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２．学会発表

H. 知的財産権の出願・登録状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

ウェルドニッヒ・ホフマン病　Werdnig-Hoffmann disease

【ICD-10】G12.0
【特記事項】厚生労働省特定疾患治療研究事業の対象疾患

■疫学　国内推定有病率／1,000～2,000人
年齢／発症は生後0～6か月　人工呼吸器の装着なしの場合，死亡年齢は平均6～9か月[1)]
男女比／1：1

■発症に関わる遺伝子　*SMN*（5q13），*NAIP*（5q13），*H4F5*または*SURF*（5q13）

■診断　脊髄性筋萎縮症（SMA Ⅰ，Ⅱ，Ⅲ，Ⅳ型　**表1**）として，認定診断基準が存在する．

下記の（1）①，②，③すべてと（2），（3）の1項目以上が陽性

（1）臨床所見：
①下記のような下位運動ニューロン症候を認める．
筋力低下
筋萎縮
舌，手指の線維束性収縮（fasciculation）
腱反射は減弱から消失
②下記のような上位運動ニューロン症候は認めない．
けい縮
腱反射亢進
病的反射陽性
③経過は進行性である．

（2）臨床検査所見：
筋電図で高振幅電位や多相性電位などの神経原性所見を認める．

（3）遺伝子診断：
survival motor neuron（SMN）遺伝子変異を認める．

表1　脊髄性筋萎縮症の分類

型	疾患名	発症年齢	最高到達運動機能
Ⅰ	Werdnig-Hoffmann病	0～6か月	never sit
Ⅱ	Dubowitz病	＜1歳6か月	never stand
Ⅲ	Kugelberg-Welander病	1歳6か月～20歳	stand and walk alone
Ⅳ	成人型	20歳＜	normal

■治療　根本的な治療法は確立していない．呼吸器感染や誤嚥に伴う呼吸不全に対し，気管挿管と人工呼吸管理を要する．鼻マスクを用いた間歇的陽圧換気（NIPPV）による呼吸不全の改善の報告があるが困難も大きい．呼吸器装着例はリハビリテーションによる関節拘縮の予防が必要である．

■関連語・同義語　脊髄性筋萎縮症（SMA）Ⅰ型，乳児型脊髄性筋萎縮症

■EBM・診療ガイドライン　厚生労働科学研究費補助金 難治性疾患克服研究事業 神経変性疾患に関する調査研究班 2009年度総括・分担研究報告書

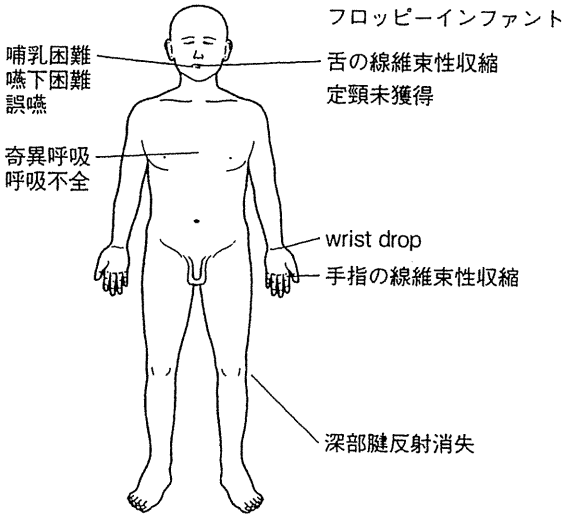
■関連団体　SMA（脊髄性筋萎縮症）家族の会（http://www.sma.gr.jp/）

■解説　脊髄の前角細胞の変性による筋萎縮と進行性筋力低下を特徴とする下位運動ニューロン病．フロッピーインファントを呈する．肋間筋に対して横隔膜の筋力が維持されているため奇異呼吸を示す．定頸の獲得がなく，支えなしに座ることができず，哺乳困難，嚥下困難，誤嚥，呼吸不全を伴う．舌の線維束性収縮がみられる．深部腱反射は消失．上肢の末梢神経の障害により，手の尺側偏位と手首が柔らかく屈曲するwrist dropが認め

られる.

（斎藤加代子，荒川玲子）

■所見



【文献】1）斎藤加代子ら：脊髄性筋萎縮症．J of Clinical Rehabilitation 2010; 19: 601-606.

Chapter Number

Database of Wards for Patients with Muscular Dystrophy in Japan

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Japan

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

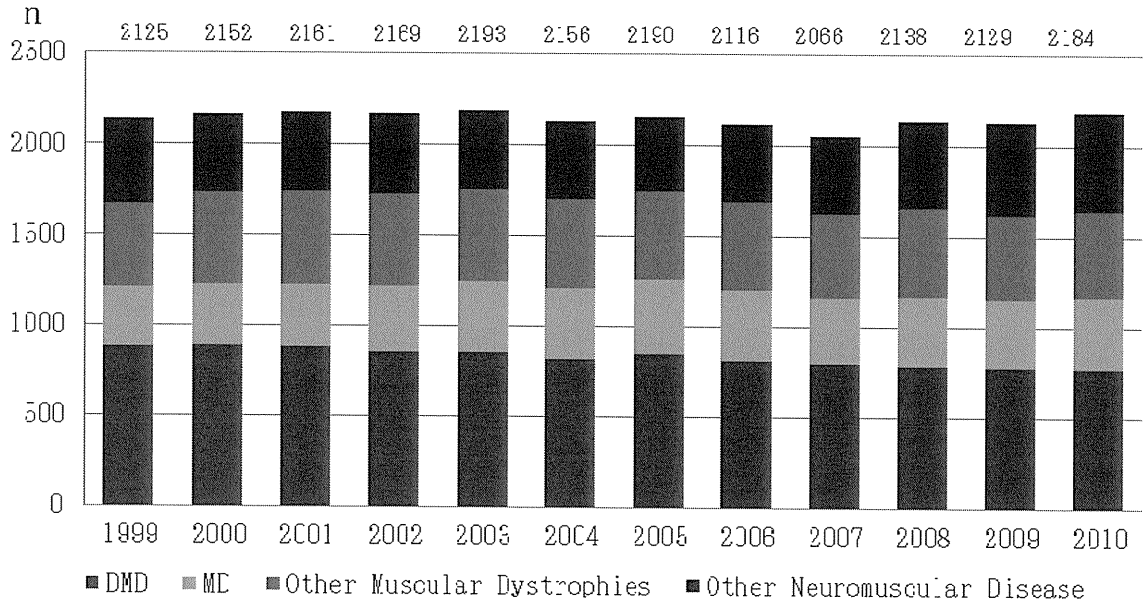
The database includes numbers of inpatients, gender, age, diagnosis, respiratory condition, nutritional state, number of death cases, causes of death, and other relevant findings from data collected annually on October 1 every year since 1999. We examined these data using longitudinal and horizontal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

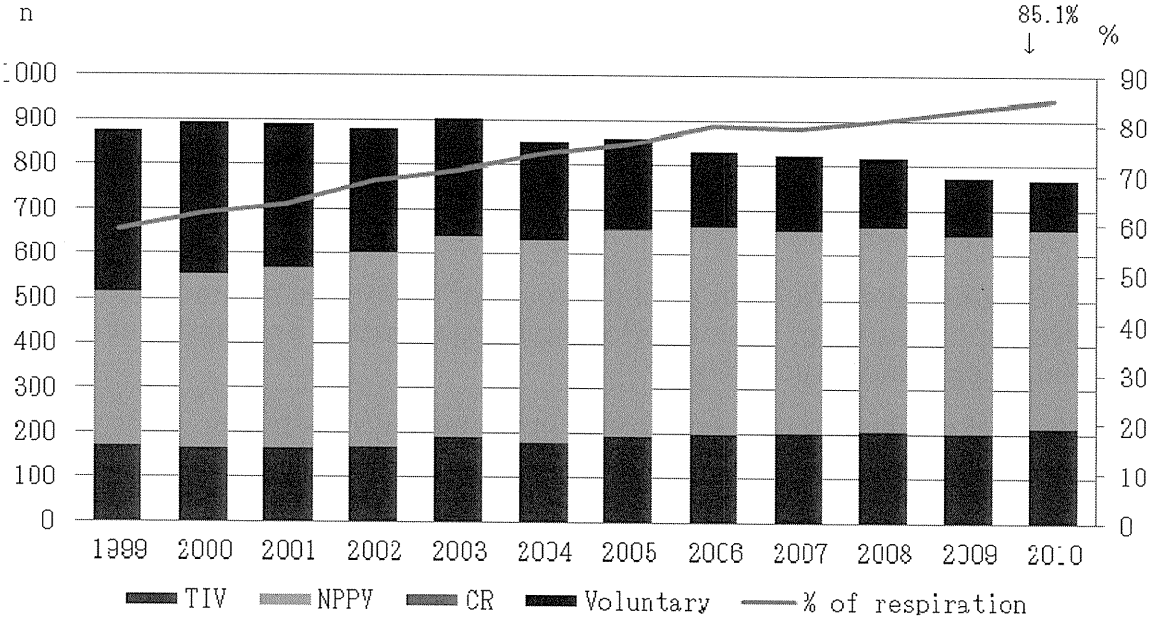
3.1 Details regarding number of inpatients

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

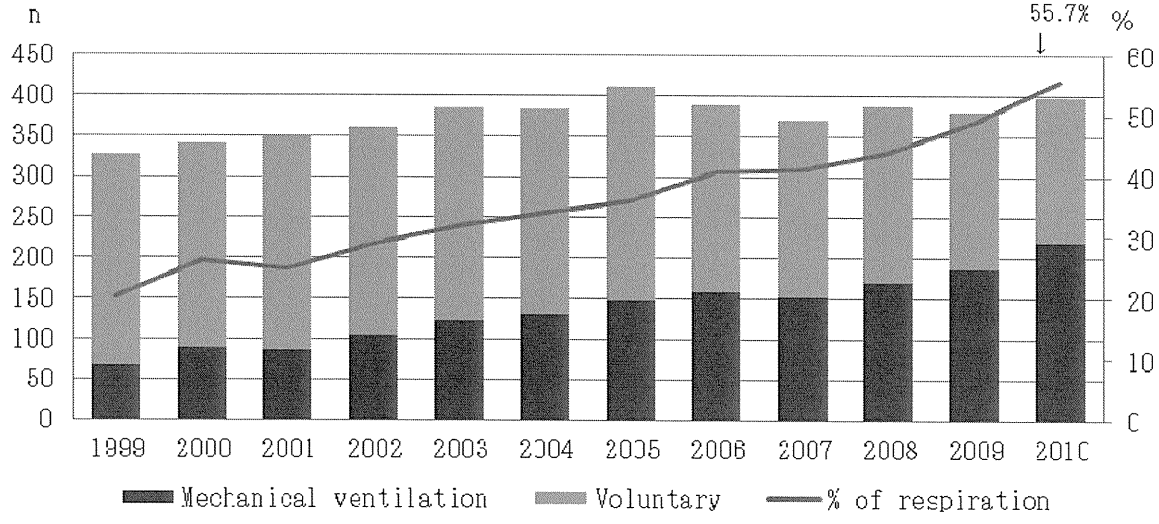
Fig. 1. Total numbers of inpatients in muscular dystrophy wards of National Hospital Organization and National Center of Neurology and Psychiatry.



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

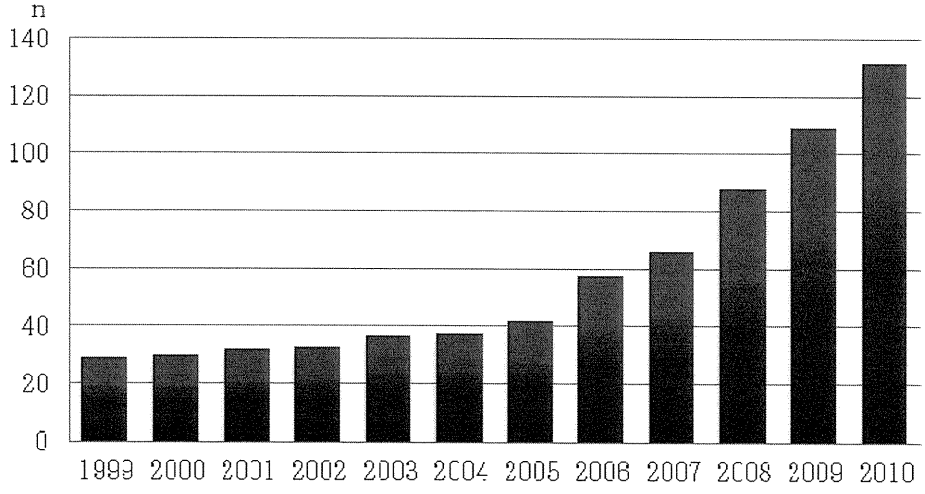
Fig. 2. Sequential changes in number of inpatients with Duchenne muscular dystrophy and rate of mechanical ventilation dependence.

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.

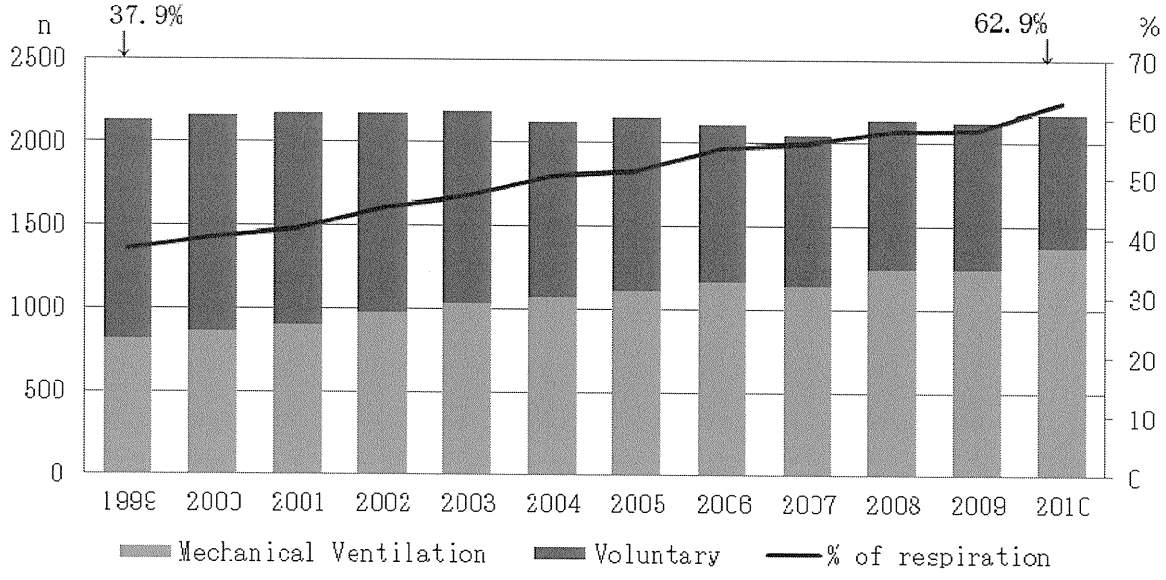


The number with amyotrophic lateral sclerosis has gradually increased every year.

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.

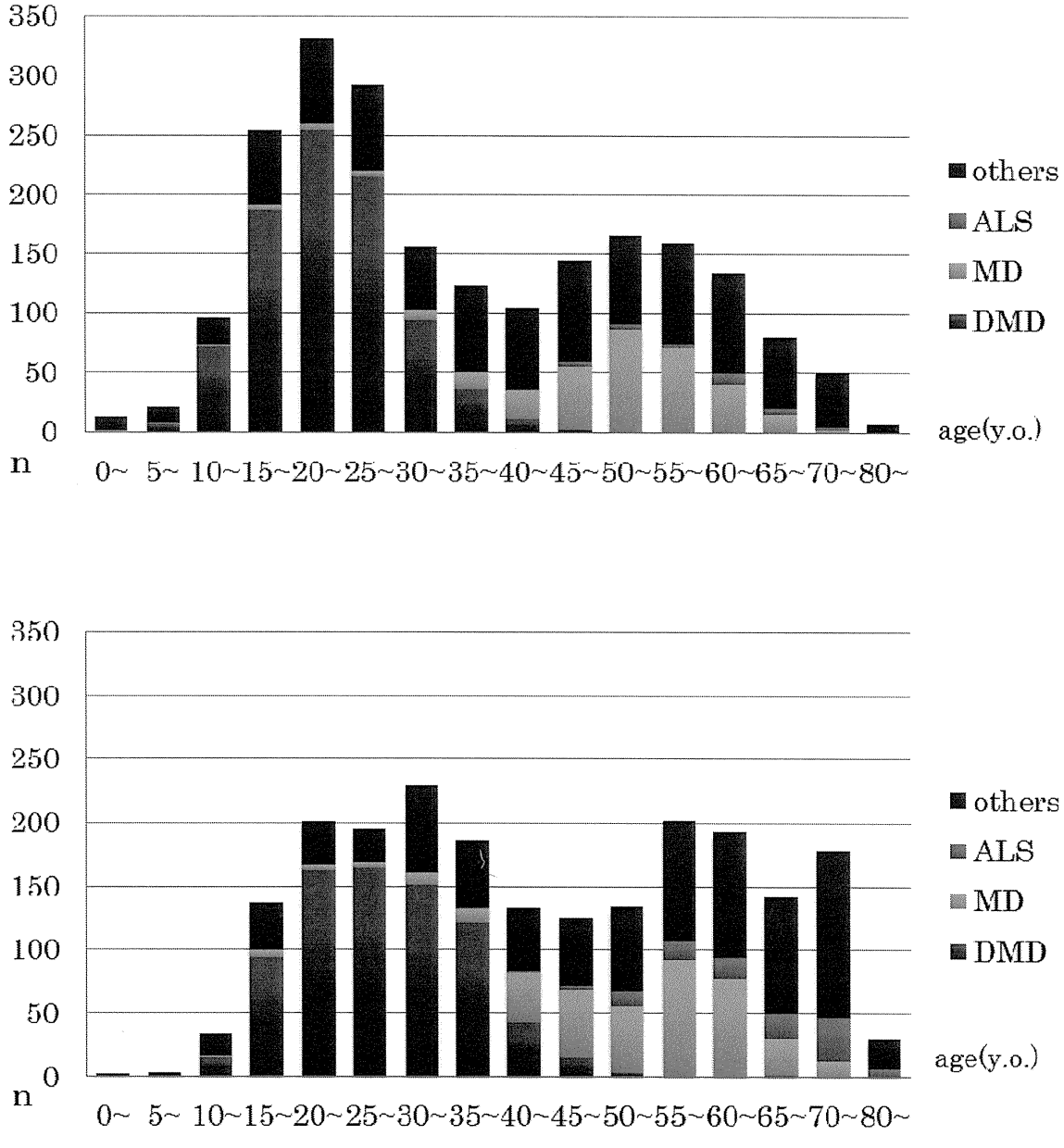
3.2 Analysis of mean age of inpatients

3.2.1 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).

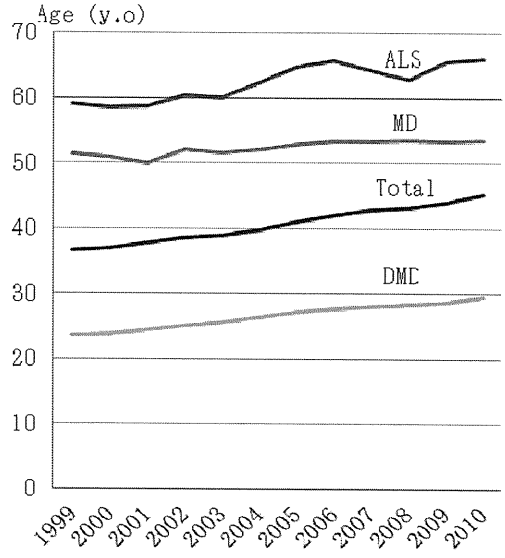
3.2.2 Sequential changes in mean age of inpatients

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).

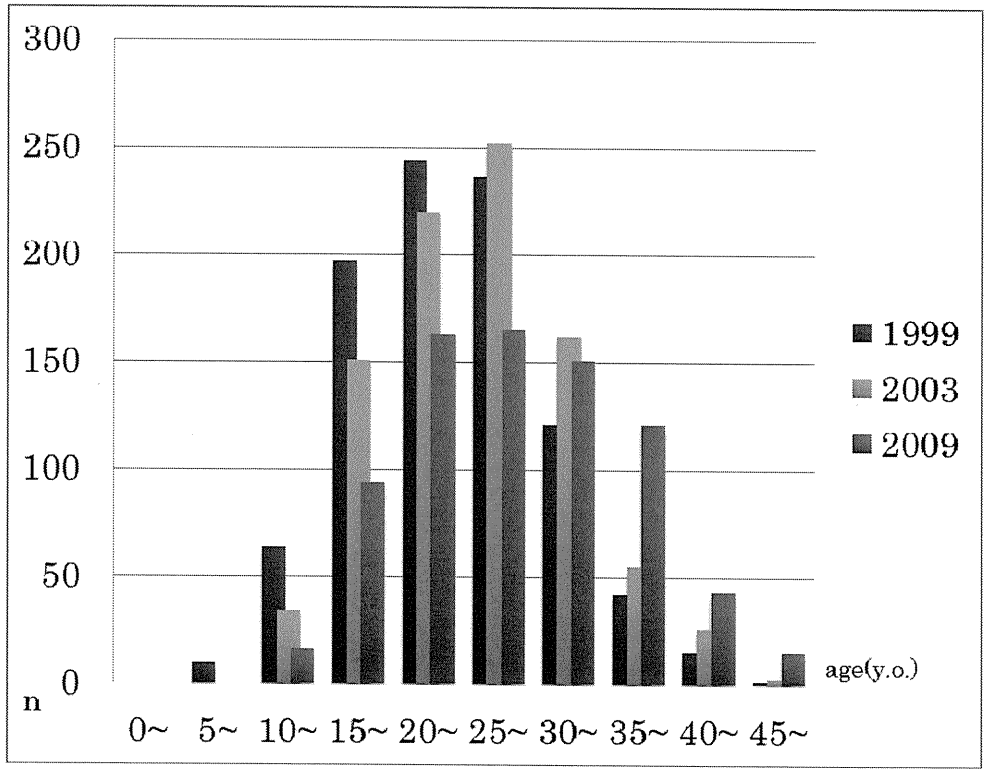
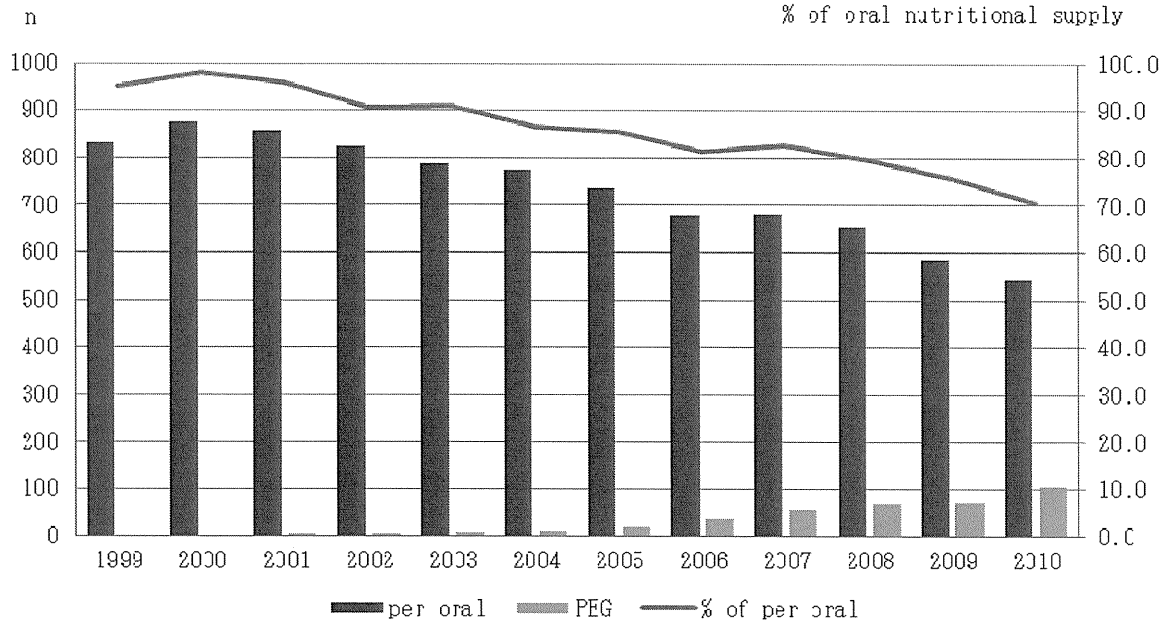


Fig. 8. Changes in age distribution of inpatients with Duchenne muscular dystrophy.

3.3 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

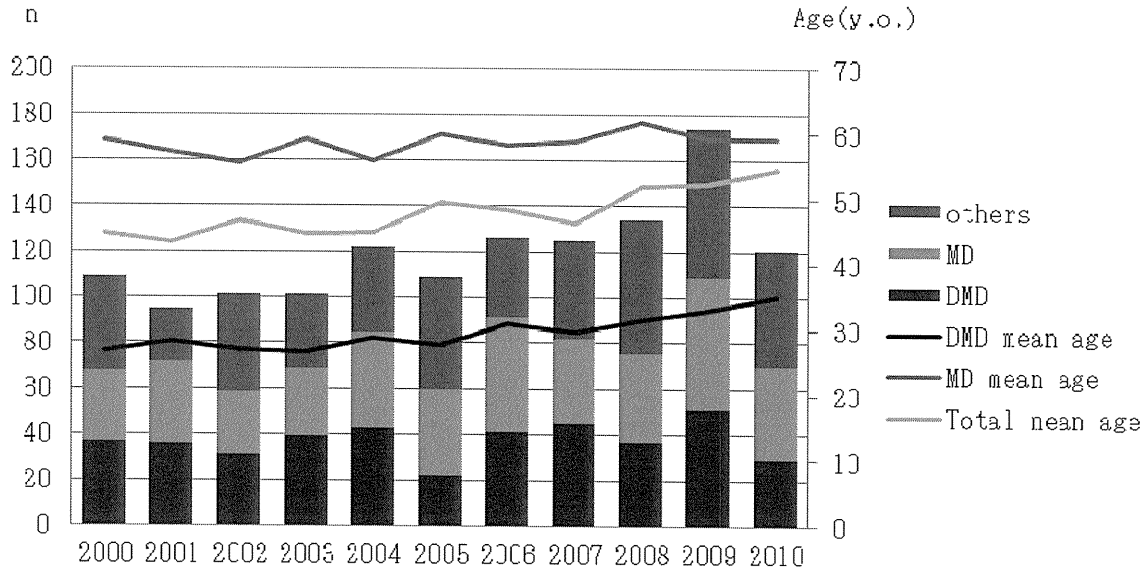
Fig. 9. Sequential changes in numbers of Duchenne muscular dystrophy patients and those who underwent an endoscopic gastrostomy patients receiving oral nutrition.

3.4 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.

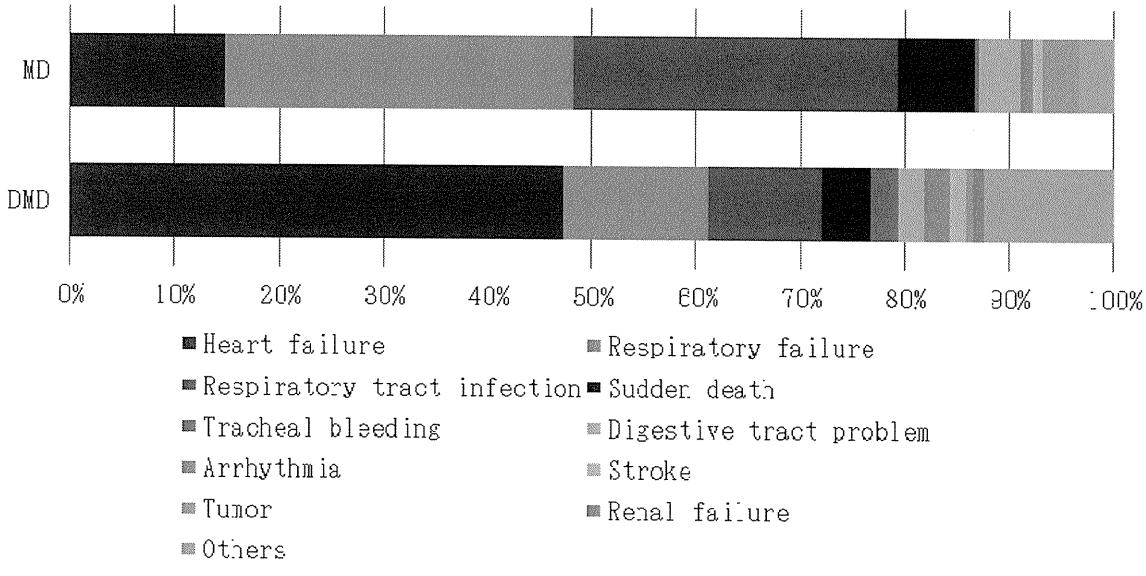
The mean age of death among Duchenne muscular dystrophy patients was 26.7 years old in 2000, which gradually increased to 35.1 years old by 2010. On the other hand, the mean age of death for myotonic dystrophy patients was 59.0 years old in 2000 and 59.1 years old in 2010, which was not significantly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



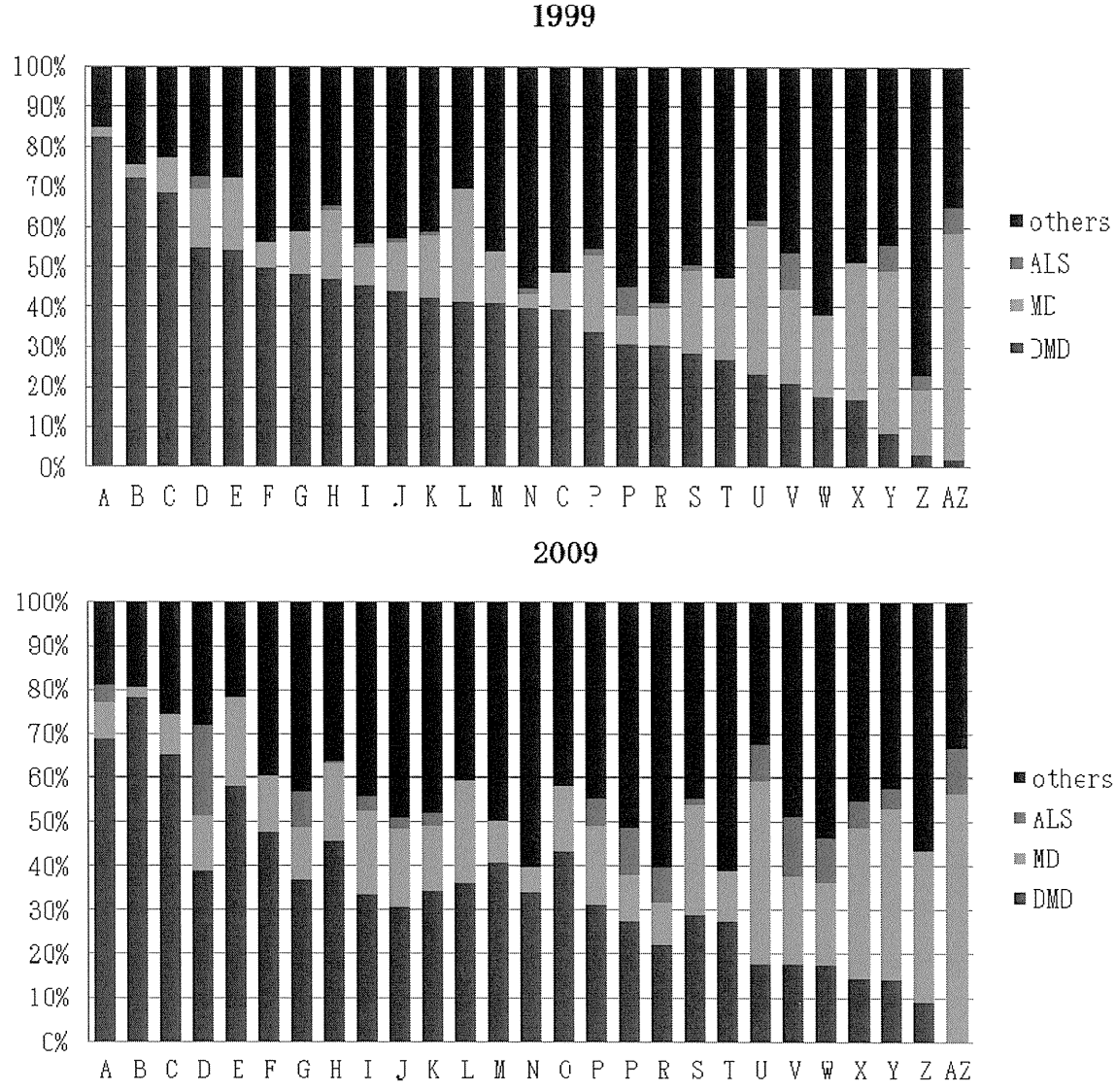
The most frequent cause of death among Duchenne muscular dystrophy patients was heart failure. In contrast, that of myotonic dystrophy patients was respiratory disorder.
DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy

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

3.5 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.



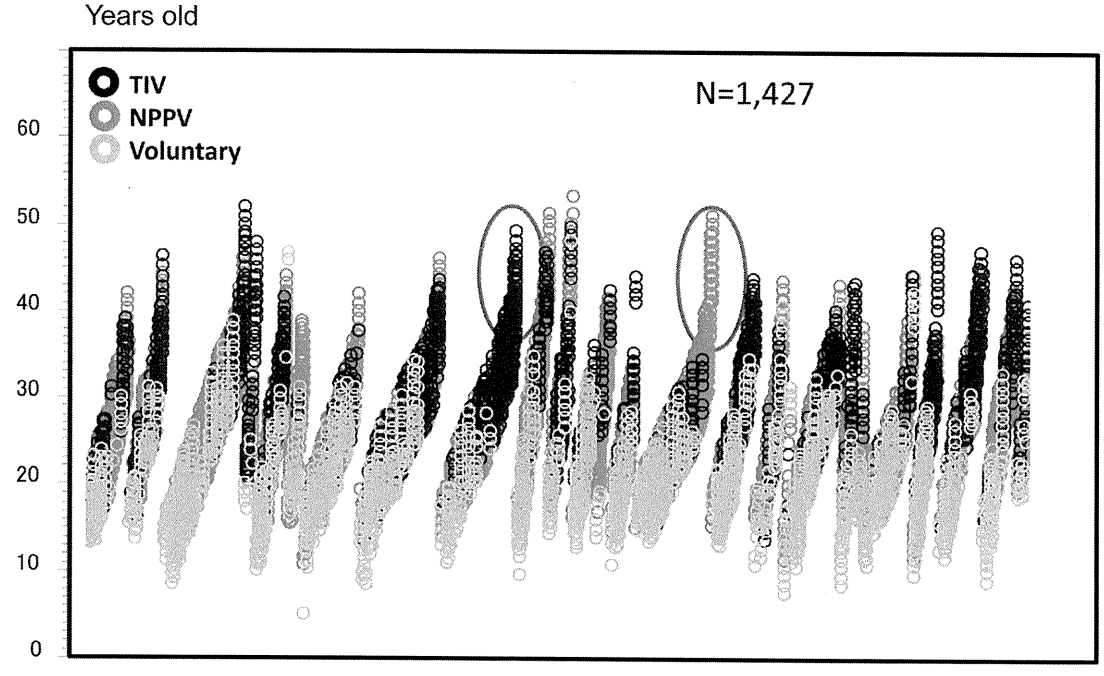
Upper: 1999. Lower: 2009. A~AZ represent the individual institution. Institute AZ, which had lowest rate of DMD patients among institutions in 1999, has no DMD patient in 2009.
DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy; ALS, amyotrophic lateral sclerosis

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

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

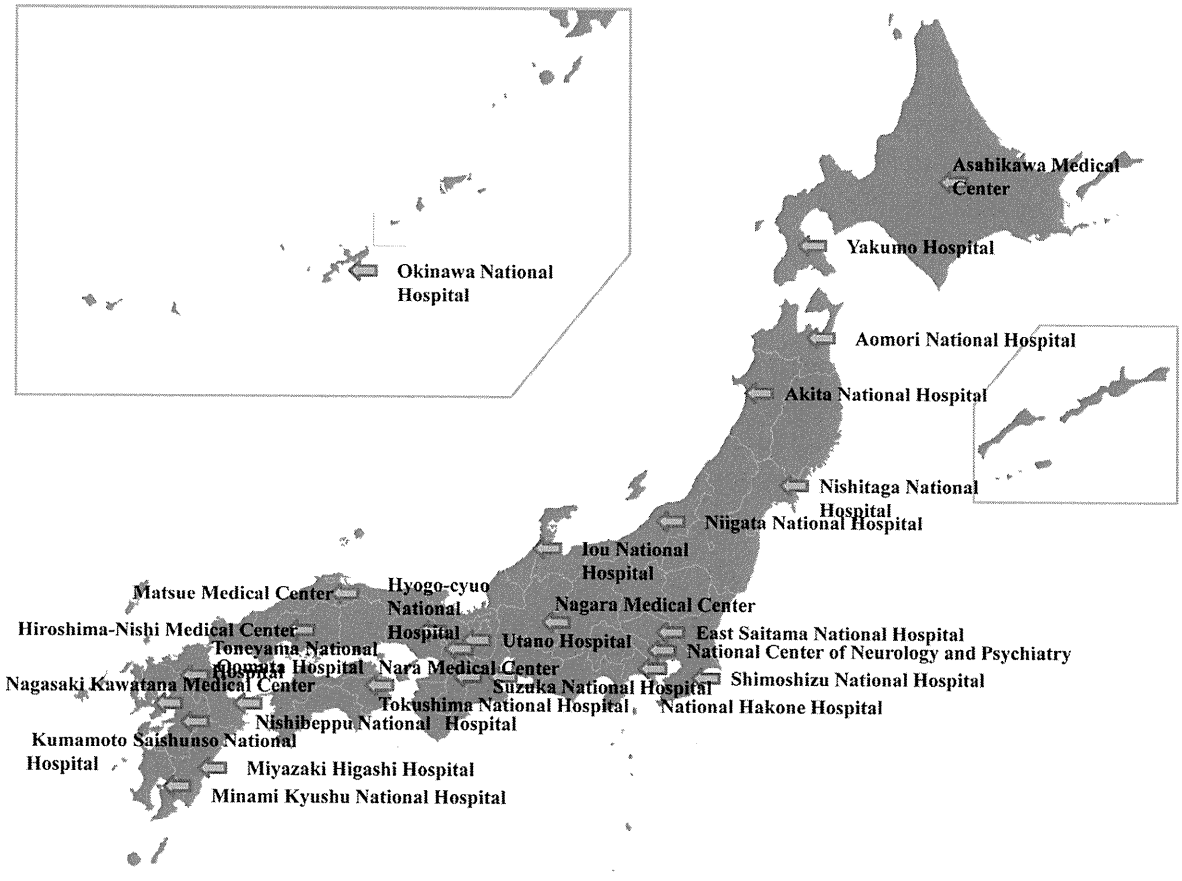

Fig. 14. Institutions specializing in muscular dystrophy treatment in Japan