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A comparative study of care practices for young boys with Duchenne muscular dystrophy between Japan and European countries: Implications of early diagnosis

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Abstract

Early diagnosis of Duchenne muscular dystrophy (DMD) is widely advocated to initiate proactive interventions and genetic counselling. Genetic testing now allows the diagnosis of DMD even prior to the onset of symptoms. However, little is known about care practices and their impact on young DMD boys and families after receiving an early diagnosis. We analysed 64 young boys (Japan, 19; the United Kingdom, 10; Germany, 18; Hungary, 6; Poland, 5; and the Czech Republic, 6) aged <5 years and diagnosed at ≤2 years old among the participants of the cross-sectional study about care practice in DMD. A combination of elevated serum creatine kinase and genetic testing usually led to the diagnosis (n = 31, 48%); 41 boys visited neuromuscular clinics more than once a year. Early diagnosis did not generally result in higher satisfaction among DMD families, and country-specific differences were observed. Psychosocial support following early diagnosis was perceived as insufficient in most countries, and deficits in access and uptake of genetic counselling resulted in lower satisfaction in the Japanese cohort. In conclusion, seamless and comprehensive support for DMD families following early diagnosis at presymptomatic stages should be taken into consideration if early genetic testing or newborn screening is made available more widely.

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Keywords: Duchenne muscular dystrophy; CARE-NMD survey; Early diagnosis; Creatine kinase; Genetic testing; Satisfaction

1. Introduction

Duchenne muscular dystrophy (DMD) is an X linked condition characterized by progressive muscle weakness and wasting due to absence of the protein dystrophin in the muscles [1]. DMD is the most common muscular dystrophy in children and affects approximately one in every 4000 newborn males [2]. Affected boys typically present with motor development disorder or speech delay and muscle weakness in early childhood [3]. Since the introduction of steroid treatment, nocturnal ventilation,
and cardiac support in the last 10–15 years, clinical outcomes and life expectancy have improved significantly [4,5]. Currently, a boy with DMD managed according to these Care Standards has a good chance of living well into his 30s [6]. In recent years, new and promising therapeutic approaches, such as exon skipping therapy, have been developed, trying to restore dystrophin expression in the muscle [7]. Some of these are currently in the clinical trial phase.

On the other hand, there has been little improvement in lowering the age at diagnosis of DMD, still averaging between 4.5 and 5.0 years despite developments in genetic testing and increasing awareness of DMD [6,8–13], although few related studies have been reported from Japan. Diagnostic delay is increasingly recognized to have a negative impact on clinical outcomes [6]. To avoid diagnostic delay, earlier creatine kinase (CK) testing in primary care is emphasized, because of its cost-effectiveness, ready availability, and high sensitivity and specificity [6,8]. In addition, newborn screening for DMD has been piloted in a number of centers in the world, especially in western countries [14]; however, screening newborns for conditions for which limited treatment options exist is controversial due to concerns about the impact a positive screening result may have on the parent–child relationship [15].

Early diagnosis is believed to provide patients and families several benefits: (1) it allows them to make informed decisions regarding future planning; (2) it ensures early access to standards of care (steroid treatment, physiotherapy, and appropriate screening for cardiomyopathy); and (3) it allows participation in research and potentially allows access to clinical trials with new investigational drugs [6]. However, there has been few research which reported care practice in young boys and their families with early diagnosis, especially before 5 years of age when steroid treatment (one of the main interventions in early disease stage) is typically initiated [4,16]. This study explores the real-life experience of DMD families with care and support including help for coping with diagnosis, following early diagnosis, and highlights some differences between Japan and European countries based on differences in culture and healthcare systems.

2. Participants and methods

2.1. Study population

The CARE-NMD project has conducted a cross-sectional, multi-center study surveying care practices and quality of life in patients with DMD in 7 European countries – Bulgaria (BG), the Czech Republic (CZ), Denmark (DK), Germany (GE), Hungary (HU), Poland (PL), and the United Kingdom (UK) since 2011, followed by Japan (JP) since 2012 [17,18]. The 7 European countries were selected because of well-established DMD patient registries and to broadly represent different healthcare systems and public expenditure on health. The health expenditure to gross domestic product ratio is below the EU average in all Eastern European and above the average in all Western European countries participating in this project. Out of the valid responses, we extracted participants diagnosed early (at ≤2 years old) and currently aged <5 years old.

2.2. Survey procedure

The study was approved by the ethics committee at the University Medical Center Freiburg, and as a condition of distribution via national DMD patient registries, was also approved by the TREAT-NMD Global Database Oversight Committee [17,18]. The approval for conducting this survey in Japan was granted by the National Center of Neurology and Psychiatry (NCNP) Ethics Committee. Survey participation was voluntary, and we regarded a reply to the questionnaire as agreement to participate. The survey consisted of 42 questions that captured socio-demographic variables, as well as information about daily life, functional abilities, disease progression, and medical and social care received. The questionnaire translated into the local language by project partners in each country was distributed in each country on behalf of the project via national DMD patient registries, which form part of the TREAT-NMD Global DMD Registries [17,18]. Data from Europe were collected between September 2011 and April 2012, and those from Japan between June 2012 and March 2013. Mail replies were inputted into the SurveyMonkey questionnaire (www.surveymonkey.com).

2.3. Measurements

For this study, we extracted the questionnaire items as follows: method of diagnosis confirmation, help given for coping with the diagnosis, neuromuscular clinic and physiotherapy attendance, information provided (genetic counselling, disease course, special learning needs, patient organizations), treatment (home stretch advice, speech therapy, psychological support), attitude towards the community, involvement with patient advocacy groups, and overall satisfaction.

2.4. Statistical analysis

We wish to compare the families’ satisfaction with the care received in Japan and European countries. While there are differences even within Europe, cultural background and healthcare in Japan are believed to have significant differences in comparison to all European countries, eg the much higher life expectancy of patients with DMD or ALS in Japan as compared to Europe. We statistically analysed questionnaire responses about information given, treatment (except for speech therapy) received, and overall satisfaction using chi-square tests. In terms of questions about information and treatment, we compared “Yes, sufficiently” (“satisfaction group”) and the others (“dissatisfaction group”). In terms of overall satisfaction, the sum of “Very satisfied” and “Rather satisfied” (satisfaction group) was compared with the others (dissatisfaction group). For the conservativeness of the statistical-test, we allocated “No response” in Japanese cohorts to “satisfaction group” and that in European cohorts to “dissatisfaction group”. We considered p-values <0.05 to be significant. Data analysis was conducted by SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) or Microsoft Excel 2010.
3. Results

3.1. Demographics

“How old were you/was your son, when DMD was confirmed either genetically or by muscle biopsy, NOT only based on symptoms or elevated CK in blood?”

Out of 2401 questionnaires sent out, 1465 replies were collected (61% response rate). The response rate of each country is shown in Table 1. A total of 110 boys (7.6%) aged <5 years were identified, of which 64 (4.8%) were diagnosed at ≤2 years: these were eligible for our study. The 64 study subjects consisted of 19 in Japan, 10 in United Kingdom, 18 in Germany, 6 in Hungary, 5 in Poland, and 6 in Czech Republic. No boys in Bulgaria or Denmark met our inclusion criteria (Fig. 1). The median age at diagnosis, current age, and time since diagnosis in the 64 boys was 1.0, 3.25, and 2.0 years, respectively (Table 2).

3.2. Diagnosis of DMD

3.2.1. Confirmation of the diagnosis

“How was the diagnosis of DMD established in your case? You may mark more than one answer.”

Fig. 2a describes the DMD diagnostic approach according to the self-reported data from patients and their families. A combination of elevated serum CK and genetic testing of blood samples led to the diagnosis in 31 (48%) cases. Other early diagnostic clues included signs at physical assessment in 13 cases (20%), and positive family history in 3 (5%, 1 Japan and 2 Czech Republic). A muscle biopsy was performed in 12 boys (19%). Genetic testing was performed in all participants and DMD confirmed as a mandatory inclusion criterion in the registry.

3.2.2. Help for coping with diagnosis offered by doctor at diagnosis (Fig. 2b)

“What kind of help for coping with the diagnosis was offered to you by your doctor at the time of diagnosis? You may mark more than one answer.”

Table 1
Participants of the CARE-NMD survey.

<table>
<thead>
<tr>
<th>Country</th>
<th>JP</th>
<th>UK</th>
<th>GE</th>
<th>HU</th>
<th>PL</th>
<th>CZ</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population (×10⁶)*</td>
<td>12.7</td>
<td>6.2</td>
<td>8.3</td>
<td>1.0</td>
<td>3.8</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Sent out, n</td>
<td>724</td>
<td>421</td>
<td>545</td>
<td>70</td>
<td>246</td>
<td>191</td>
<td>73</td>
</tr>
<tr>
<td>Total replies received, n (%)</td>
<td>394 (54)</td>
<td>226 (54)</td>
<td>420 (77)</td>
<td>57 (81)</td>
<td>142 (58)</td>
<td>89 (53)</td>
<td>40 (55)</td>
</tr>
<tr>
<td>Replies re: boys aged &lt;5yo, n (%)</td>
<td>30 (7.6)</td>
<td>13 (5.8)</td>
<td>34 (8.1)</td>
<td>9 (15.8)</td>
<td>10 (7.0)</td>
<td>10 (11.2)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Replies re: boys aged &lt;5 and diagnosed ≤2yo, n (%)</td>
<td>19 (4.8)</td>
<td>10 (4.4)</td>
<td>18 (4.3)</td>
<td>6 (10.5)</td>
<td>5 (3.5)</td>
<td>6 (6.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>


Table 2
Demographics.

<table>
<thead>
<tr>
<th></th>
<th>JP (n = 19)</th>
<th>UK (n = 10)</th>
<th>GE (n = 18)</th>
<th>HU (n = 6)</th>
<th>PL (n = 5)</th>
<th>CZ (n = 6)</th>
<th>Total (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis: (years. months) Median, range</td>
<td>1.3</td>
<td>0.9</td>
<td>0.11</td>
<td>1.0</td>
<td>1.0</td>
<td>0.11</td>
<td>1.0</td>
</tr>
<tr>
<td>Current age: (years. months) Median, range</td>
<td>0.7–2.0</td>
<td>0.1–2.0</td>
<td>0.3–1.8</td>
<td>0.6–1.6</td>
<td>0.5–2.0</td>
<td>0.3–2.0</td>
<td>0.1–2.0</td>
</tr>
<tr>
<td>Time since diagnosis: (years. months) Median, range</td>
<td>3.6</td>
<td>3.5</td>
<td>2.8</td>
<td>2.7</td>
<td>3.2</td>
<td>3.6</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>1.5–5.0</td>
<td>2.5–4.8</td>
<td>0.10–4.6</td>
<td>1.10–4.8</td>
<td>2.4–4.5</td>
<td>1.6–4.4</td>
<td>0.10–5.0</td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>2.3</td>
<td>1.11</td>
<td>1.6</td>
<td>2.0</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>0.7–4.5</td>
<td>0.9–4.2</td>
<td>0.5–3.9</td>
<td>1.2–3.7</td>
<td>1.2–3.5</td>
<td>0.9–3.6</td>
<td>0.5–4.5</td>
</tr>
</tbody>
</table>

JP, Japan; UK, the United Kingdom; GE, Germany; HU, Hungary; PL, Poland; CZ, the Czech Republic.
At the time of DMD diagnosis, 38 (59%) parents/caregivers reported being offered “some help”, 12 were offered “not appropriate” help, 7 responded that help was “not needed”, and 3 responses were “unknown”. In the Japanese cohort, 9 parents/caregivers (47%) answered with “offered some help”, which was lower than that for the 6 European cohorts (United Kingdom: 10, 70%; Germany: 12, 67%; Hungary: 3, 50%; Poland: 3, 60%; Czech Republic: 4, 67%). Then, “what kinds of help did your doctor offer?” was asked to those who had been offered some help (more than one answer was allowed). Twenty-five parents/caregivers reported being given “Brochures/Website” (Japan: 4, United Kingdom: 6, Germany: 9, Hungary: 1, Poland: 1, and Czech Republic: 4), 21 reported being allowed “Sufficient time to talk to doctor or a second appointment with the doctor” (Japan: 3, United Kingdom: 4, Germany: 9, Hungary: 1, Poland: 0, and Czech Republic: 4), 11 reported “Referral to support group” (Japan: 0, United Kingdom: 0, Germany: 9, Hungary: 1, Poland: 1, and Czech Republic: 0), 11 reported “contact with social worker/care coordinator” (Japan: 0, United Kingdom: 3, Germany: 8, Hungary: 0, Poland: 0, and Czech Republic: 0), 10 reported “Taking part in courses for families with DMD” (Japan: 4, United Kingdom: 1, Germany: 1, Hungary: 0, Poland: 0, and Czech Republic: 4), and 9 reported “Contact with psychologist” (Japan: 2, United Kingdom: 2, Germany: 2, Hungary: 0, Poland: 1, and Czech Republic: 2). It seemed that the parents/caregivers of more boys in United Kingdom, Germany, and Czech Republic received help for coping with diagnosis than in Japan, Hungary, and Poland.

3.3. Attendance at neuromuscular clinics

“Do you/does your son attend a clinic where the medical staff specialize in neuromuscular disorders? If yes, how often?”

The frequency of attendance at a neuromuscular (NMD) clinic which was recognized as a specialized clinic by the parents/caregivers is shown in Fig. 3a. Half of the boys (n = 32) attended at least once every 6 months, 19 (30%) at least once a
year, 9 (1%) less than once a year, and 4 (6%) did not attend at all. In the Japanese cohort, 17 (89%) boys attended more than once annually, which was a slightly higher percentage than the 6 European countries: United Kingdom (n = 7, 70%), Germany (n = 14, 78%), Hungary (n = 5, 83%), Poland (n = 3, 60%), and Czech Republic (n = 5, 83%).

3.4. Information about DMD which a medical professional ever talked (Fig. 4)

“As a medical professional ever talked to you/your son about...”

3.4.1. Genetic counselling

In terms of satisfaction among the parents/caregivers of the 64 boys with the information received on genetic counselling, 45 (70%) answered “sufficiently”, 8 (13%) “Yes, but not enough”, 7 (11%) “No, not at all”, 2 (3%) “I don’t know”, and 2 (3%) didn’t answer. In the Japanese cohort, 9 (47%) answered “sufficiently”, 4 (21%) “Yes, but not enough”, 4 (21%) “No, not at all”, and 2 (11%) “I don’t know”. The Japanese cohort’s satisfaction with information on genetic counselling was significantly lower than that of the European cohorts (p = 0.009).

3.4.2. The disease course and main problems that may arise

About the satisfaction with information on DMD overall, 41 (64%) of parents/caregivers replied “sufficiently”, 17 (27%) “Yes, but not enough”, 4 (6%) “No, not at all”, 1 (2%) “I don’t know” and 1 didn’t answer. There was no significant difference between the Japanese cohort and European cohorts (p = 0.504).

3.4.3. Adequate schooling or special learning needs of some children with DMD

Regarding satisfaction with information given about education, the parents/caregivers of only 12 boys (19%) answered “Yes, sufficiently”, 13 (20%) “Yes, but not enough”, 29 (45%) “No, not at all”, and 7 (11%) “I don’t remember”. There was no significant difference between the Japanese cohort and European cohorts (p = 0.759).

3.4.4. Patient organizations

About the satisfaction with information on patient organizations, the parents/caregivers of 27 boys (42%) reported...
“Yes, sufficiently”, 13 (20%) “Yes, but not enough”, 20 (31%) “No, not at all”, and 2 “I don’t remember”. No significant difference was shown between the Japanese cohort and European cohorts ($p = 0.264$).

3.5. Treatment of DMD (Fig. 3b, Fig. 5)

3.5.1. Professional physical training, stretching or exercises and instruction of home stretch

“Does your son currently receive physical training, stretching, or other physical exercises from a qualified professional?”

“Have you/has your son ever been instructed in doing stretching at home?”

As shown in Fig. 3b, 13 boys (20%) received physiotherapy ≥60 minutes weekly, 15 (23%) <60 minutes weekly, 12 (19%) had previously received physiotherapy, while 23 (36%) had never received it. In the Japanese cohort, no one received physiotherapy for more than 60 minutes weekly, and 4 (21%) boys received less than 60 minutes weekly. The percentage of boys receiving regular physiotherapy in Japan was lower than in the 6 European countries. The result of United Kingdom was similar to that of Japan in that 5 (50%) boys in United Kingdom had never received PT. On the other hand, all Hungarian boys received regular PT.

About the satisfaction with home stretch advice, the 23 (36%) parents/caregivers answered “Yes, sufficiently”, 17 (27%) “Yes, but not enough”, 17 (27%) “No, not at all”, 5 (8%) “I don’t need it”, and 1 (2%) “I don’t remember”. There was no significant difference between the Japanese cohort and European cohorts ($p = 0.104$).

3.5.2. Speech therapy

“Does your son currently receive speech therapy?”

In terms of speech therapy, 4 (6%) boys (1 PL, 2 DE, and 1 UK) received “60 minutes or more weekly”, 5 (8%) boys (1 Czech Republic, 1 Poland, 1 Germany, 1 United Kingdom, and 1 Japan) “less than 60 minutes weekly”, 4 (6%) boys (2 Germany and 2 United Kingdom) “had received it before” and 46 (72%) had “never received” speech therapy.
3.5.3. Psychological support for coping with the diagnosis

“Have you/has your son received psychological support for coping with the diagnosis or in managing daily life?”

In terms of satisfaction with the psychological support provided, the parents/caregivers of 6 (9%) boys replied “Yes, sufficiently”, 8 (13%) “Yes, but not enough”, 36 (56%) “No, not at all”, and 11 (17%) “I don’t need it”. There was no difference between the Japanese cohort and European cohorts regarding satisfaction with psychological support ($p = 0.605$) received.

3.6. Involvement with community, patient advocacy group (Fig. 6)

3.6.1. Attitude towards community

“Do you/does your son believe that you are/your son is viewed on equal terms by other citizens in your local community?”

The parents/caregivers of 32 (50%) boys believed that their affected boys were viewed on equal terms by other citizens in the local community “Yes, always”, 21 (33%) “Most of time”, 3 (5%) “Sometimes”, 2 (3%) “Seldom”, and 2 (3%) “Never”. In the Japanese cohort, 7 (37%) answered “Yes, always” or “Most of time”, 1 (5%) “Sometimes”, 2 (11%) “Seldom” and 1 (5%) “Never”.

3.6.2. Members of patient advocacy groups

“Is anyone in the family a member of a patient advocacy group for Duchenne or neuromuscular disease in general?”

Overall, 23 (36%) of the boys’ family members were involved with a patient advocacy group for DMD or NMD. Czech families were involved with a patient advocacy group most frequently ($n = 4, 67\%$), while no Polish families were involved (Japan; 6, 32%, United Kingdom; 3, 30%, Germany; 9, 50%, Hungary; 1, 17%, Poland; 0, 0%, Czech Republic; 4, 67%). This distribution was similar to the provision of information about patient organizations, as shown in Fig. 4d.

3.7. Satisfaction with overall treatment

“How satisfied are you with your overall medical treatment?”

In terms of satisfaction with overall treatment (Table 3), the parents/caregivers of 11 (17%) answered “Very satisfied”, 28 (44%) “Rather satisfied”, 18 (28%) “Rather unsatisfied”, and 3 (5%) “Not satisfied at all”. In the Japanese cohort, no responses of “very satisfied”, 6 (32%) “Rather satisfied”, 9 (47%) “Rather unsatisfied”.

![Fig. 6. Involvement. (a) Attitude towards community, and (b) members of patient advocacy groups, by country.](image)

Table 3

<table>
<thead>
<tr>
<th>Country, and response, n (%)</th>
<th>JP (n=19)</th>
<th>UK (n=10)</th>
<th>GE (n=18)</th>
<th>HU (n=6)</th>
<th>PL (n=5)</th>
<th>CZ (n=6)</th>
<th>Total (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very satisfied</td>
<td>0 (0)</td>
<td>4 (40)</td>
<td>6 (33)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Rather satisfied</td>
<td>6 (32)</td>
<td>3 (33)</td>
<td>10 (56)</td>
<td>2 (33)</td>
<td>3 (60)</td>
<td>4 (67)</td>
<td>28 (44)</td>
</tr>
<tr>
<td>Rather not satisfied</td>
<td>9 (47)</td>
<td>2 (20)</td>
<td>2 (11)</td>
<td>3 (50)</td>
<td>1 (20)</td>
<td>1 (17)</td>
<td>18 (28)</td>
</tr>
<tr>
<td>Not satisfied at all</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>No response</td>
<td>3 (16)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

JP, Japan; UK, the United Kingdom; GE, Germany; HU, Hungary; PL, Poland; CZ, the Czech Republic.
unsatisfied” were given, while 1 (5%) respondent answered “Not satisfied at all”. Satisfaction in the Japanese cohort was significantly lower than that in European cohorts ($p = 0.046$).

4. Discussion

This was an observational cross-sectional study focusing on care practices for young boys diagnosed DMD at ≤2 years and their families. Our study revealed diagnostic method, some discrepancies between care practices and care recommendations, and some differences of parents’ satisfaction with care practice between Japanese and European cohorts.

4.1. Study findings

4.1.1. Diagnosis

In the Japanese cohort, early diagnosis was most frequently established by means of the combination of elevated serum CK and genetic testing, consistent with the European countries. In three quarters of the boys, family history or physical assessment was not reported as a diagnostic clue, which may imply that their muscle condition was pre-symptomatic, and the traditional diagnostic pathway (for example, noticing delay in attainment of independent walking) was not used for their early diagnosis. Currently, genetic testing is performed for diagnosis in most cases, showing a specific mutation in DMD gene. All of CARE-NMD study participants provided their genetic testing result to register the DMD registry in each country. Muscle biopsy is now only recommended when initial genetic testing is inconclusive or the patient has an unusual phenotype [6]. In our cohort, only 19% of boys had a muscle biopsy performed, while 49.3% of 1062 patients with DMD (mean age: 13.0 years old) in the total CARE-NMD survey cohorts [18] reported diagnosis by muscle biopsy, which supports the suggestion that genetic testing development ensures easier, faster and less invasive diagnosis of DMD in young cohorts.

4.1.2. Discrepancy between real world care practice and DMD guideline recommendations

In this study, most boys (60–89% of each country) attended NMD clinics at least once a year. This might suggest that early diagnosis ensures early access to NMD clinics. However, some discrepancy between care practice and guideline recommendations were also observed [4]. First, wide variation in physiotherapy accessibility and/or home stretch advice was observed in the 6 countries. The international guideline recommends preventive measures to maintain muscle extensibility and/or minimize contractures between the pre-symptomatic and early ambulatory stage [4]. However, in our cohort, all Hungarian boys accessed regular physiotherapy, while less accessibility was shown in the boys of Japan, Czech Republic, and the United Kingdom. The related study documented very low rates of access to professional physiotherapy in the United Kingdom generally with low rate in the paediatric cohort [17]. Second, psychological support, information on cognitive delay, and speech therapy seemed to be insufficient overall, despite the fact that family support, early assessment and/or intervention for development, learning, and behaviour is recommended in the pre-symptomatic stage [4].

In the current study, care practice varied by country and/or individual. The heterogeneities and poor agreement with DMD clinical guidelines were also shown in the previous reports from Western countries examining different aspects of self-reported real-world DMD care in various settings by country [17–19]. The first compared care practice in 201 adult (≥18 years) DMD patients extracted from CARE-NMD survey participants in 7 European countries (United Kingdom, Germany, Hungary, Poland, Czech Republic, Bulgaria, and Denmark) [17,18]. The second analysed the experience of medical management of 770 DMD patients (aged ≥5 years) in Germany, Italy, the United Kingdom, and the United States in comparison to the clinical guidelines [19]. Neither international studies related DMD focused on paediatric cohorts aged <5.0 years with early diagnosis, or socio-epidemic comparative studies between Asian and Western countries had been reported. Although this study sample was very small, the observed heterogeneities support the previous findings [17–19].

As noted in previous studies, there are several potential reasons for differences between care guidelines and implementation. First, we noted differences in the delivery of and access to care in general, and the availability of specialized NMD clinics [17–19]. Second, national healthcare systems differ; government funded programs versus private insurance schemes and the degrees of cost sharing for services might affect the provision of healthcare, as well as the ability and willingness to utilize healthcare services. Third, at the time this study was conducted, clinicians may not yet have been aware of the international guidelines. This survey was conducted in between 2011 and 2012, while the international guidelines were published in 2010 [4,5], followed by Japanese care guidelines in 2014 [20]. Finally, there may be factors specific to those boys in the early ambulatory stage of the condition, such as that they attend NMD clinics less frequently than those in later stages. Alternatively, it is also possible that they attend a non NMD clinic more often. Later on, at least 6-monthly assessment is recommended to define disease phase and determine need for intervention and management with steroid therapy [4,18].

4.1.3. Care practice in Japan

In this study, characteristic care practices in Japan were observed in comparison to the 5 European countries. In spite of a higher percentage of regular NMD clinic attendance in Japanese cohorts, significantly lower satisfaction with information on genetic counselling and overall care and treatment was observed.

Generally, the Japanese healthcare system allows easy access to medical care and treatment from primary to tertiary. Moreover, in some hospitals, CK is performed as a routine blood test, which might be different from healthcare systems of the other countries [6,8–13] and which may result in an incidental elevated CK finding. Moreover, health insurance has covered MLPA genetic testing to diagnose on DMD/BMD since 2006 [21], with genetic counselling since 2012 [20]. The additional genetic testing with whole-exon sequence for small DMD gene mutation is available from the research institute of NCNP free of charge to patients who are willing to participate in the Japanese national
registry of muscular dystrophy (Remudy) [22,23]. Interestingly, Japanese cohort’s satisfaction with information on genetic counselling and overall treatment was significantly lower than that of European cohorts, in spite of the accessibilities of diagnostic testing from CK to genetic testing and higher regular attendance of neuromuscular clinic. In addition, satisfaction with information on genetic counselling was lower than that with information provision on the main problems associated with DMD, which was not observed in European cohorts. In a previous Japanese survey of 66 families affected by muscular dystrophy, information on the nature of the disease and prognosis was provided more often than genetic information (such as relationship between dystrophy and genetic abnormality, and the availability of carrier tests) by attendant physicians [24]. Interestingly, the Japanese population, not limited to DMD families, is generally reporting lower satisfaction according to the OECD Better Life Index [25] and World Happiness Report [26]. In addition, we hypothesize that the lower satisfaction of DMD families may be multifactorial and includes the availability or access to genetic counselling, provision of help for coping with diagnosis, and cultural attitudes and belief towards genetic diseases which are often hidden or not talked about. For older, more disabled patients with DMD, Japan provides 27 hospitals with specialized wards, where experienced multidisciplinary teams provide care [23]. In contrast genetic counselling, which is more important for younger patients and families, has not been fully established and costs are not fully covered by the public requiring direct payment by the families. However, as genetic testing and genetic research become more popular in Japan, the establishment of a national genetic counselling system was required [27]. In fact, specific genetic counselling departments have recently been set up, and more than 100 hospitals have opened genetic counselling clinics as of November 2014 [28].

Second, genetic issues have been treated as a taboo topic by clinicians traditionally, although the situation has improved. Several factors such as culture, society, history, and genetic literacy should be considered that shape the opinion of the wider public towards genetic issues [29]. Indeed, the discrimination against minorities, including people with hereditary diseases and disabilities globally, although diminishing, still exists. In Japanese custom, the “family” has traditionally been more valued than the “individual”. Consequently, having a hereditary disease used to be recognized as “family’s shame” and was kept in secret in some families [30]. Moreover, it has been discussed that insufficiency of genetic education in school interfered with promoting genetic literacy [29,31,32]. In the previous surveys, lower literacy and interest in science and technology was shown for the Japanese population in comparison to the United States and Europe [33,34]. To improve genetic education, efforts have been made in schools and in the general public [31]. Finally, the availability of help for coping with diagnosis has been correlated to the parents’ satisfaction. According to Green [35], the only independent predictors of parents’ satisfaction with diagnosis of DMD were obtaining the information that they wanted and feeling that they had understood and remembered it. In this study, fewer than half of the Japanese cohort reported being “offered some help” at the time of diagnosis, which was not significantly different between Japanese and European cohorts. Moreover, support tools for coping with diagnosis offered to Japanese families seemed to be limited in comparison to those of the United Kingdom, German, and Czech families. Among 377 Japanese participants in CARE-NMD survey, the satisfaction with overall treatment is slightly better in the patients diagnosed at 2–5 years old in comparison to the patients diagnosed at 0–1 year old. (Supplementary Table S1).

The attitude towards the community seemed to be positive among all the cohorts, which might be associated with the early disease stage we analysed, because the consequences of DMD (for example, physical limitations) can result in social isolation, withdrawal, and less access to social activities [4]. The families’ participation in patient advocacy group showed inconsistency by country, in a distribution similar to the provision of information on patient organizations by clinicians. Even if patients’ families were offered the information, participation in patient communities would depend on individual perception. For some families with young boys in the pre-symptomatic stage of DMD, participation in patient communities may be challenging.

4.2. Optimization of early diagnosis

To optimize early diagnosis, it is important to make DMD care guidelines accessible to healthcare staff, patients, and their caregivers. It also requires worldwide efforts to pre-identify multidisciplinary care centres with committed neuromuscular leaders and nurse specialists, genetic counselling resources, and access to other specialty care so that early diagnosis can offer benefits to the boys and their families. One example of this is provided by the cystic fibrosis care system, where consistent interventions are used across care centers, and clinical outcomes arise from a series of ongoing assessments with results recorded in a central patient registry and reported regularly to the public. Additionally, ongoing efforts have been invested to link paediatric and adult care clinics, providing a seamless transition from paediatricians to internists with multidisciplinary teams [36]. Our findings suggest that for families with young boys diagnosed with DMD, obtaining helpful information appears to be challenging. It was notable that “brochures/websites” were the most frequently used form of assistance in coping with the diagnosis. As this suggested, information packages for families, including language-specific web resources providing information on care guidelines, up-to-date treatment options, supportive technologies, and opportunities for clinical trials are essential for patients and families to cope with diagnosis, have a raised awareness and become empowered. In fact, up-to-date, useful information on DMD has been currently accessible on various websites, which are more available in English than in the other languages including Japanese. As the CARE-NMD website (http://www.care-nmd.eu) and DMD Care Guidelines App (http://www.treat-nmd.eu/care/dmd/family-guide/smartphone) provides, it is important to make essential information for DMD available worldwide. Moreover, it is important to facilitate additional innovative services which meet the unique needs of the DMD population, for example, information and/or communication by using social media [37].
4.3. Future research

The importance of natural history data of infant and young boys with DMD is widely recognized [3,38–40]. It is hoped that the effect of early interventions (medication with steroids [36,41], new drugs, physiotherapy and speech therapy) on physical outcomes, social interaction [42], quality of life, and satisfaction with care will be revealed in the near future. Therefore, it is important to carry out a preliminary study in young boys with early diagnosis. Consequently, some of these strategies may have the potential to decrease the burden of the disease and improve the overall quality of life and daily functioning for DMD patients [43].

4.4. Study limitation

We recognize some limitations due to the cross-sectional study design which used existing survey data regarding care and treatment, and may be subject to recall bias. The sample sizes from each country are too small to give accurate information about treatment options, and therefore the benefits and harms of early diagnosis could not be assessed. In addition, our small sample might have some possible sources of selection bias. Caregivers that are particularly involved in the care for their child may be more interested and motivated to be involved in our study, resulting in an overestimation of the overall care experience. On the other hand, patient-caregiver pairs that were particularly dissatisfied with care could possibly also have been more motivated. In spite of these limitations, we believe that overall our study is likely to be a representative snapshot of the experience of early diagnosis of DMD in the 6 countries surveyed.

5. Conclusion

This study described current care practices for young boys diagnosed early with DMD. This has not been fully described in previous studies. In the long term, whether or not early diagnosis is beneficial for our cohorts in real world remains unknown. However, we provide some evidence that there are still a lot of issues to be addressed to optimize the early diagnosis of DMD from the perspective of the parents. International research and clinical trials in DMD have been well developed, and diagnostic testing development will increase the number of young boys diagnosed early, while we also need to keep in mind their heterogenic background. Seamless support and care for DMD families with early diagnosis at presymptomatic stages may be required, as more patients will be diagnosed early in the future with the ease of genetic testing and potential newborn screening programs on the horizon.

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FT, SR, JK, HL, BK, HN and EK contributed to the design of the study. HN was the principal investigator. FT, HK, SR, JK, HL, KB, EK participated in the study as investigators. FT, KM and HN analysed the data. FT and HN wrote the first draft of the paper. HK, ZY, SR, JK, TK, HL, KB, EK, ST, KW reviewed each draft of the paper. All authors interpreted the data, contributed to subsequent versions of the text, and approved the final version of the manuscript.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.06.557.

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