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ORIGINAL ARTICLE

Long-term outcomes for females with early-onset dystrophinopathy

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Abstract

Aim: To study long-term disease course for females with early-onset dystrophinopathy, including common (female) symptoms, challenges in social participation, the need for care, and current healthcare management to support guideline development.

Method: Twelve females with early-onset dystrophinopathy were followed for a median period of more than 17 years (range 1–36).

Results: One patient died owing to end-stage cardiac failure. Cardiac abnormalities were observed in three of the remaining 11 participants. Respiratory function was reduced in seven of 10 participants. Fatigue, myalgia, lower back pain, and arthralgia were reported in more than six of the participants. Functional status varied from exercise intolerance to wheelchair dependency. Most or all of the 10 participants reported restrictions in participation in work (n = 10), household duties (n = 10), sports (n = 9), and education (n = 8). Only a few participants received followed-up pulmonary (n = 2) or rehabilitation (n = 3) care.

Interpretation: Females with early-onset dystrophinopathy experience a wide range of impairments, comorbidities, limitations in activities, and restrictions in social participation. The whole spectrum should be acknowledged in the healthcare setting. Neuromuscular and cardiac follow-up are indispensable. Additional respiratory assessment and rehabilitation care are expected to improve health status and support daily activities and participation.

Dystrophinopathies are X-linked recessive disorders resulting from pathogenic variants of the large dystrophin gene located at Xp21. The resulting lack of (normal) dystrophin protein typically leads to a multi-system disorder with limb-girdle muscle weakness, and cardiorespiratory involvement manifestations in male children.[1] There is a growing body of literature showing that female carriers of pathogenic variants in the dystrophin gene can also become symptomatic.[2–4] Several mechanisms can explain the development of dystrophinopathy in females with a pathogenic dystrophin gene variant.[5–9]

Clinical features and age at onset in females with dystrophinopathy vary widely. An epidemiological review described clinical and genetic characterizations in a series of 93 patients; 42 of these were diagnosed before 20 years of age,

This original article is commented on by Politano on pages 1001–1002 of this issue.

Abbreviations: DMD, Duchenne muscular dystrophy; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation..

and nine before 2 years of age. Fifteen per cent of the patients were non-ambulatory, and two presented with respiratory dysfunction. This and two other studies reported cardiac abnormalities in approximately two-thirds of the females with dystrophinopathy, including asymptomatic left ventricle systolic dysfunction, particularly in females older than 40 years.[2,10,11] Other frequent symptoms are fatigue and exercise intolerance.[3,12] Furthermore, cognitive impairments are also reported in females with dystrophinopathy.[2,12]

Muscle weakness is, in contrast to males with dystrophinopathy, often asymmetric. A recent magnetic resonance imaging study in symptomatic and asymptomatic females with a dystrophin gene variant showed an increased fat fraction of the upper and lower leg muscles in 72% of the participants.[3] According to a large Scottish study, the average life expectancy was not reduced, and cardiomyopathy was not a major cause of death for females with dystrophinopathy.[13]

The rarity of dystrophinopathy in young females contributes to a diagnostic delay, particularly in the absence of a positive family history.[2,9] The few studies on females with early-onset dystrophinopathy showed that signs and symptoms of muscle weakness, cognitive impairment, and cardiomyopathy may manifest at a young age.[9,12,14–16] Unfortunately, the long-term disease course, knowledge of comorbidity, specific female symptoms (e.g. related to menstrual cycle and reproduction), the consequences for social participation, and with all this the exact need for care, are largely unknown. By studying a relatively large cohort of females with childhood-onset dystrophinopathy, we aimed to improve counselling on long-term prognosis and implementation of adequate follow-up programmes.

What this paper adds

- No standard diagnostic procedures seem to exist for female patients suspected for dystrophinopathy.
- Female participants with early-onset dystrophinopathy experienced a broad scope of burdening symptoms, such as fatigue, myalgia, lower back pain, and arthralgia.
- None of participants worked full time, all felt restricted in paid work, and most felt restricted in education.
- Most participants showed decreased lung function, while only one was symptomatic.
- Availability of rehabilitation care may improve support for daily activities and participation for females with early-onset dystrophinopathy.

METHOD

Participants

Females with early-onset dystrophinopathy (i.e. onset of symptoms before the age of 16 years) were traced with the collaboration of three medical centres in the Netherlands and were invited to participate in a structured visit in 2021. Written informed consent was requested from all participants and/or from their parents. Data were anonymized and handled according to guidelines for good clinical practice. This study was approved by the Medical Ethics committee for Research Involving Human Subjects Region Arnhem and Nijmegen, the Netherlands (no. 2020–7126).

Data collection

Data from the initial diagnostic trajectory were collected from the medical files of the participants, which included age and symptoms at onset, age at the first investigation by a paediatrician, age at diagnosis, and results of ancillary investigations (serum creatine kinase, muscle biopsy, and genetic analysis including pattern of X-chromosome inactivation in leukocytes). Age at onset was defined as the age at which the first symptoms were noticed by the parents. Age at diagnosis was the age that the dystrophinopathy was confirmed. Follow-up duration was defined as the time between the age at diagnosis and the visit in 2021.

Outcome measures

The visit in 2021 consisted of a semi-structured interview by a neuromuscular specialist, cardiological screening, and a visit with a physiotherapist, who also performed spirometry. Outcome measures were classified in body functions and structures, activities, and participation, in line with the International Classification of Functioning, Disability and Health.[17,18]

Body functions and structures

Anthropometric measures were conducted. Heart rate, blood pressure, cardiac ultrasound, and electrocardiography were used to screen for cardiac abnormalities. Normal heart rate was defined as 50 to 100 beats per minute. Blood pressure was defined as high above 140/90 mmHg. Cardiac ultrasound assessed the ventricular volumes and function.[11,19,20] Spirometry (the mean of three measurements was used) assessed the forced vital capacity, the first second of forced expiration, and peak expiratory flow, maximal expiratory pressure, and maximal inspiratory pressure. The passive ranges of motion of upper and lower extremities were measured.

We used the list of symptoms that was previously used in males with Duchenne muscular dystrophy (DMD),[21] and supplemented these with specific female topics such as 'menstrual problems' and 'pregnancy'. The list evaluated the occurrence of symptoms and their impact or perceived burden

on daily activities on a scale from 1 to 10, which was calculated in percentages (0–100%). Cognitive symptoms and comorbidities were asked separately.

Activities

Functional status was assessed using the Vignos Scale for Lower Extremity and the Brooke Scale for Upper Extremity,[22,23] the Motor Function Measure,[24] the North Star Ambulatory Assessment,[25] and the Performance Upper Limb, version 2.0.[26,27]

Social participation

The degree of participation was surveyed during the semi-structured interview with the participants; in addition, the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) was administered. The USER-P originally consisted of 11 domains, distributed over three subscales: (1) frequency of participation, (2) experienced participation restrictions, and (3) satisfaction with participation.[28,29] The frequency domain is divided into 'frequency A' (hours a week, for education, [paid] work, and household duties) and 'frequency B' (times a month, for sports, going out, visiting friends and family, leisure activities, and digital contacts). The sum scores for the frequency, restrictions, and satisfaction scales were converted to a centile score from 0 to 100; the higher the percentage, the better the outcome (higher frequency, less restrictions, higher satisfaction).[28,30] Additionally, the restriction and satisfaction subscales were dichotomized; 'restrictions' were present when the activity was performed 'with difficulty', 'with assistance', or when 'not possible'. 'Satisfaction' was present when participants reported satisfaction as 'very satisfied' or 'satisfied' on domains of the USER-P.

Statistical analysis

Descriptive analyses were used; continuous variables were expressed in median (range), dichotomous variables were expressed in frequencies (percentage).

RESULTS

Participants' characteristics at diagnosis

We traced 12 females with early-onset dystrophinopathy (Table 1). The median age at onset of symptoms was 4 years, and the median age at diagnosis was 8 years. Early symptoms, presenting at preschool age, were delayed milestones in speech and/or motor development, and feeding difficulties. Frequent symptoms manifesting at primary school age were exercise intolerance, fatigue, and myalgia. Most participants were referred because of elevated serum creatine kinase levels. Two out of 12 participants had a positive family history for dystrophin mutations. Participant 9 was diagnosed after her two sons were diagnosed with DMD. Different underlying genetic mechanisms were identified. The median age at the visit in 2021 was 23 years, the median follow-up duration was 17 years 2 months. Participant 3 unfortunately died owing to dystrophinopathy-related cardiac failure at the age of 37 years. She was non-ambulant and had limited arm function before she passed away, according to her relative.

To illustrate specific features in clinical presentation and consequences for social participation, Appendix S1 provides detailed case descriptions of two participants.

Body functions and structures

Anthropometrics

Median body height of the outgrown participants of our population (excluding participant 10) was 161.5 cm (range 146.3–170.0). Median body weight was 65.6 kg (range 48.0–105.0). Median body mass index was 23.9 (range 17.6–40.0).

Cardiorespiratory status

A normal heart rate was found in 10 out of 11 participants (one exception of 109) (Table 2). Blood pressure was elevated in one participant (participant 2, 160/65 mmHg). In three out of 11 participants, minor abnormalities were seen in electrocardiography or cardiac ultrasound (no symptoms). Left ventricular ejection fraction was less than 55% in participant 8 (no symptoms). Spirometry was performed optimally in eight out of 11 participants; in two participants, the forced vital capacity was less than 60%; participant 2 had no symptoms, and participant 12 used non-invasive ventilation. The maximal inspiratory pressure was low for participant 5, who avoided aerobic training because of shortness of breath.

Symptoms and comorbidity

Figure 1 shows the 10 most frequent symptoms, prevalent in five or more participants. The complete list can be found in Table S1. Most prevalent were fatigue (n = 8), followed by myalgia, low back pain, and arthralgia (all n = 6), and a relatively large number perceived constraint in daily activities (median > 50%). Other common symptoms were muscle cramps, daytime sleepiness, constipation, obesity, and coldness of feet and hands. Most symptoms were often not treated. One participant experienced pelvic floor instability and dyspareunia; no other female-specific symptoms were mentioned.

TABLE 1 Participants' characteristics at diagnosis

Participant	Age at onset, years	Presenting symptoms	Age at first medical visit, years	Age diagnosed (diagnostic delay[b]), years	Family history	Serum creatine kinase, U/l	Dystrophic muscle/negative fibres, %[c]	Pathogenic dystrophin variant	Karyotype	Xia pattern, %[a]
1	0	Failure to thrive, feeding problems	4 months	10 months (6 months)	–	5451	+/74	c.(8967_9117)_(9778_9856)del 45,X/46,XX	45X0/46XX (50%–50%)	60:40
2	6 months	Feeding problems, delayed speech development, frequent falling	2	4 (3)	–	10 362	+/25	e 58: c.8641del p.(Leu2881)*	46,XX	90:10
3	1	Feeding problems, waddling gait, delayed speech	5	6 (5)	–	14 936	++/50	Del.e.6–48	46,XX	100:0
4	1	Delayed motor development, waddling gait	3	4 (3)	–	23 000	+++/62	46,X,t(X;13)(p21;q22)	46,XX	100:0
5	1	Delayed motor development, myalgia, frequent falls	2	6 (5)	–	1993	–/normal	Del. e.51–55	46,XX	NA
6	2	Fatigue, delayed motor development, waddling gait	4	9 (7)	–	8249	+/60	e. 54: c.7928 T > A p.(Leu2643)*	46,XX	80:20 / 90:10
7	4	Fatigue, delayed motor development, epilepsy	NA	8 (4)	+	1744	NA	Dupl.e.2	46,XX	NA
8	7	Exercise intolerance, shortness of breath	7	7 (6 months)	–	5563	+/25	Del e.49–54	46,XX	50:50
9	7	Fatigue, myalgia, exercise intolerance	18	30 (23)	–	726	NA	Del. e. 57	46,XX	NA
10	7	Fatigue, myalgia, exercise intolerance	7	8 (1)	–	2436	NA	e. 39: c.5530C > T p.(Arg1844*)	46,XX	NA
11	12	Fatigue, exercise intolerance	15	15 (3)	+	NA	NA	e. 63: c.9249G > A p.(Trp3083*)	46,XX	NA
12	12	Fatigue, vertigo, difficulties climbing stairs	14	15 (2)	–	3180	++	Del. E. 46–52		

[a]X-chromosome inactivation (analysis in leukocytes); the notation stands for percentage of maternal:paternal activation.

[b]Diagnostic delay is the time between the onset of symptoms and receiving the diagnosis.

[c]Presence of dystrophic muscle fibres: –, no dystrophic fibres present; +, ++, and +++, mild, moderate, and severe dystrophic changes.

Abbreviations: NA, not available; U/l, units per litre;

TABLE 2 Body functions and structures: medication, cardiorespiratory function, and pROM at the visit in 2021

Participant	Age at visit, years	Medication	Cardiorespiratory symptoms	Electrocardiography	Cardiac ultrasound	FVCp	FEV1	PEF, l/minute	MIP, cm/H_2O	MEP, cm/H_2O	pROM limitations
1	18	Vitamin B_{12}, lisinopril, calciferol, oral anticonceptives, pain medication during menstruation	None	Normal	Mild systolic dysfunction (ejection fraction 57%)	70	76	301	NP	NP	None
2	29	None	None	Normal	Normal	59	53.5	252	67	78.5	Asymmetric equinovarus/ long finger flexors
3	NA										
4	20	Lisinopril, prednison, calcichew	None	Normal	Normal	95	94	295	83.5	72	Dorsal flexion both ankles
5	42	Vitamin C, colecalciferol, oral anticonceptives, probiotics, levocitiricin, biotin	Shortness of breath during exercise, nightmares, night sweating	Normal	Normal	70	70	336	45	89	None
6	20	Calcichew, oral anticonceptives	None	Early R top transition, high R in V2	Normal	91	92	305	82	68.5	Dorsal flexion
7	28	Clobazam, domperidon, lamotrigin, sumatriptan	None	Normal	Normal	NA					None
8	23	Vitamin B_{12}, oral anticonceptives	None	Normal	Ejection fraction 52%	77.3	75.3	408	98	84.5	Long finger flexors/ supination
9	56	Vitamin C, colecalciferol, pantoprazol	None	Normal	Normal	79	84	415	43	60	Dorsal flexion both ankles/ long finger flexion/ supination
10	9	Colecalciferol	None	Normal	Normal	74	60	NA	NA	NA	Full
11	17	Colecalciferol	Palpitations	Normal	Normal	77	74	372	NA	NA	Full
12	45	Omeprazol	Coldness, shortness of breath, pitting oedema in both legs	Normal	Normal	15	17	130	NP	NP	NP

Abbreviations: FVCp, forced vital capacity in percentage of predicted of norm values based on age, length, weight, and sex; FEV1, first second of forced expiration in percentage of predicted of norm values based on age, length, weight, and sex; MEP, maximal expiration pressure in centimetres of water column;[41] MIP, maximal inspiration pressure in centimetres of water column;[41] NA, not available (participant 7, not done because of technical problems; participant 10, suboptimal performance because of suboptimal blowing technique; participant 11, suboptimal performance because of anxiety for the nose clip); NP, not performed; PEF, peak expiratory flow (norm values based on age, length, weight, and sex) in litres per minute;[40] pROM, passive range of motion.

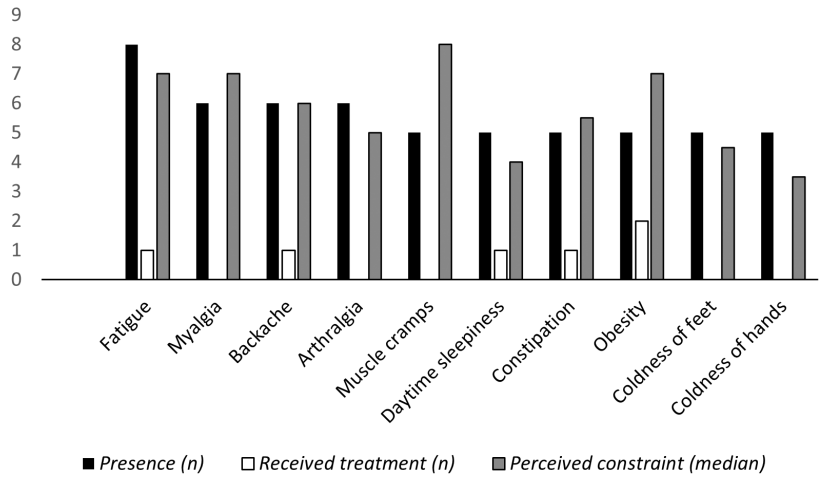

FIGURE 1 Presence of symptoms, received treatment, and perceived constraint. Presence: number of participants who experienced the symptom (*n*). Received treatment: number of participants who received treatment according to the participant (advice, medication, or therapy). Perceived constraint (median): percentage of participants who perceived constraints in daily activities due to the symptom; on a scale from 1 to 10, higher scores indicate more perceived constraint (burden) in daily activities; median 1–10

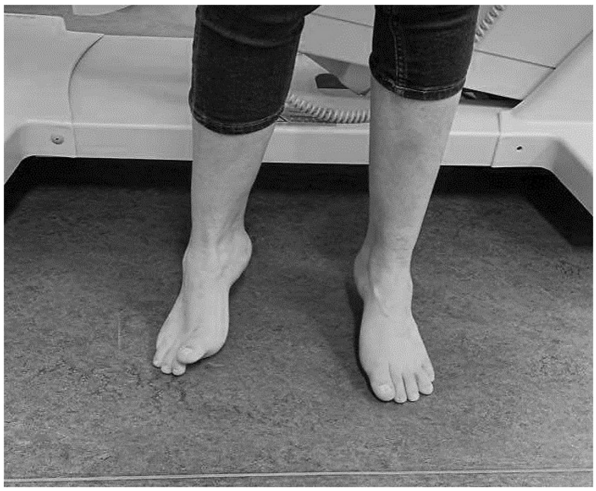

FIGURE 2 Equinovarus deformity of patient 2

Low blood pressure, epilepsy, arthrosis, asthma, attention-deficit/hyperactivity disorder, autism spectrum disorder, and depressive feelings were all reported once among the total study population. Anxiety was reported twice and cognitive impairments were reported three times.

The passive range of motion was decreased in four out of 10 participants, mainly in the long finger flexors, supination of the forearms, dorsal flexion, and equinovarus deformities (Figure 2).

Activities

Maximal Vignos and Brooke scores were obtained for six out of 11 participants (Table 3). Of the remaining five participants, two experienced difficulties in climbing stairs, two could walk short distances with assistance, and one was fully wheelchair bound. The timed tests, Motor Function Measure, North Star Ambulatory Assessment, and Performance Upper Limb scores largely matched with the Vignos and Brooke scores.

Social participation

Table 4 describes the living situation, education/occupation, daily activities, and individual USER-P scores.

USER-P

The USER-P scores described a median of 20% and 40% respectively on the frequency A and B subscales. A median restriction of 60% was experienced by the participants, and the median satisfaction score was 89%. All participants experienced restrictions in performing paid work and household duties (Figure 3). Participants were most satisfied with the items that were not much restricted.

Care management

All participants had regular follow-up with a neuromuscular specialist. Nine participants had received cardiac follow-up during the previous 5 years. Two participants were seen by a pulmonologist. Three participants were seen in a rehabilitation centre for (intermittent) multidisciplinary guidance; one participant received physiotherapy within her care setting.

DISCUSSION

The visit of females in 2021 with early-onset dystrophinopathy showed a wide range of burdening symptoms and decreased social participation. One participant died owing

TABLE 3 Activities at the visit in 2021

Participant	Age at visit, years	Vignos Scale	Brooke Scale	Age at losing ambulation, years	MFM total, %	10-Metre running test, seconds	6MWT, metres	Stairs-up, seconds	TUG floor, seconds	PUL, total	NSAA, total	Remarks
1	18	2	1	NA	97.2	6.3	NP	7.7	6.96	42	26	6MWT could not be performed owing to behavioural problems
2	29	3	2	NA	70.8	11.8	262	9.8	16	34	10	
3	NP											Participant died
4	20	6	3	20	59.4	NA	NA	NA	NA	26	NA	Transition phase in losing ambulation
5	42	1	1	NA	100	2.9	624	1.44	1.76	42	34	
6	20	1	1	NA	91.7	6.2	515	3	5.9		30	PUL was not performed owing to practical reasons
7	28	1	1	NA	100	2.7	640	1.25	2.34	42	34	
8	23	1	1	NA	100	3.5	497	2.53	3.22	41	33	
9	56	6	1	48	63.5	NP				30		Non-ambulatory
10	9	1	1	NA	100	3.2	512	1.53	1.8	42	34	
11	17	1	1	NA	100	2.6	493	1.5	1.36	42	34	
12	45	9	4	36	NP							Non-ambulatory. Not able to perform owing to weakness after admission to intensive care unit

Abbreviations: 6MWT, six-minute walking test; MFM, Motor Function Measure (total score = 100%); NA, not applicable; NP, not performed; NSAA, North Star Ambulatory Assessment (range 0–34, higher scores indicate better performance); PUL, Performance Upper Limb (range 0–42, higher scores indicated better performance); TUG, Timed Up and Go Test.

TABLE 4 Social participation reported during the visit in 2021

Participant	Age at visit, years	Living situation	Education/occupation	Daily activities	USER-P frequency A,[a] %	USER-P frequency B,[a] %	USER-P restrictions,[b] %	USER-P satisfaction,[c] %
1	18	In care setting	Special education (illiterate), social work place	Physiotherapy, group activities	5	29	33	NP
2	29	Independently with help of mother and external guidance	Special education, social work place	Fitness	27	34	67	66
3	NP							
4	20	With parents	University	Supported handbike training, writes stories as hobby	25	47	44	91
5	42	With partner	Regular education, works part time in a shop, part-time disability allowance	Fitness and caregiver for disabled husband	20	57	90	94
6	20	With parents, some weekends at a foster place	Special education, social work place	Race running (stopped with soccer owing to muscle symptoms)	10	40	56	75
7	28	Independently	Education for social worker (stopped as a nurse owing to muscle symptoms)	Runs occasionally (maximum 3km) (stopped with karate and basketball owing to symptoms)	20	51	80	85
8	23	With partner	Secondary vocational education	Fitness, karate, and strolling	25	63	85	95
9	56	With partner and son	Regular education, stopped vocational education and job in a shop owing to muscle symptoms, full disability allowance	Caregiver for her son with Duchenne muscular dystrophy, physical exercises at home	15	NP	62	89
10	9	With parents	Regular education	Gymnastics, roller skating	NP			
11	17	With mother and siblings	Vocational education and side job in restaurant	Plays with siblings, cycles to school and work	30	23	59	96
12	45	In setting with instant care facilities	Regular education, special education, administrative work, now disability allowance for 90%	Tablet, craft, painting (endurance is limited)	5	40	54	65

[a]USER-P frequency: a higher score indicates more time is spent on activities (A is hours spent per week; B is times a month).

[b]USER-P restrictions: a higher score indicates fewer restrictions.

[c]USER-P satisfaction: a higher score indicates greater satisfaction.

Abbreviations: NP, not performed (the mother of participant 1 completed the USER-P as the participant was not able to because of cognitive impairments—it did not feel appropriate for her to score satisfaction; participant 3 died; participant 9 scored more than one missed value on the frequency leisure activities domain—this domain could not be calculated; participant 10 was younger than 16 years, the USER-P in this study was not validated for this age); USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation.

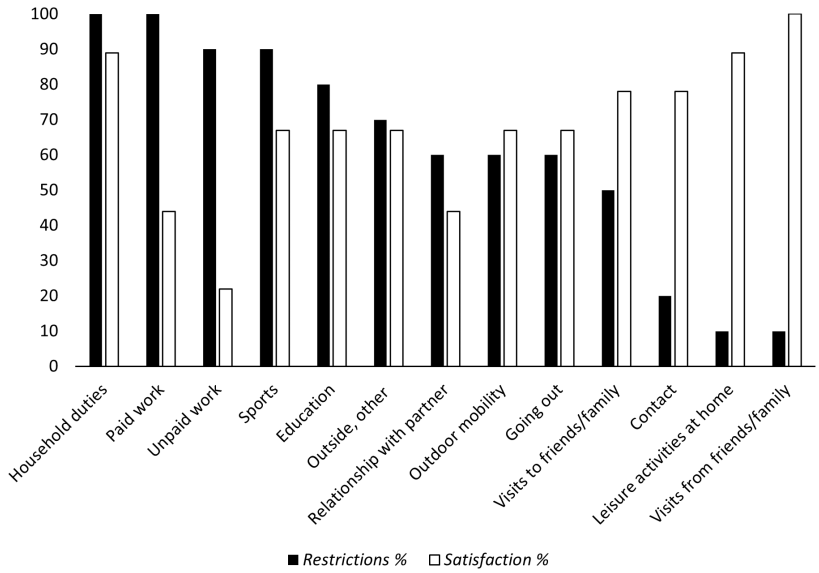

FIGURE 3 Experienced restrictions and satisfaction on different domains of the Utrecht Scale for Evaluation of Rehabilitation-Participation. Percentage of participants experiencing restrictions due to the dystrophinopathy (total group of 10 participants). Percentage of participants experiencing satisfaction (total group of nine participants). Sports also included physiotherapy sessions

to end-stage cardiac failure; in the other participants, cardiac abnormalities were minor and only present in three participants. Respiratory function, however, was decreased in seven of 10 participants. Fatigue, myalgia, lower back pain, and arthralgia were common and limited daily activities. Moreover, participation was restricted considerably, especially in paid work, education, and household activities.

The disease onset in the participants with manifesting muscle weakness before the age of 4 years mimics the onset in male patients with DMD of the same age, including delayed motor milestones, delayed speech development, and feeding difficulties.[31] The disease course in females is milder than in male patients, despite the underlying genetic mechanisms. Besides, clinical severity was not clearly related to the pathogenic variant in this cohort. A possible explanation is that analysis of X-chromosome inactivation in leukocytes does not reflect inactivation in (all) muscle cells, while additional determinants may influence dystrophin transcription and X-chromosome inactivation.[6,7]

The diagnostic delay was remarkably long and consisted of both patient and doctor delay, as is also seen in other X-linked disorders.[32] Interestingly, routine diagnostic procedures for neuromuscular disorders (e.g. electromyography, magnetic resonance imaging, and muscle ultrasound) were not regularly performed. New diagnostic guidelines are needed to enhance timely diagnoses for females presenting with exercise intolerance, fatigue, and myalgia in childhood; also in the absence of a positive family history.

Anthropometrics of the outgrown participants showed a relatively short mean adult height (161.5 cm) compared with the mean height of Dutch females (170.7 cm);[33] this corresponds to the known short stature in male patients with DMD.[34] Two participants were obese, and one participant was underweight according to the World Health Organization guidelines for healthy weight;[33] moreover, obesity was considered a large constraint in daily activities as reported by our participants. Losing weight can be more difficult as exercise is often restricted and resting expenditure energy is decreased in affected muscle tissue.[35] We believe that preventive measures, such as limited dietary intake and exercise, are important and female patients with dystrophinopathy should be educated on this topic after being diagnosed.

As for cardiac involvement, although one participant died at age 37 years owing to end-stage cardiac failure, other participants showed fewer and minor cardiac abnormalities compared with other studies.[8,10,11] This low prevalence likely relates to the young age of our population, and (in accordance with this) is similar to the cardiac involvement of 19% found in young females by Mercier et al.[12] Nevertheless, cardiac screening is important because cardiac abnormalities may remain asymptomatic for a long time, while medical treatment is indicated and lifesaving in case of cardiomyopathy.

Reduced respiratory function has been reported less frequently in the literature about female patients with dystrophinopathy,[2] while our study showed a decreased forced vital capacity in seven of 10 participants who performed spirometry. We hypothesize that gradual progression of the disease and restrictions in sports causes habituation in participants and that limited respiratory capacity remains unnoticed. However, failure to recognize these symptoms can have major consequences, as shown in participant 12. Therefore, we recommend including respiratory assessment in the standards of care for female patients with dystrophinopathy.

The symptoms that were prevalent in the current study, such as fatigue and musculoskeletal pain, are similar to the symptoms previously described in a male cohort of patients

with DMD.[21] Interestingly, Reumers et al.[32] showed fatigue and exercise intolerance were also frequent symptoms in a study of carriers of manifest X-linked myotubular myopathy. Symptoms such as cognitive impairments, anxiety, and autism also frequently occurred in our participants, which is in line with the findings in the male population with DMD.[36,37] The phenotype–genotype correlation for cognitive impairment was found particularly in participants who had pathogenic variants in the distal dystrophin region, which was previously reported both in males and in females.[12,38] Problems on specific female items such as menstrual cycle, pregnancy, and sexual functions were not prominent in our study; however, we can imagine those systems could also be affected. Participants may have been hesitant to discuss these issues and the sample of our population could have been too small. Overall, despite the high prevalence of many symptoms, the participants reported that most symptoms were not treated. Thus, subsequent management of a broad scale of symptoms needs attention.

The activity level of our participants showed a variety of exercise intolerance and fatigue at one end and loss of ambulation with a limited hand function (Brooke Scale 4, Motor Function Measure 59.4) at the other. Most of our study population were still ambulant and the age at losing ambulation was older than 20 years.

Social participation was very restricted in the participants in the current study, especially (paid) work, household duties, and sporting activities. The USER-P scores of our participants are comparable to patients with spinal muscular atrophy and spinal cord injury.[29,39] In comparison, male patients with DMD report more restrictions in social activities instead of in vocational items, and they are also relatively satisfied.[21] We hypothesize that females with dystrophinopathy have higher expectations from work and household activities than their male peers and therefore feel more restricted. However, they report high satisfaction, which may be the reason why they do not easily ask for support or have rehabilitation goals. Some participants in our study felt that their symptoms were not always taken seriously by those around them, and tended to overburden themselves in fulfilling their 'duties'. Besides, the disease progresses slowly, so the participants tended to become accustomed to their situation. The presence of cognitive impairments may also have had a great impact on their participation. Acknowledgement and proactive assessment of symptoms as well as support of activities, with the help of aids and/or rehabilitation programmes, could better match the patients' abilities, which may result in an improvement in participation.

All participants in the current study were increasingly embedded in a care setting, with regular visits to a neuromuscular specialist and cardiologist. However, only a few of them were embedded in respiratory care or rehabilitation settings. As we learned that respiratory symptoms are prevalent, that many symptoms limit the daily activities of the participants, and that social participation was restricted in most of the domains, we expect respiratory and rehabilitation care can have added value for this population.

There were some limitations to this study. Despite the rarity of females with early-onset dystrophinopathy, we were able to perform a long-term assessment of 11 patients. Of course, this number is limited compared with studies in male patients. Notably, during data collection, we found that the disclosure of this research increased awareness of females with dystrophinopathy among clinicians and patients. Further international research is needed to enlarge the sample size of female patients with (early-onset) dystrophinopathy, which was the topic of the 263rd European Neuromuscular Center workshop. Irrespective of the small sample size, this study further contributes to a better understanding of a broad range of symptoms and entry points to improve care management. Another consideration for further research is to include specific outcome measures to estimate the personal and environmental factors, which are also domains of the International Classification of Functioning, Disability and Health model,[18] and can further complete the scope of care needs for this population.

CONCLUSION

Our study shows that females with early-onset dystrophinopathy have had a diagnostic delay, often have decreased respiratory functions, experience a wide range of burdensome symptoms, and have a reduced social participation. This knowledge can contribute to the development of diagnostic and follow-up guidelines for this group of patients. We emphasize the importance of acknowledgement of symptoms; therefore we strongly recommend that all females with early-onset dystrophinopathy should be seen by a neuromuscular specialist and a cardiologist. Also, low-threshold additional respiratory screening and referral to a multidisciplinary rehabilitation setting is indicated.

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CONFLICT OF INTEREST

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1: Case descriptions.
Table S1: The complete list of symptoms: their presence, if the symptom is treated and the median perceived constrained.

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