Pain Characteristics Among Individuals with Duchenne Muscular Dystrophy According to Their Clinical Stage

Aram Kim
Myongji Hospital
Mina Park
Uijeongbu St. Mary's Hospital, The Catholic University of Korea
Hyung-Ik Shin (hyungik1@snu.ac.kr)
Seoul National University

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Abstract

Background: Assessment of pain is not routine, standardized, or well-understood in individuals with Duchenne muscular dystrophy (DMD), even though pain is a common problem reported by more than half of DMD patients. Previous studies in this area included multiple neuromuscular diseases with highly variable phenotypes. Therefore, our aim was to focus on DMD specifically and evaluate comprehensive pain characteristics according to the disease stages, from ambulatory to late non-ambulatory.

Methods: This was a cross-sectional study conducted in an out-patient pediatric rehabilitation clinic. Participants were 148 males with confirmed DMD, 14.5±5.3 years of age. Face-to-face interviews were conducted using a structured questionnaire regarding pain frequency, duration, intensity, location, aggravating/relieving factors, pain interference (Brief Pain Inventory), pain quality (PainDETECT Questionnaire), and functional ability (DMD Functional Ability Self-Assessment Tool). Pain characteristics were analyzed according to the clinical stage: ambulatory (Amb), early non-ambulatory (ENA), and late non-ambulatory (LNA).

Results: Of the 148 participants who completed the assessment, 66 (44.6%) reported pain during the previous 4 weeks. There were no differences in the pain duration or intensity among the three groups. Pain location (Amb: calf, ENA: knee, LNA: lumbosacral region), aggravating factor (Amb: ambulation, ENA: transfer, LNA: sitting), and relieving factor (Amb: rest and massage, ENA and LNA: positional change) differed according to the clinical stage. Individuals in the LNA stage reported an increase in the frequency of pain and number of pain sites. The effect of pain on mood was also found to be greater in the LNA group than in the other clinical stages.

Conclusion: Pain characteristics including location, aggravating/relieving factors, pain frequency, and pain interference change as the disease progresses in patients with DMD. Clinicians could more efficiently and critically assess and manage the patients' pain aspect, based on these findings.

Background

Duchenne muscular dystrophy (DMD) is a progressive X-linked recessive disorder that causes skeletal muscle weakness, with involvement of the cardiac and respiratory muscles in the later stages of disease progression. The life expectancy of individuals with DMD is generally 25-26 years, with cardiorespiratory failure being the principal cause of death [1]. Although there is currently no cure for DMD, comprehensive multidisciplinary care, including assisted ventilation as needed, can prolong survival, with some individuals surviving into their 40s [2–4]. Improving the quality of life (QOL) during this prolonged survival period is an essential goal of the medical care of patients with DMD. In previous studies, pain was associated with the physical health domain of QOL in adults patients with DMD, and several areas of daily life (leisure activity, ability to move, and mood) were found to be affected by pain in patietns with muscular dystrophy [5, 6].

Pain is a common aspect of DMD, reported by more than half of individuals with DMD [5, 7, 8]. Pangalia et al.[6] and Zebracki et al.[9] reported a prevalence of pain of 73.4% and 54%, respectively, among individuals with DMD, with an intensity of pain, measured on a 10-point numeric rating scale (NRS), of 2.59±1.21 and 1.73±1.58, respectively. The common sites of pain were the legs, pelvic region, and back [6, 9]. However, the pain characteristics in DMD have not been evaluated according to the clinical stages of the disease, namely the ambulatory (Amb), early non-ambulatory (ENA), and late non-ambulatory (LNA) stages. Knowledge of the characteristics of pain at the different clinical stages could be the first step in facilitating the development of an effective management strategy for each patient group. Accordingly, our aim in this study was to conduct a comprehensive evaluation of pain characteristics (frequency, duration, intensity, location, quality, aggravating/relieving factors, and pain interference on daily activity) among individuals with DMD, according to the different clinical stages of the disease.

Methods

Participants

Participants were boys with a diagnosis of DMD who visited our pediatric rehabilitation clinic between April 2020 and February 2021. The diagnosis of DMD was confirmed by genetic testing, including multiplex polymerase chain reaction and direct sequencing to detect mutations of the dystrophin gene. If deletion and duplication testing were negative, dystrophin gene sequencing was performed to identify point mutations, small deletions, or insertions. Other inclusion criteria were age ≥7 years and no significant cognitive impairment at the discretion of the rehabilitation physician.

After the participants understood the purpose and content of this study, they signed a written informed consent form. This study was approved by our Institutional Review Board (IRB No. 2004-193-1119).

Measures

Face-to-face interviews were conducted using a structured questionnaire on pain and related factors. If the study participant could not read or understand the questionnaire, one of the authors read and explained the item to help them complete the questionnaire. The survey required about 20 min to complete for those with pain and about 10 min for those without pain. Demographic information (surgical history, presence of scoliosis) were obtained from the medical chart. One of the authors measured the major joint range of motion and recorded the presence of contracture.

Pain frequency, duration, and intensity

Pain frequency was rated using a 7-point Likert scale, with anchors at ‘1’, none of the time, and ‘7’, all day, as previously described [10]. Pain duration was measured using a 4-point Likert scale [11], as follows: ‘1’, <1 h; ‘2’, a few hours; ‘3’, half of the day; and ‘4’, all day. Pain intensity was measured using an 11-point NRS, with anchors at ‘0’, no pain, and ‘10’, pain as bad as could be. The NRS has been reported to be reliable and valid for children as young as 5 years of age [8]. The location of pain was marked using a body map for children, as per Savedra et al.[12, 13], and was coded as follows: head, chest-abdomen,

spine (cervical, thoracic, lumbosacral), upper extremities (shoulder, elbow, wrist-hand), and lower extremities (buttock, hip, thigh, knee, calf, ankle-foot).

Aggravating and relieving factors

The participants were asked to freely dictate or write down the aggravating/relieving factors for pain and were allowed to list more than one factor. We provided some examples of relieving factors, such as rest, positional change, and massage, and of aggravating factors, such as sitting, excessive activity, and transfer activity.

Pain interference

Pain interference was assessed using items from the Korean version of the Brief Pain Inventory (BPI) [14]. The amount of pain interference in the past week was rated using an 11-point NRS, with anchors as '0', does not interfere, to '10', interferes completely. We assessed the following domains of the BPI: general activity, sleep, social activity, and mood; working ability and enjoyment of life were not included.

Pain quality

The Korean version of the PainDETECT Questionnaire (KPD-Q) was used to screen for the neuropathic component of pain [15, 16]. The KPD-Q is a self-administered questionnaire consisting of four sections: pain intensity, gradation of pain (seven questions addressing the quality of the neuropathic pain), pattern of pain, and pain radiation. The cut-off values were as follows: score $\leq$ 12, a neuropathic component is unlikely; 13 $\leq$ score $\leq$ 18, uncertain; score $\geq$ 19, a neuropathic component is likely [15].

Functional Ability

The DMD Functional Ability Self-Assessment Tool (DMDSAT) was used to assess functional ability. The DMDSAT consists of 24 items across 4 domains of function: arm function, mobility, transfers, and ventilation status. The DMDSAT has good reliability and validity across the entire clinical profile of DMD [17]. The total scale score of the DMDSAT ranges between '0' and '23,' with higher scores indicative of higher functional activity.

Statistics

All analyses were performed using SPSS (version 25.0 for Windows, IBM Corp., Armonk, NY, USA). Descriptive statistics were used to report characteristics of the study sample and pain symptoms. Non-parametric Kruskal-Wallis and Fisher tests were used to analyze differences between clinical stages: Amb, ENA, and LNA. The ENA group was defined as a non-ambulatory state in those <15 years of age; the LNA group was defined as a non-ambulatory state in those $\geq$15 years of age [17, 18]. A Bonferroni correction was used for post hoc analysis. The correlation between functional ability and pain intensity was assessed using Spearman's correlation. The level of significance was set at $P<0.05$ for all analyses.

Results

Clinical characteristics

The study sample included 148 participants, with a mean age of 14.5±5.3 years. The characteristics of our study sample are summarized in Table 1. Most participants had a contracture at least one site. Participants with advanced DMD were more likely to have scoliosis and a history of spinal surgery, as well as a lower DMDSAT score: Amb, 20.38±2.96; ENA, 8.39±2.14; and LNA, 5.73±2.96. A non-invasive ventilator was used by 16/51 (31.4%) of participants in the LNA group.

Table 1
Demographic and clinical characteristics of the participants

		Ambulatory, N=62	Early non-ambulatory, N=35	Late non-ambulatory, N=51	Total, N=148
Age*		10.73±3.19	12.86±1.63	20.33±3.68	14.54±5.28
Contracture	Total*	43 (69.4%)	34 (97.1%)	49 (96.1%)	126 (85.1%)
	Ankle*	42 (67.7%)	32 (91.4%)	47 (92.2%)	121 (81.8%)
	Knee*	2 (3.2%)	21 (60.0%)	39 (76.5%)	62 (41.9%)
	Hip*	1 (1.6%)	1 (2.9%)	8 (15.7%)	10 (6.8%)
	Shoulder	0	0	2 (3.9%)	2 (1.4%)
	Elbow*	0	0	6 (11.8%)	6 (4.1%)
	Wrist*	0	0	13 (25.5%)	13 (8.8%)
Scoliosis*		0	9 (25.7%)	29 (56.9%)	38 (25.7%)
Spinal surgery*		0	0	10 (19.6%)	10 (6.8%)

* Significant difference between the groups (P<0.05).

Pain

Prevalence of pain

Overall, 66/148 (45%) of participants reported having had pain during the previous 4 weeks. There were no significant differences in the prevalence among the three groups: Amb (24/62; 38.7%), ENA (17/35; 48.6%), and LNA (25/51; 49%).

Pain frequency, duration, and intensity

The most commonly reported pain frequency was ‘several times per week’ in the Amb and ENA groups, and ‘daily’ in the LNA group (P=0.023). A post hoc analysis indicated that the LNA group reported higher

frequency of pain compared to both the Amb (P=0.015) and ENA (P=0.006) groups (Figure 1). There were no differences in the pain duration or intensity among the three groups. More than half of the participants across all groups reported a pain duration of less than one hour. The worst and average pain intensity during the previous 4 weeks for all the participants were 4.89±2.04 and 3.47±1.87 on the 11-point NRS, respectively, corresponding to a moderate pain intensity. The LNA group had a higher number of pain sites compared to both the Amb and ENA groups (P=0.042; Table 2).

Table 2
Pain intensity, duration, and number of pain sites for the 66 participants with pain

		Ambulatory, N=24	Early non-ambulatory, N=17	Late non-ambulatory, N=25	Total, N=66	P-value
Intensity	Worst pain	4.83±2.14	4.06±1.56	5.52±2.08	4.89±2.04	0.059
	Average pain	3.33±2.18	2.82±1.43	4.04±1.70	3.47±1.87	0.112
Duration	Less than 1 hour	16 (72.7%)	13 (81.3%)	13 (56.5%)	42 (68.9%)	0.371
	A few hours	2 (9.1%)	3 (18.8%)	7 (30.4%)	12 (19.7%)	
	Half of the day	2 (9.1%)	0	2 (8.7%)	4 (6.6%)	
	All day	2 (9.1%)	0	1 (4.3%)	3 (4.9%)	
Number of pain sites*		1.46±0.72	1.47±0.94	2.24±1.51	1.76±1.18	0.042

* Significant difference between the groups (P<0.05).

Pain location

The Amb group reported calf pain most frequently (Amb, 62.5%; ENA, 11.8%; LNA, 20%; P=0.001). In contrast, participants in the LNA group reported pain in the lumbosacral region (Amb: 12.5%; ENA: 17.6%, LNA: 44.0%; P=0.04), chest-abdomen (Amb: 0%; ENA: 5.9%; LNA: 24%; P=0.013), and buttocks (Amb: 0%, ENA: 0%, LNA: 16%; P=0.04) more frequently than the Amb and ENA groups (Figure 2).

Aggravating and relieving factors for pain

The pain aggravating and relieving factors are reported in Supplimentary table 1. Of the 24 ambulatory patients with pain, 19 responded to the question regarding aggravating factors. The most common aggravating factor was ambulation (14/24), followed by excessive activity (3/24). Of the 25 participants in the LNA group, 20 responded to the question regarding aggravating factors. The most common aggravating factor in this group was sitting (13/25), followed by lying down (4/25). The most common

relieving factors for pain were ‘resting’ (5/24) and ‘massage’ (5/24) in the Amb group and ‘positional change’ in the ENA (6/17) and LNA (9/25) groups.

Pain interference

Among the pain interference items, only general activity items correlated with both the worst and average pain intensity (correlation coefficient, 0.465 and 0.419, respectively; P<0.001). Mood was more affected by pain in the LNA group than in the other groups (P=0.046; Table 3).

Table 3
Pain interference for the 66 participants with pain

	Ambulatory, N=24	Early non-ambulatory, N=17	Late non-ambulatory, N=25	Total, N=66	P value
General activity	1.79±1.67	2.35±2.42	3.40±2.72	2.55±2.38	0.09
Mood*	1.25±2.11	1.94±2.44	2.76±2.49	2.00±2.40	0.046
Social activity	0.50±0.98	0.94±2.16	1.80±2.81	1.11±2.18	0.28
Sleep	1.08±2.15	1.12±1.62	2.84±3.54	1.76±2.76	0.12
* Significant difference between the groups (P<0.05).					

Pain quality

All except three patients reported a KPD-Q score <12, which corresponded to ‘neuropathic component is unlikely’. Two participants reported KPD-Q scores between 13 and 18, corresponding to ‘uncertain’ pain characteristics. A 14-year-old boy reported a score >19, corresponding to ‘neuropathic pain component is likely.’ He experienced pain of moderate intensity several times a month at three body sites (knees, thoracic spine, and lumbosacral spine) which he described as ‘burning,’ ‘tingling,’ and ‘like an electric shock.’

Discussion

We identified a higher frequency of pain and a greater number of pain sites in individuals in the LNA stage of DMD than in those in the Amb and ENA stages, and the pain interference on the mood was greater in the LNA group than other groups. Our results indicate the need for pain assessment in individuals with DMD, particularly in the LNA stage. In addition, pain assessment focusing on different clinical stages (Amb, ENA, and LNA) is required because pain location and aggravating/relieving factors differed depending on the stage of the disease.

The prevalence of pain in our study sample was 44.6% (66/148 participants), which is lower than the previously reported prevalence of 54–73.4% [6, 7, 9]. Previous studies on pain in neuromuscular patients

included several motor neuron diseases other than DMD, such as spinal muscular atrophy and Becker muscular dystrophy [7, 9], or reported pain prevalence only for individuals with DMD ≥20 years of age [6]. This difference in study population might be related to the difference in pain prevalence.

To the best of our knowledge, only one previous study, by Lager et al.[7] has evaluated pain in the ambulatory and non-ambulatory clinical stages of progressive neuromuscular disease. The most frequently reported pain sites were the 'neck and back' in the non-ambulatory group, compared to the 'legs' in the ambulatory group, a finding which is similar to our study. They reported that the prevalence, intensity, and frequency of pain did not differ between the two groups, with a reported frequency of pain of 'a few times a week.' An increase in the frequency of pain in the non-ambulatory stage might not have been detected in their study because the sample size was small (55 participants), with mixed disease entities, including muscular dystrophy and spinal muscular atrophy.

In the assessment of pain quality in our study among patients with DMD, their pain quality were classified as nociceptive pain (resulting from activation of nociceptors innervating ligaments, small joints, muscle, and tendon) rather than neuropathic pain (resulting from a lesion or dysfunction of the peripheral or central nervous system) [15]. This finding underlines the fact that the pain in DMD patients could be mainly related to musculoskeletal conditions and this would be an important consideration because impairments in musculoskeletal structure and function are different according to the clinical stage of the disease: ankle plantar flexion contracture tends to begin in the Amb stage, hip and knee joint contractures tend to occur in the non-ambulatory stage [19, 20], and scoliosis also generally develops in the non-ambulatory stage[4].

Among participants in the Amb group in our study, calf pain was the typical pain reported, being aggravated by "standing, walking, and running" and relieved by "rest." These results are similar to those of a previous study which reported that calf pain among patients in the early stage of DMD was related to prolonged daily toe walking, overuse syndrome (sprain and strain), and muscular fatigue due to an increase demand on the gastrocnemius-soleus muscle complex [21]. This pain could be managed by tailoring the intensity of ambulation and exercise, maintaining range of motion of the ankle.

DMD patients in the ENA group reported the knee as the most common site of pain, "transfer activity" as the most common aggravating factor, and "positional change" as the most common relieving factor. A potential hypothesis is that movement of the knee joint may be induced by transfer activity, resulting in pain provocation. Eventhough joint contracture itself does not cause the pain, pain occurs when the joint and its capsule are pushed to their end range [22]. This hypothesis suggests the need to prevent or alleviate joint contracture even in the non-ambulatory stage.

Individuals in the LNA group reported the lumbosacral region as the most common site of pain, with other sites including the chest-abdomen and buttocks (Figure 2). They also indicated "sitting" as the most common pain aggravating factor, with "positional change" as the most frequently used pain relieving method. Scoliosis and pelvic obliquity, which progress in the LNA period of the disease, are factors which negatively impact body alignment and posture and might lead to the pain described by these individuals.

Moreover, the progression of muscle weakness makes it difficult for these individuals to correct their posture by themselves, further causing or worsening pain [22]. These explanations emphasize the importance of maintaining spine and pelvis alignment as well as developing an appropriate positioning program as the disease progresses to the LNA stage.

Study Limitations

The limitations of the study need to be acknowledged in the interpretation of results. Foremost, all participants were recruited from a single clinic at a tertiary hospital. The characteristics of pain may vary depending on how a particular clinic manages musculoskeletal conditions. Furthermore, because this was a cross-sectional study, we could not confirm the association between musculoskeletal problems (joint contractures and scoliosis) and pain; a longitudinal study should be conducted to investigate these associations.

Conclusion

In patients with DMD, pain is a common symptom at all clinical stages. In particular, it is important to assess pain of patients in the LNA stage, because higher frequency of pain, pain in more parts of the body, and more interference on mood by pain were noted in this group than in the other groups. Since each clinical stage has different characteristics, the prevention and coping strategies should be modulated accordingly.

Abbreviations

Amb
ambulatory
BPI
Brief Pain Inventory
DMD
Duchenne muscular dystrophy
DMDSAT
DMD Functional Ability Self-Assessment Tool
ENA
early non-ambulatory
KPD-Q
Korean version of the PainDETECT Questionnaire
LNA
late non-ambulatory
NRS
numeric rating scale

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Conception and design: HS; Acquisition of data/Analysis and interpretation of data: AK, MP; Drafting of the manuscript: AK; Revision of the manuscript: HS. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2004-193-1119). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from participants or legal guardians of every child.

Consent for publication

Not applicable

Conflicts of interest/Competing interests

None

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Figures

Figure 1

Pain frequency according to the clinical stage among the 66 participants with pain

Figure 2

Pain location according to the clinical stage among the 66 participants with pain

Supplementary Files

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- Supplementarytable1.docx