system for patients and caregivers is not perfect. Our study also showed that burden of caregivers was supposed to be severe. The system for patients and caregivers should be adjusted (Dybwik, 2011). And safety net systems also should be adjusted to avoid accidental event leading to patient's death.

The muscular dystrophy wards may be requested to offer the circumstances for those who have difficulties in continuing HMV. There is necessarily needs for hospitalization of HMV patients (Windisch, 2008).

Study limitation: This study has limitation on bias of collecting patients' information. Specifically, information of HMV patients were reported from 14 institutes among 27 institutes, and MV inpatient information is the result of extraction from muscular dystrophy wards database. Extracted data from database has some ambiguous points in connection with obscure time-sequential analysis.

On analysis of institutes-restricted HMV patients group and MV inpatients group, differences in regard to therapeutic conditions among institutions may be problem.

5. Acknowledgments

This study was supported by a Research Grant for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare of Japan.

We are grateful to the members of the FUKUNAGA (1999-2005) and SHINNO (2006-2011) muscular dystrophy research groups of the National Hospital Organization for the data collection.

Institutions specializing in muscular dystrophy treatment in Japan (Fig.4)

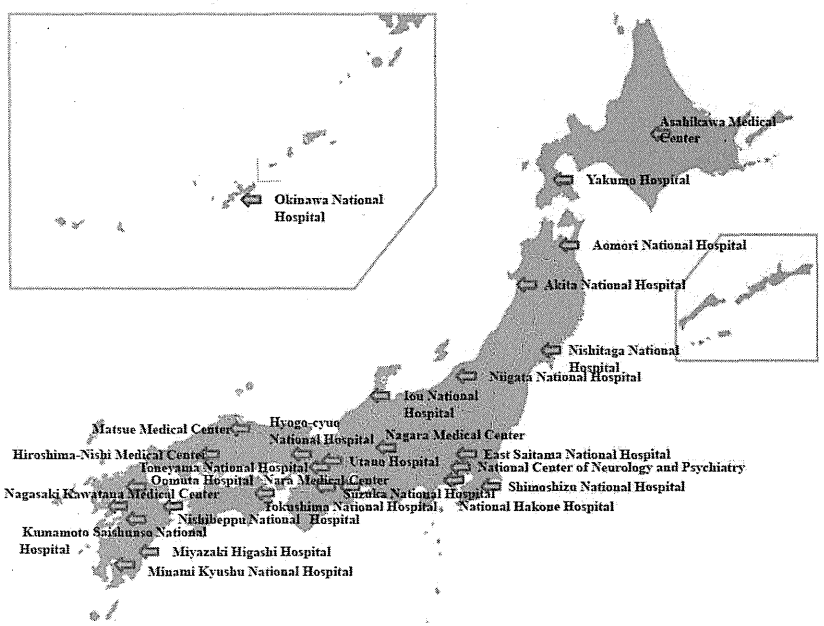

Fig. 4. Institutions specializing in muscular dystrophy treatment in Japan

National Hospital Organization:

Asahikawa Medical Center, Yakumo Hospital, Aomori National Hospital,

Akita National Hospital, Nishitaga National Hospital, East Saitama National Hospital,

Shimoshizu National Hospital, National Hakone Hospital, Niigata National Hospital,

Iou National Hospital, Nagara Medical Center, Suzuka National Hospital,

Nara Medical Center, Utano Hospital, Toneyama National Hospital,

Hyogo-cyuo National Hospital, Hiroshima-Nishi Medical Center, Matsue Medical Center,

Tokushima National Hospital, Oomuta Hospital, Nagasaki Kawatana Medical Center,

Kumamoto Saishunso National Hospital, Nishibeppu National Hospital,

Miyazaki Higashi Hospital, Minami Kyushu National Hospital, Okinawa National Hospital

National Center of Neurology and Psychiatry

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社会脳シリーズ 2

道徳の神経哲学

神経倫理からみた社会意識の形成

学阪直行 編

新曜社

7　快感脳・暴力脳・社会
――ブレインマシンインターフェースの余白に

美馬達哉

はじめに

ブレインマシンインターフェース（ＢＭＩ：Brain Machine Interface）――すなわち人間の脳と機器を直結して通信し、機器を直接操作したり、脳に直接情報を入力したりする技術――の研究や開発に関わっていると、必ず「人間をリモートコントロールで自由に支配できるのですか？」という疑問をぶつけられる。あるときは冗談交じりに、またあるときは不安げに。

たとえば、ＢＭＩ実用化の一つとして、電気刺激を脳内に与えることで脳活動を調節して神経難病の治療に役立てる脳深部刺激療法（ＤＢＳ：Deep Brain Stimulation）がある。個々の患者さんの病状にもよるが、パーキンソン病によるふるえや歩行困難の症状は、ペースメーカのように身体に埋め込まれた装置のスイッチを入れることで、誰の目にも明らかなほど改善する。その劇

的な効果を見れば、医療機器として開発された技術がもし悪用されたら人間がリモートコントロールされるのではないか、と心配するのも当然だ。

しかし、少なくともいまのところ脳の機能と心や意思との関係は、一つ一つの思考内容や行為の精密なコントロールを可能とするほどには解明されていない。さきほど例に挙げたパーキンソン病の場合でも、脳内のある場所でドパミンという物質が減少しているために症状が引き起こされていることは確実にわかっている。だが、なぜドパミンを作り出す神経細胞が減ってしまうのか、どういう脳内の神経経路の異常によってパーキンソン病の症状が現れるかなどは謎に包まれている。病因に立ち戻って考えれば、パーキンソン病はそもそも脳内の電気不足を原因とする病気ではない以上、DBSはある種の間接的な方法による治療でしかあり得ない。DBSの治療的有効性は、さまざまな脳部位に電気刺激などを行うなかで経験的に確かめられただけで、どういう生物学的作用があるのかについて論争が続いている。

その意味では、人間を正確に操作して、奴隷のように働かせたり、犯罪に荷担させたり、特定の思想を信じさせたりすることは技術的に不可能だ。それにもかかわらず、BMIが人間をリモートコントロールする技術となってしまうことへの懸念が語られるには、いくつかの理由がある。

一つは、米国で発展したBMI研究の研究資金の多くが、米国の国防高等研究計画局（DARPA）に由来していたことだ（モレノ／久保田監訳 2008）。軍関係の予算から研究費を支出された研究が、ただちに殺人や兵器開発のための技術に結びつくわけではない。だが、そこには、軍事

目的での科学研究をどのように考えるかという倫理的問題が含まれている[1]。たとえば、神経科学領域の研究でいえば、リハビリテーションに役立つはずの脳可塑性の研究や精神疾患の治療に役立つはずの精神薬理学の研究が、米国中央情報局（CIA）の研究資金援助で行われ、冷戦期には効率的な洗脳手法や尋問用の自白剤の開発目的に使われた例が知られている[2]（McCoy 2006）。

こうした現状を踏まえて、ロボットやBMI研究で知られる国際電気通信基礎技術研究所（ATR）の川人光男らは、研究開発者の守るべきBMIの倫理4原則として、次のようなものを提案している（川人 2010）。

1　戦争や犯罪にBMIを利用してはならない
2　何人も本人の意志に反してBMI技術で心を読まれてはいけない
3　何人も本人の意志に反してBMI技術で心を制御されてはいけない
4　BMI技術は、その効用が危険とコストを上回り、それを使用者が確認するときのみ利用されるべきである

だが、BMIに対する懸念は、軍事目的への応用可能性という点だけから生じたものではない。治療目的の場合であっても、人間の脳に電極を埋め込んで電気刺激を与えて行動変容を引き起こす研究は、20世紀の半ばごろに、社会的・倫理的問題を引き起こした歴史をもっている。

ここでは、ニューオーリンズのチュレーン大学のロバート・ヒースによって1950年代に行われた快感脳の研究と、ボストンのヴァーノン・マークとフランク・アーヴィンによって1960年代に行われた暴力脳の研究を紹介し、そこに含まれる諸問題を考えることにしよう。

それは、神経科学の臨床応用に内在する負の歴史であると同時に、こんにち社会脳と呼ばれる領域とも密接に関連する分野、すなわち人間の気持ちや感情とその生物学的な基盤としての脳の関係を探ろうとする「情動脳」研究の臨床応用可能性という問題に深く関わっている。

辺縁系の神話と情動脳

快感や恐怖や不安のような人間の気持ちの状態をどうやって科学的に扱えばよいのか。この問いに答えるための道筋をつくったのは、心理学者ウィリアム・ジェームズだった。彼は1892年に出版された『心理学』のなかで、「泣くから悲しい」という有名な（あるいは悪名高い）説を開陳している（ジェームズ／今田寛訳 1993 下、p. 205）。心理的な感情が身体の反応を生み出すのではなく、身体反応から結果として感情が生み出されるということをもう少し詳しく説明して、ジェームズは次のように述べている。

> …自然な考え方は、ある事実の心的知覚が情動と呼ばれる心的感動を喚起し、この心の状態が身体的表出を惹き起こすと考えることである。私の説はこれに反して、身体的変化は刺激を与える事実の知覚の直後に起こり、この変化の起こっているときのこれに対する感じがすなわち情動であるというものである。（ジェームズ／今田寛訳 1993 下、p. 204）

ジェームズ自身は、ある種の刺激に対する生物学的ないし身体的なプロセスとそれに対する意識的な感じ方を、両方とも「情動」と呼んでいるが、こんにちの情動研究での一般的な用語でいえば、（しばしば無意識的な）生物学的過程を情動（emotion）、それを意識化した感じ方を感情（affect）と分けることが多い。ジェームズが主張するように情動が感情を生み出すのか、それとも感情が情動を生み出すのか、あるいは情動と感情はある程度並行して生じているのか、そうした問題は現在でも完全には解決されていない。しかし、少なくとも、情動は重要な研究分野の一つであるという点については、神経科学者のほとんどが同意するだろう（たとえば、苧阪 2010）。

さて、この情動の問題を動物実験で研究する糸口となったのは、恒常性（ホメオスタシス）概念の提唱で知られる生理学者ウォルター・キャノンらの研究だ（Cannon 1929）。キャノンは、ネコの脳を表面から段階的に除去する実験を行った。そして、大脳皮質全体を取り除いたネコ（除皮質ネコ）でも、痛みを与えると、うずくまり背中を反らせて、毛を逆立て、爪を立ててうなったり、かみつこうとしたりすることを発見した。しかし、こうした「怒り」のような身体的反応

は、その内側にある脳の部位である視床下部までも除去すると、消え去ってしまったという。この実験からキャノンは、除皮質ネコは、大脳皮質をもっていないので感情を意識することはできないが、身体的反応としての情動の表現はできると考え、この現象を「仮性の怒り（sham rage）」と呼んだ。

その後1937年に、神経解剖学者のジェームズ・パペッツは、視床下部だけでなく、海馬、視床前部、帯状回なども含む神経回路[3]（辺縁系）が情動において重要であるという理論を唱えた（Papez 1937）。この説（パペッツ回路）を、進化論的な文脈のなかで解釈して、人々の脳に関する考え方に後々まで続く大きな影響を与えたのが、ポール・マクリーンによる三位一体脳モデル（基底核・辺縁系・大脳皮質）である（MacLean 1990／法橋登訳 1994）。彼によれば、人間の脳は、前言語的で定型的な行動をつかさどり、は虫類から受け継いだ「反射脳」（基底核に相当する）、内臓のコントロールや情動に関連し、旧ほ乳類とも共通する「情動脳」（辺縁系）、理性や思考と関係し、新ほ乳類で大きく進化した「理性脳」（大脳皮質）の三つに分けられるという。

ただし、こんにちでは、マクリーンの壮大な説はもちろんパペッツの回路についても、ある種の「神話」ではないかとも批判されている。その急先鋒は、情動研究の第一人者であるジョゼフ・ルドゥーだろう。彼は次のように繰り返し述べている。

> 残念ながらさまざまの理由から、辺縁系がエモーショナル・ブレインを構成するという考え方は受け入れられていない。（LeDoux 1996／松本・川村訳 2003, p. 121）

> 辺縁系はいまだに（神経科学と大衆文化の両面で）脳がいかにして情動をつくるかについての説明として優勢を保っているが、それは情動脳の理論としては欠陥が多く不適切である。（LeDoux 2002／森監修、谷垣訳 2004, p. 313）

そもそも、中枢神経系はあまりに複雑にしかも密接に相互作用し合っているので、そこから特定の回路だけを取り出すのは抽象的すぎる考え方である。また、辺縁系（その概念が有用かどうかにも議論があるが）は情動や内臓機能だけに関わるわけではないことが知られているし、大脳皮質と情動の密接な関係も解明されつつあるからだ。つまり、情動脳とは、部位による程度の差はあっても、結局のところ脳全体に外ならないのである。

そうした難点にもかかわらず、1950年代、ある特定の脳部位ないし神経回路が情動の中枢であるという考え方は、魅力的な仮説として多くの精神医学者を引きつけた（そもそも、ルドゥーが著書のなかで繰り返し批判していること自体、マクリーンの考え方がいかに広く受け入れられているかを逆説的に示している）。なかでもとくに注目されたのは、脳内の「報酬中枢」の存在という仮説であった。それは、現在でも、強化学習の脳内機構や脳内報酬系の研究、また依存症の解明に向けた研究などに大きな影響を与えている。

快感脳とその臨床応用

1954年[4]、マッギル大学のジェームズ・オールズとピーター・ミルナーは、ラットの脳に電極を植え込んで、そこに電気パルスを流す実験を行った（Olds & Milner 1954）。そして、ラットがレバーを押すと電気刺激されるようにすると、特定の部位の脳への電気刺激が餌や水と同様の報酬であるかのように、ラットは1分間に100回以上もレバーを押し続けたという。こうした自己刺激が生じる場所は、最初は大脳半球の内側にある中隔とされたが、その後の多くの追試から視床下部と考えられるようになった。だが、その後の研究の結果、視床下部刺激そのものではなく、近くを走る内側前脳束という神経線維連絡が刺激されたために、その線維が向かう腹側被蓋野（VTA）という部位でドパミン神経が活性化されることが究極の原因と考えられている（Mogenson 1980）。

この自己刺激が、報酬なのか、モティヴェーションなのか、学習の強化因子なのか、主観的な快楽なのか、についてはいまだ確定されていない。だが、当時、脳内の特別な部位として「快感脳」が存在して、その場所の電気刺激で快楽を引き起こすことができるというアイデアは、魅力的なものとされた。

「快感脳」を実際に臨床応用したのが、1950年以降に、ニューオーリンズのチュレーン大学神経精神科のR・ヒースによって行われた精神疾患患者への「中隔刺激」による治療である（Heath 1963）。こうした危ういまでに実験的な治療が行われた背景には、さまざまな要素がある。一つは、1960年代まで向精神薬による治療はほとんど実用化されておらず、ローマの精神科医ウゴ・ツェルレッティ（Cerletti 1940）によって1938年に統合失調症の治療法として開発された電気けいれん療法が高く評価されていた時代だったことだ。脳全体にけいれんを起こすほど強い電気を流すよりは、脳の特定の部位に電気パルスを与える方が優れた手法だと思われたのではないだろうか。また、1930～50年代に行われていた精神外科手術（ロボトミー）よりは、一時的に電極を挿入して脳を刺激する方が好ましいと考えられたという面もあるかもしれない。ここでは、まずは、その臨床実験の概要を紹介しよう（Valenstein 1973）。

ヒースは、統合失調症を、外界への関心が低下して、情動をうまく意識できなくなることが原因の精神疾患だと考えた[5]。そこで、当時は情動の中枢と考えられていた辺縁系のなかでも中隔の刺激を用いた臨床研究を行ったのだ。最初の19名の統合失調患者への治療の結果は成功として、1954年に報告されている。その後1970年代までには、合計するとおよそ100名の患者に手術が行われた。

当初は、こんにち使われている定位的脳神経外科の手術法（頭蓋骨を基準として脳の内部の空間座標を決めて、頭蓋骨に小さな穴を開け、電極を刺入する手法）が一般的でなかったため、手術では