Female dystrophinopathy: Review of current literature

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Abstract

Skeletal muscle or cardiac symptoms are known to appear in a certain proportion of female patients carrying the dystrophin gene mutation. There is limited high-quality evidence to guide the treatment of female carriers of Duchenne muscular dystrophy/Becker muscular dystrophy (DMD/BMD). The available evidence is mainly based on expert opinions and clinical experience. To improve this situation, we reviewed 1002 reports published from 1967 to 2017 to assess the following themes: epidemiology, clinical symptoms, cardiomyopathy, burdens on parents or caregivers, pregnancy or delivery, and prognosis. We aimed to provide guidance for the provision of support, care, and education for patients, caregivers, and health care professionals. There were 271 reports before 1987, and 731 reports after 1987 when dystrophin was first recognized. In this review, we mainly selected 37 papers that were reported after 1987. In seven large research papers, the incidence of skeletal muscle damage among female carriers, including asymptomatic carriers, was reported as 2.5%–19%, and the incidence of dilated cardiomyopathy was 7.3%–16.7% for DMD and 0%–13.3% for BMD. We integrated and summarized the genetically definite manifesting carriers with skeletal muscle symptoms from 10 case series. In combined data, among 93 manifesting carriers, 16 (17.2%) presented with cardiac abnormalities. The frequency of manifesting carriers complicated by cardiomyopathy increased with age. Reports on cardiac magnetic resonance in female carriers and the burden on caregivers are increasing, whereas literatures concerning pregnancy, delivery, and prognosis in female carriers are limited. This represents a future direction for research.

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1. Introduction

Duchenne muscular dystrophy (DMD) and the milder allelic Becker muscular dystrophy (BMD) are X-linked genetic disorders caused by mutations in the dystrophin gene [1,2]. In most cases, clinical symptoms are caused by inactivation of the X-chromosome bearing the normal gene in the early embryonic stage [3]. Therefore, DMD and BMD usually affect males, with the majority of females having mutation in a single allele being asymptomatic carriers. However, some female carriers can experience symptoms varying from mild muscle weakness to more severe clinical courses. These patients are classified as “manifesting carriers” [4,5].

In 1974, Moser and Emery first reviewed the clinical characterization of female carriers of DMD with respect to the differential diagnosis from autosomal-recessive limb-girdle muscular dystrophy [4]. Thereafter, some experts reported cases of skeletal muscle weakness and dilated cardiomyopathy [6–12]. In particular, cardiomyopathy in female DMD and BMD carriers is an extremely serious problem. The incidence of cardiomyopathy increases with age, even in patients with normal electrocardiograms and no skeletal muscle symptoms [7,13–15]. Therefore, in the clinical guidelines in Europe and the United States [16,17], adult dystrophinopathy carriers are recommended to undergo echocardiography every 5 years. In re-

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cent years, cardiac magnetic resonance (CMR) has attracted attention as a useful tool for the early detection of cardiomyopathy. CMR can detect the earliest signs of cardiomyopathy in DMD patients [18–20]. Some papers have shown that late gadolinium enhancement (LGE) enables the detection of myocardial fibrosis in cardiomyopathy patients [21,22]. Developments in the medical sciences, including respiratory care, nutritional support, and cardio-protective agents, have extended the life expectancy of DMD patients [21,23], allowing large numbers of patients to live at home. However, this places even greater burdens on caregivers and parents. Most patients living at home are cared for by parents, leading to increased burdens on female carriers of dystrophinopathy who must care for their sons or relatives. Recently, some clinical papers have been conducted to clarify the psychological, emotional, social, and financial problems faced by female dystrophinopathy carriers.

To date, no review of the current findings regarding female dystrophinopathy carriers has been performed. Considering this factor, the present review focuses on the current understanding of the following themes in the context of female DMD/BMD carriers: (1) incidence of skeletal muscle weakness and cardiomyopathy in female carriers, (2) clinical and genetic characterization of female dystrophinopathy, (3) CMR studies in female carriers, (4) burdens on the caregivers or parents of patients with dystrophinopathy, (5) prognoses, and (6) pregnancy or delivery. We aim to provide guidance for the provision of support, care, and education for patients, caregivers, and health care professionals.

2. Methods

2.1. Eligibility criteria and data extraction

Eligible papers included randomized controlled trials (RCTs), cohort studies, cross-sectional studies, and three or more case series. We excluded case reports. Furthermore, we only included full-length articles published in the English language and involving humans. We applied no publication date restrictions. Two authors (MI and MK) extracted the data from the included papers. The other three authors (KA, TM, and EK) checked the extracted data and any disagreements were resolved by discussion.

2.2. Search strategy and eligibility assessment

A literature search was conducted in MEDLINE (Ovid, from January 1967 to April 2017) by one of the authors (MI). The last search was performed on April 28, 2017. We used the following search terms: Duchenne muscular dystrophy, Becker muscular dystrophy, dystrophinopathy, female, carriers, mother, genotype, inactivation, cardiomyopathy, magnetic resonance imaging (MRI), CMR, LGE, pregnancy, delivery, quality of life (QOL), burden, caregiver, treatment, and prognosis. Two authors (MI and EK) screened the identified papers for eligibility, first by assessing the title and abstract and then by reading the full text. In addition, the reference lists of included studies were screened. We also considered papers referred to us by experts. A summary of the search process is provided in Fig. 1.
2.3. Statistical analysis

Statistical analysis was conducted using JMP® Version 9.0. (SAS Institute, Inc., Cary, NC, USA). Statistical comparisons were performed using two-factor analysis of variance. The Wilcoxon analysis was applied to detect differences between two groups. Significance was established at p < 0.05.

3. Results

3.1. Study selection

A total of 1002 articles were recovered. There were 271 reports before 1987 and 731 reports after 1987 when dystrophin was first recognized. After reviewing the titles and abstracts, 931 papers were found to be ineligible. The full texts of the remaining 71 papers were reviewed, and another 44 papers were excluded. We included 10 records screened from the reference lists of related literature and referred to us by experts. Finally, 37 papers after 1987 were mainly included in the review.

3.2. Change in the number of reports by searching particular combinations of terms every 10 years

Representative search results of word combinations are shown in Fig. 2. In the retrieval of the word combination of “Duchenne muscular dystrophy” and “female carriers,” there were 834 reports, with most reports being published in 1987–1996 (Fig. 2a). Using the word combination “Duchenne or Becker muscular dystrophy” and “female carriers” and “cardiomyopathy,” 61 reports were retrieved, which gradually increased (Fig. 2b). Using the word combination “Duchenne or Becker muscular dystrophy” and “female carriers” and “CMR or LGE,” 15 reports were retrieved, all published since 2010 (Fig. 2c). Using the word combination “Duchenne or Becker muscular dystrophy” and “caregiver,” 61 reports were retrieved. Most reports were published in 2007–2017 (Fig. 2d).

3.3. Incidence of skeletal muscle damage and cardiomyopathy in female carriers

In large research papers (including cohort papers) [6–12], the prevalence of skeletal muscle damage and dilated cardiomyopathy (DCM) in Japan and European countries among female carriers, including asymptomatic carriers, was 2.5%–19% and 7.3%–16.7% for DMD and 0%–13.3% for BMD (Table 1). Hoogerwaard et al. reported that 6 of 129 DMD and BMD carriers (5.4%) had dilated cardiomyopathy without muscle weakness [9]. Grain et al. reported that 8 of 56 (14.2%) DMD and BMD carriers (14.2%) showed abnormal echocardiograms without muscle weakness [10]. During the survey period of some reports [7,11], four carriers died (three
Table 1
Incidence of skeletal muscle damage and cardiomyopathy in female carriers of DMD or BMD.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Country</th>
<th>Number of carriers</th>
<th>Mean age (range)</th>
<th>Diagnosis of carriers</th>
<th>Skeletal muscle involvement</th>
<th>Assessment of skeletal muscle involvement</th>
<th>Cardiomyopathy</th>
<th>Assessment of cardiomyopathy</th>
<th>Number of deaths from cardiomyopathy (age at death)</th>
<th>Follow-up duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norman and Harper (1989)</td>
<td>UK (Wales)</td>
<td>119 (DMD)</td>
<td>2.5%</td>
<td>Pedigree analysis Elevated CK</td>
<td>Manual muscle testing</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Politano et al. (1996)</td>
<td>Italy</td>
<td>197 (DMD 152 BMD 45)</td>
<td>32.8 years (5–60)</td>
<td>Pedigree analysis Elevated CK</td>
<td>Physical examination (skeletal muscle wasting and weakness)</td>
<td>DCM:DMD 8.5% BMD 13.5%</td>
<td>Electrocardiography</td>
<td>DCM 2 (one died at the age of 42 years) BMD 1 (65 years)</td>
<td>3–10 years (mean:62 months)</td>
<td></td>
</tr>
<tr>
<td>Sumita et al. (1998)</td>
<td>Brazil</td>
<td>107 (DMD/BMD)</td>
<td>4.7%</td>
<td>Pedigree analysis Elevated CK</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoogerwaard et al. (1999)</td>
<td>Netherlands</td>
<td>129 (DMD 85 BMD 44)</td>
<td>36.9 years (18–58)</td>
<td>DMD 19% BMD 14%</td>
<td>Manual muscle testing</td>
<td>DCM:DMD 8% BMD 0%</td>
<td>Electrocardiography</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Grain et al. (2001)</td>
<td>UK</td>
<td>56 (DMD 41 BMD 15)</td>
<td>12%</td>
<td>Pedigree analysis Elevated CK</td>
<td>Muscle symptoms Manual strength evaluation</td>
<td>Abnormal echocardiograms: DMD 12.2% BMD 20.0%</td>
<td>Echocardiography</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Schade van Westrum et al. (2011)</td>
<td>Netherlands</td>
<td>99 (DMD 60 BMD 39)</td>
<td>45 years (32–68)</td>
<td>Pedigree analysis Elevated CK</td>
<td>NA</td>
<td>DCM:DMD 16.7% BMD 2.6%</td>
<td>Electrocardiography</td>
<td>DCM 1 (57 years)</td>
<td>9 years</td>
<td></td>
</tr>
<tr>
<td>McCaffrey et al. (2017)</td>
<td>UK (DMD/BMD)</td>
<td>130</td>
<td>19%</td>
<td>Pedigree analysis Elevated CK</td>
<td>Muscle symptoms Manual muscle testing</td>
<td>LV dysfunction:12% (LVEF &lt; 55%)</td>
<td>Echocardiography</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; NA, not available; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction.

with DMD, age at death 42–57 years; one with BMD, age at death 65 years). Politano et al. showed that 14 carriers (11 DMD and 3 BMD) presented with deterioration in cardiac function [7]. Schade van Westrum et al. showed that 9 of 11 carriers with DCM (10 DMD, one BMD) developed cardiomyopathy in the follow-up period [11].

3.4. Clinical and genetic characterization of female dystrophinopathy

We reviewed 10 case series papers describing clinical and genetic characterizations of female dystrophinopathy [24–33] (Table 2). We integrated and summarized the genetically definite manifesting carriers with skeletal muscle symptoms from the case series. From a total of 93 patients, 31 (33.0%) had no family history. Moreover, 20 of 42 patients (47.6%) with onset or diagnosis before the age of 20 years had no family history. The age range was 1–73 years (mean age: 20.8 ± 17.4) and 36 patients (38.7%) were aged ≥20 years. Regarding dystrophin gene mutation, 51 patients (54.8%) had deletions, mostly located between exons 44 and 55 (27 patients). Fifteen patients (16.1%) had duplications and 17 (18.3%) had point mutations. Other mutations (7.5%) showed splice insertion intron (n = 2), frameshift mutation (n = 2), skipping mutation (n = 1), subexonic insertion exon (n = 1), and triplication (n = 1). Three patients (3.2%) had translocations. We considered the presence of cardiomyopathy as cases in which cardiomyopathy was clearly described or detected by echocardiography or MRI in the literature. Fourteen patients (15.1%) were non-ambulatory (mean age: 30.0 ± 20.4 years), including two patients with translocations. The presence or absence of difficulty in walking was unrelated to age. Sixteen patients (17.2%) presented with cardiac abnormalities. The mean age of patients with cardiomyopathy (38.2 ± 15.9 years) was significantly higher than that of patients without cardiomyopathy (20.9 ± 18.3 years, p < 0.001). The frequency of manifesting carriers complicated with cardiomyopathy increased with age (≤20 years, 20.0%; 21–40 years, 26.7%;
Table 2
Clinical and genetic characterization of female dystrophinopathy (symptomatic female carriers) patients.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Number of objects</th>
<th>No family history a</th>
<th>Current age (years)</th>
<th>Age at onset (years)</th>
<th>Cognitive impairment a</th>
<th>Non-ambulant a</th>
<th>Respiratory impairment a</th>
<th>Cardiomyopathy a</th>
<th>Genetic mutation a</th>
<th>Skewed X inactivation a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soltanzadeh et al. (2010)</td>
<td>15</td>
<td>8</td>
<td>NA</td>
<td>3–47</td>
<td>NA</td>
<td>4</td>
<td>6</td>
<td>Del 6, Dup 3,</td>
<td>7 (informative</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pm 4, Others 3</td>
<td>14, 50.0%</td>
<td>NA</td>
</tr>
<tr>
<td>Golla et al. (2010)</td>
<td>4</td>
<td>3</td>
<td>4–10</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>1</td>
<td>Del 3, Pm 1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Seemann et al. (2011)</td>
<td>8</td>
<td>NA</td>
<td>5–22</td>
<td>3–9</td>
<td>4 (LD, BP, delayed speech)</td>
<td>2</td>
<td>1</td>
<td>Del 4, Pm 2, Translocations 2</td>
<td>4 (informative</td>
<td>6, 66.7%</td>
</tr>
<tr>
<td>Brioschi et al. (2012)</td>
<td>7</td>
<td>NA</td>
<td>4–43</td>
<td>2–43</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>Del 4, Pm 2,</td>
<td>2 (informative</td>
<td>6, 33.3%</td>
</tr>
<tr>
<td>Mercier et al. (2013)</td>
<td>26</td>
<td>8</td>
<td>3–73</td>
<td>1–22</td>
<td>7 (ID, LD)</td>
<td>5</td>
<td>5</td>
<td>Del 14, Dup 4,</td>
<td>12 (informative</td>
<td>19, 63.2%</td>
</tr>
<tr>
<td>Giliberto et al. (2014)</td>
<td>4</td>
<td>NA</td>
<td>17–41</td>
<td>3–10</td>
<td>3 (MR, LD, BP)</td>
<td>0</td>
<td>0</td>
<td>Del 3, Dup 1</td>
<td>4 (informative</td>
<td>100%</td>
</tr>
<tr>
<td>Imbomoni et al. (2014)</td>
<td>7</td>
<td>3</td>
<td>1–18</td>
<td>1–8</td>
<td>5 (ID)</td>
<td>1</td>
<td>1</td>
<td>Del 2, Dup 2,</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lee et al. (2015)</td>
<td>4</td>
<td>NA</td>
<td>30–38</td>
<td>15–31</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>Del 3, Pm 3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Papa et al. (2016)</td>
<td>8</td>
<td>4</td>
<td>5–18</td>
<td>0–4</td>
<td>3 (BP, attention deficit, dyslexia)</td>
<td>0</td>
<td>0</td>
<td>Del 5, Pm 3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cotta et al. (2017)</td>
<td>10</td>
<td>5</td>
<td>15–68</td>
<td>6–46</td>
<td>NA</td>
<td>1</td>
<td>3</td>
<td>Del 9, Pm 1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>31</td>
<td>1–73</td>
<td>0–47</td>
<td>22</td>
<td>14</td>
<td>2</td>
<td>Del 51, Dup 15,</td>
<td>29 (informative</td>
<td>49, 59.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pm 18, Others 7, Translocations 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA, not available; LD, learning disabilities; BP, behavioral problems; ID, intellectual disability; MR, mental retardation; Del, deletion; Dup, duplication; Pm, point mutation.

a Numbers expressed in comparison with manifesting carrier population.

b XCI ratios > 80:20 were considered to represent the “skewed” pattern.

<40 years, 53.3%; p < 0.01). Two patients presented with respiratory dysfunction at 10 and 16 years. In the five reports on cognitive function and psycho-psychological evaluation, some psycho-psychological abnormalities (intellectual disability, learning disability, behavioral problems, mental retardation, and delayed speech) were found in 24 patients. The X-chromosome inactivation (XCI) pattern was skewed toward a nonrandom pattern (skewed X inactivation) in 33.3%–100% of patients [24,26–29]. Among 51 informative cases, there were significantly more skewed inactivation patterns in manifesting carriers of DMD or BMD aged <15 years (p < 0.05).

3.5. CMR of female carriers

We reviewed eight large research papers describing CMR and LGE assessment of female carriers [34–41] (Table 3). The age range of patients was 11–69 years. Left ventricular dysfunction was present in 14%–40% of DMD carriers and in 0%–6% of BMD carriers. LGE positivity was detected in 35%–65% of DMD carriers and in 19%–20% of BMD carriers. Cardiomyopathy appeared mostly in the left ventricular posterior wall. Carriers older than 40 years had more extensive lesions than did those younger than 40 years [35]. Female carriers demonstrated the same LGE patterns as their male relatives [41].

3.6. Burden of dystrophinopathy in caregivers or parents

We reviewed 12 large research papers describing psychological evaluation, economic burdens, and QOL evaluation in caregivers and parents of DMD or BMD patients [42–53] (Table 4). One report described the percentage of carriers in subjects (carrier, 57.1%, and noncarrier, 28.1%) [43]. Child care and nursing care impose heavy burdens on parents. Appropriate instruction is important so that the burdens remain manageable, particularly when the caregiver is a manifesting carrier. In recent years, the life span of DMD and BMD patients has been prolonged along with the home-living period. As such, the QOL of the patient and their parent/caregiver in this setting is important. As parents age, the burdens can increase, especially in the case of mothers who exhibit dystrophinopathy symptoms.

3.7. Pregnancy or delivery in female carriers

Literature on pregnancy or delivery in DMD and BMD carriers is poor. In the 179th European Neuromuscular Cen-
tre workshop, pregnancy in women with neuromuscular disorders, including DMD and BMD, was first reviewed by 16 doctors and scientists [54]. Some specific recommendations were described in relation to muscular dystrophy patients with cardiomyopathy or respiratory failure. Approximately two-thirds of all patients with limbic-type muscular dystrophy experience muscle weakness during pregnancy and because declines of ADL are likely related with weight gain and diaphragm elevation, maintenance of appropriate momentum is also important [54,55]. In the published case reports, some cases of cardiomyopathy developed after delivery [24,56,57]. In another case, skeletal muscle weakness progressed significantly after delivery [58]. In the future, it will be necessary to study the emergence of cardiomyopathy in the management of pregnancy in this patient group.

### 3.8. Treatments and prognosis

There is currently no definitive evidence guiding the management of female dystrophinopathy. There have been no large-scale clinical papers concerning myocardial intervention in female patients, such as β-blockers, ACE inhibitors, or corticosteroids. Thus, medical experts follow the current treatment guidelines for male DMD/BMD patients. The prognoses of female carriers depend on the severity of cardiomyopathy. However, there are fewer reports on the prognosis of female patients in this context. The only paper published to date is the report of causes of death by the British Family Income Survey and Death Diagnostic Manual [59]. In this report, the mortality rate was not different to that predicted from the general population.

### Table 3

Cardiac magnetic resonance findings of female carriers.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Number of objects</th>
<th>Asymptomatic carriers</th>
<th>Age (years)</th>
<th>Subjects</th>
<th>CMR findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwase et al. (2010)</td>
<td>7</td>
<td>45–62</td>
<td>DMD carriers</td>
<td>LV dysfunction 14%, LGE (+) 56%</td>
<td></td>
</tr>
<tr>
<td>Walcher et al. (2011)</td>
<td>5</td>
<td>41–68</td>
<td>DMD carriers</td>
<td>Decrease of LVEF 10.5±11%</td>
<td></td>
</tr>
<tr>
<td>Mavrogeni et al. (2013)</td>
<td>35</td>
<td>31–69</td>
<td>DMD and BMD mothers and carriers</td>
<td>Progression of LGE volume 11.7±9.5%</td>
<td></td>
</tr>
<tr>
<td>Giglio et al. (2014)</td>
<td>30</td>
<td>21 (70%)</td>
<td>DMD carriers</td>
<td>LV dysfunction: DMD 40%, BMD 0%</td>
<td></td>
</tr>
<tr>
<td>Schelhorn et al. (2015)</td>
<td>15</td>
<td>14–46 (mean 32.3±10.2)</td>
<td>DMD carriers</td>
<td>LV dysfunction 33%, LGE (+) 60%</td>
<td></td>
</tr>
<tr>
<td>Lang et al. (2015)</td>
<td>22</td>
<td>13–60</td>
<td>DMD carriers</td>
<td>LV dysfunction 18%, LGE (+) 35%</td>
<td></td>
</tr>
<tr>
<td>Wexberg et al. (2016)</td>
<td>20</td>
<td>17 (89.5%)</td>
<td>DMD carriers</td>
<td>LGE (+) 45%</td>
<td></td>
</tr>
<tr>
<td>Florian et al. (2016)</td>
<td>36</td>
<td>mean 44±14</td>
<td>DMD and BMD carriers and male relatives</td>
<td>LV dysfunction: DMD 20%, BMD 6%</td>
<td></td>
</tr>
</tbody>
</table>

DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; CMR, cardiac magnetic resonance.

### Table 4

Burdens on caregivers or parents of patients with dystrophinopathy.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Number of objects</th>
<th>Age (years)</th>
<th>Subjects</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nereus and Bobo (2003)</td>
<td>127</td>
<td>Mean 38.2</td>
<td>Mothers of DMD patients</td>
<td>The Parenting Stress Index-Short Form (ZBI)</td>
</tr>
<tr>
<td>Kenneson and Bobo (2010)</td>
<td>1238</td>
<td>Mean 43</td>
<td>Caregivers of DMD/BMD patients (carrier, 57.1%, and noncarrier, 28.1%)</td>
<td>Zarit Caregiver Burden Interview (ZBI)</td>
</tr>
<tr>
<td>Pangalila et al. (2012)</td>
<td>80</td>
<td>Mean 57</td>
<td>Parents of DMD patients</td>
<td>Caregiver burden</td>
</tr>
<tr>
<td>Landfeldt et al. (2014)</td>
<td>770</td>
<td>Mean 43</td>
<td>DMD patients</td>
<td>Economic burden</td>
</tr>
<tr>
<td>Thomas et al. (2014)</td>
<td>60</td>
<td>Mean 43.4</td>
<td>Caregivers of DMD patients</td>
<td>Psychosocial challenges</td>
</tr>
<tr>
<td>Nizoo et al. (2014)</td>
<td>20</td>
<td>Mean 43.4</td>
<td>Mother-caregiver of DMD patients</td>
<td>The questionnaire of Female Sexual Function Index (FSFI), the Pittsburgh questionnaire (PSQI)</td>
</tr>
<tr>
<td>Magliano et al. (2014)</td>
<td>336</td>
<td>Mean 42</td>
<td>Parents of DMD/BMD patients</td>
<td>Family Problems Questionnaire (FPQ), Parents QOL and burden</td>
</tr>
<tr>
<td>Yamaguchi and Suzuki (2015)</td>
<td>18</td>
<td></td>
<td>Parents of DMD patients</td>
<td>Semi-structured interview (emotional, physical, determination)</td>
</tr>
<tr>
<td>Landfeldt et al. (2016)</td>
<td>770</td>
<td></td>
<td>Caregivers of DMD patients</td>
<td>Health-related quality of life (HRQL), EuroQOL (EQ-5D), SF-12, Zarit Caregiver Burden Interview (ZBI)</td>
</tr>
<tr>
<td>Peay et al. (2016)</td>
<td>144</td>
<td></td>
<td>Mothers of DMD/BMD patients</td>
<td>Psychological adaptation (PAS), ZBI, Revised Life Orientation Test (LOT-R), Resilience scale for adults (RSA)</td>
</tr>
<tr>
<td>Slirman et al. (2017)</td>
<td>191</td>
<td>Mean 45.1</td>
<td>Caregivers of DMD/BMD patients</td>
<td>The caregiver questionnaire, the double ABCD model</td>
</tr>
<tr>
<td>Hollin et al. (2017)</td>
<td>82</td>
<td></td>
<td>Caregivers of DMD patients</td>
<td>Best-worst scaling survey (BWS)</td>
</tr>
</tbody>
</table>

DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy.
4. Discussion

In this study, we reviewed reports concerning the epidemiology of female DMD/BMD carriers, clinical images of manifesting carriers, CMR for early cardiomyopathy diagnosis, and papers on the QOL and burden of the caregiver or parents of DMD/BMD patients. To research more information on older documents, we performed a literature search from 1967 to 2017 (included reports before 1987 when dystrophin was first recognized). Because the accuracy of diagnosis criteria changes after discovery of dystrophin, we considered that studies that involved genetic testing for diagnosis better reflect the current situation. Therefore, we mainly reviewed selected 37 papers after 1987. To date, no review has focused on the clinical manifestations of female dystrophinopathy. In Japan, there are high ethical hurdles to the investigation of genetic diseases and genetic specialists and counselors, even in the major institutes, have limited up-to-date clinical information regarding this relatively well known muscular disease [60]. There are concerns about a lack of genetic knowledge and health management for female dystrophinopathy on both patients and medical professionals.

In Table 2, a summary of genetically confirmed female carriers suggests that the frequency of carriers complicated with cardiomyopathy increased with age. Holloway et al. reported that the average life expectancy of DMD/BMD carriers was not reduced by the presence of the mutation [59]. However, some reports have demonstrated that during the follow-up period, the myocardial disorder progressed to DCM, death due to heart failure in patients in their 40s and 50s [7,11], and cardiomyopathy exacerbated by exercise in one case [61]. We consider that the prognosis of female dystrophinopathy could be worse than that previously reported [59] and that aggressive health management, including cardioprotection therapy, could be effective for preventing these issues. Two reports [28,32] in Table 2 showed manifesting carriers for dystrophinopathies at pediatric age. Nine of 93 cases (9.7%) are the very young cases and developed at age 1 year or younger. They showed muscle symptoms (delayed walking, abnormal gait, myalgia, and muscle weakness) and hyperCKemia. Moreover, three of the seven cases are without family history. Papa et al. suggested testing for DMD gene mutations in female children with persistent hyperCKemia [32]. The XCI pattern was skewed toward a nonrandom pattern in 59.2% (29/49) of informative cases in this study. This incidence was higher than that reported by Sumita et al. in asymptomatic carriers (37%) [8]. Some papers have reported that the DMD phenotype in female carriers of a dystrophin mutation was correlated with a skewed XCI pattern [24,26,30,62]. DMD carriers with moderate/severe muscle involvement exhibit a moderately or extremely nonrandom XCI, particularly if presenting with early symptom onset. DMD carriers with mild muscle involvement present with a random XCI [63]. DMD or BMD carriers with a nonrandom XCI pattern present with earlier symptom onset. In 93 cases, there were significantly more skewed inactivation patterns in manifesting carriers of DMD or BMD aged <15 years (p < 0.05).

In recent years, the number of highly progressed DMD patients requiring all-day mechanical ventilation support living at home with their families has increased [64]. The physical burdens associated with nursing care could exacerbate cardiomyopathy in the mother, who might have female dystrophinopathy, and could worsen her prognosis. Female carriers may show dilated cardiomyopathy and abnormal echocardiogram without muscle symptoms [9,10]. Even in asymptomatic carriers, the cardiomyopathy may be remarkable and exacerbated and it could be necessary to evaluate cardiac function regularly. In cardiac function assessment, cardiac MRI and LGE detection as described above may be useful for decision-making in early intervention. Detection by LGE can be performed earlier than echocardiography for the measurement of ejection fraction, which is useful for the early detection of cardiomyopathy.

Reports on the burdens and QOL of the caregivers and parents of DMD/BMD patients have increased recently. It is established that the burdens of care for family caregivers impair the physical and mental health of the caregivers themselves [52,53]. The QOL of caregivers involved in dementia care, elderly care, and the care of handicapped people is important in the context of the increased use of home-based care. We believe that the increased reports of nursing care burdens on DMD/BMD patients follow this wider trend. It is a serious problem in that muscle symptoms or cardiomyopathy may be worsened by care burden, if caregiver is a carrier (e.g., mother of DMD/BMD patients). In Japan, because of high ethical and social hurdles associated with hereditary diseases, gene analysis of carriers is not standard. Therefore, we often experience many cases of which undiagnosed carriers with muscle symptom or cardiomyopathy care for DMD and BMD patients. The recent cohort series report, which spanned 22 years, highlighted the importance of regular health checkups for mothers of DMD patients [65]. In the 12 reports describing care burden and QOL in caregivers and parents of DMD or BMD patients (Table 4), only one report described about the percentage of carriers [43]. In the future, reports on the problem of nursing burden peculiar to carrier are expected.

There is a limited range of literature regarding pregnancy and delivery in female carriers. Generally, circulating blood volume increases from mid-to-late pregnancy, followed by an increase in the cardiac load. Thus, perinatal management is important for cases of cardiomyopathy, including dilated cardiomyopathy. During pregnancy, body weight gain and diaphragm elevation may result in cardiac and physical overload, decreased ADLs, and skeletal muscle damage. Therefore, weight control and moderate exercise are recommended by DMD guidelines (Societas Neurologica Japonica, Japanese Society of Child Neurology, National Center of Neurology and Psychiatry. Practical Guidelines for Duchenne Muscular Dystrophy 2014, Tokyo: Nankodo Co. LTD.; 2014).

In Japan, from 2016, female dystrophinopathy patients who satisfy certain diagnostic criteria and disease severity could be recognized as having a designated intractable disease, leading to wider social recognition of the disease. In the future, after preparing social and psychological care support sys-
tems for female carriers, a prospective multiple-center cohort study, including some major hospitals with traditional muscular dystrophy wards, are planned. We also plan to study dystrophinopathy in both men and women equally in a national dystrophinopathy registry run by Remudy [66] in order to examine the epidemiology of female dystrophinopathy; estimate the number of patients with the disease; and clarify the clinical features, problems of family and caregivers, and effects on pregnancy and delivery of the disease.

The present study had some limitations that should be discussed. First, our method involved the examination of reports by searching only the NCBI database. Most of the papers were case series and observational studies. Therefore, it is possible that we did not include important case reports and reports that are not registered in the NCBI database, written in languages other than English, or published before the search period. Thus, our analysis lacked statistical power due to the small number of papers. There was also a lack of interventional and randomized controlled papers. We reviewed papers written in English. However, depending on the country region, it seems that many reports are not published as papers in peer-reviewed journals. Second, in Table 1, not all objects were diagnosed by gene analysis, although selected studies were reported after 1987 when dystrophin was first recognized. Some cases might have been limb-girdle dystrophy. Third, in Table 2, our statistical analysis for the combined data may be not informative because of differences in the definition of onset, which also depends on various conditions, including the degree of physical loading in each subject, age range of the study population, geographical characteristics, and accuracy of the clinical examination methods used for cardiomyopathy.

In conclusion, reports on CMR analysis for myocardial injury, caregivers for dystrophinopathy patients, psychological evaluation of parents, and QOL have increased in recent years. However, reports on pregnancy, birth, treatment, and prognosis, which can be important problems, are limited, and future studies are expected. We are confident that the present review would be useful for knowledge dissemination among medical professional and caregivers.

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