Prevalence of chronic pain in a national cohort of patients with limb-girdle muscular dystrophy: a cross-sectional study

Rikke Nicoline Stokholm\textsuperscript{a,b}, Charlotte Handberg\textsuperscript{a,c} and Lone F. Knudsen\textsuperscript{c}

\textsuperscript{a}Department of Public Health, Aarhus University, Aarhus C, Denmark; \textsuperscript{b}University Research Clinic for Cancer Screening, Department of Public Health Programmes, Randers Regional Hospital, Randers NO, Denmark; \textsuperscript{c}National Rehabilitation Center for Neuromuscular Diseases, Aarhus C, Denmark

ABSTRACT

\textbf{Purpose:} The aim was to investigate the prevalence, characteristics, predictors, and consequences of chronic pain in a national cohort of patients with limb-girdle muscular dystrophy (LGMD).

\textbf{Materials and methods:} Questionnaires were sent to all Danish LGMD patients (\geq 18 years of age) registered with the National Rehabilitation Center for Neuromuscular Diseases.

\textbf{Results:} Of 209 patients, 121 responded. 44.7\% of the patients experienced persistent (daily or constant) chronic pain lasting more than 3 months. 21.0\% of patients experienced chronic pain that was not daily. Most pain patients experienced three or more pain problems, primarily in the lower back, neck, shoulders, hips, and legs. Symptoms suggestive of neuropathic pain were sometimes present. Patients with persistent chronic pain reported moderate pain interference with daily activities, greater psychological distress, and lower quality of life compared to patients without pain but did not differ regarding physical functioning. Sex, age, LGMD duration, LGMD type, mechanical ventilation use, mobility, arm function, or performance on activities of daily living did not predict chronic pain.

\textbf{Conclusion:} Chronic pain is common in patients with LGMD. Chronic pain should be considered an important component of LGMD and addressed in the clinic and rehabilitation setting from a biopsychosocial perspective.

\section*{IMPLICATION FOR REHABILITATION}

\begin{itemize}
  \item Chronic pain is highly prevalent in patients with limb-girdle muscular dystrophy.
  \item Health professionals need to systematically ask patients about pain and the influence of pain on everyday life irrespective of LGMD-duration and extent of muscle wastage.
  \item Chronic pain and psychological distress need to be addressed in the clinic and rehabilitation setting as an additional disabling component of LGMD and this should be done within a biopsychosocial framework.
\end{itemize}

Introduction

Limbgirdle muscular dystrophy (LGMD) is a heterogeneous group of genetically inherited conditions that primarily affect skeletal muscles [1–3]. LGMD can have its onset in childhood or adulthood, and the major symptoms are progressive weakness and muscle atrophy of the proximal or disto-proximal muscles such as shoulder and hip areas, thigh muscles and the pelvic girdles due to protein defects in muscle maintenance and repair [1–3]. LGMDs are classified by inheritance patterns into autosomal dominant (LGMD dominant type) and autosomal recessive (LGMD recessive type) subtypes [2], and the clinical severity varies from mild to severe depending largely on the individual genetic mutation [4]. Patients with LGMD may experience problems with walking, standing up from a sitting position, and raising their arms [5–7], and some patients eventually require wheelchair assistance [8]. In some forms of LGMD, patients develop cardiac abnormalities and weakness in the respiratory muscles [2,8,9].

To the best of our knowledge, only five studies have investigated pain in patients with LGMD. These studies indicated that pain is present in many patients with LGMD [10–14]. However, the presence and characteristics of persistent chronic pain (lasting more than 3 months) in LGMD have been investigated in only one study which found chronic pain in 50\% of patients in a small sample of 15 LGMD-patients [13]. The remaining studies have investigated the frequency of pain within the past week and up to 3 months [11,12,14] without taking into consideration the duration of pain. Furthermore, studies on pain in LGMD to date, have been based on small sample sizes (n = 2, 12, 15, 31, or 44) [10–14], and, in some studies, patients with LGMD were pooled with patients with other types of NMD for the statistical analyses [10,14]. Nonetheless, the studies suggest that pain in LGMD has a negative impact on daily activities and quality of life (QoL) [10,11,14], and that severe pain is associated with emotional distress including greater depression scores [13,14], suggesting that pain is an ongoing and disabling problem in LGMD.
To develop effective and targeted rehabilitation initiatives for patients with LGMD, it is important to gain more knowledge about chronic pain in this population. Thus, the prevalence, characteristics, causes, consequences, and predictors of chronic pain in patients with LGMD need to be investigated further. The National Rehabilitation Center for Neuromuscular Diseases, which is a specialized unit for neuromuscular rehabilitation, provides rehabilitation for approximately 3500 people with neuromuscular diseases and holds a national register of people with LGMD in Denmark, making such an investigation possible [15,16]. As in most other countries, the autosomal recessive subtypes are the far most common type of LGMD in Denmark [4].

The aims of this study were to (1) investigate the prevalence of persistent chronic pain in a national sample of patients with LGMD, (2) describe the pain in terms of intensity, location, neuropathic pain characteristics, and causation, (3) investigate physical functioning, performance on activities of daily living (ADL), psychological distress, QoL, and the interference of pain with daily activities, and (4) assess what factors predict persistent chronic pain in patients with LGMD.

Materials and methods

Participants and procedure

In January 2020, an electronic questionnaire was sent to all 209 adult patients (≥ 18 years of age) with LGMD registered with the National Rehabilitation Center for Neuromuscular Diseases [15,16]. Patients registered had all been diagnosed with LGMD by a specialist neurologist or geneticist prior to referral to the center based on histological or genetic findings. For patients with a registered email address, a link to the questionnaire was sent via email (n = 134). For the remaining patients, a link to the electronic questionnaire was sent by postage. Each patient received written information about the project together with the questionnaire and were informed that answering the questionnaire was considered consent. In Denmark, questionnaire studies do not require approval from the Regional or National Committee on Health Research Ethics.

The patients were asked to complete the questionnaire regardless of whether they experienced pain or not to reduce response bias. Patients who had not answered the questionnaire were sent a reminder 2 weeks later and again after another 10 days. One hundred and twenty-one patients with LGMD answered the questionnaire, resulting in a response rate of 57.9%.

Demographic information

The questionnaire contained questions on basic demographic and descriptive information (age, sex, LGMD type (dominant or recessive), time since LGMD diagnosis, whether they had received back surgery, time since back surgery, and use of mechanical ventilation).

Pain information

All patients were asked to rate the frequency of pain in the last week by selecting: "constant pain", "pain every day, but not all the time", "pain, but not every day", and "no pain". Patients who reported pain were asked to answer further questions about their pain, including number of pain problems, daily consumption of analgesics, and the use of other types of pain treatments. They were also asked about the interference of pain with seven daily activities (general activity, mood, mobility, normal work, relations with other people, sleep and enjoyment of life) during the last 24 hours using the Brief Pain Inventory (BPI) [17]. However, to encompass patients who might use wheelchair, the "walking ability" item was modified to "mobility (ability to get around)". This modified version of the BPI has been found valid and reliable for use with patients with a disability and pain [18–20].

For the three worst pain problems, patients were asked about pain location, pain intensity, pain duration, neuropathic pain characteristics, and perceived cause of pain as described below. The decision to limit questions to encompass only the three worst pain problems was an attempt to limit the length of the questionnaire and the time required for the patients to answer it in order to reduce the risk of respondent fatigue. This is an approach also used for pain research in patients with spinal cord injury [21].

Pain location was assessed by asking the patients to select between 22 specific sites (head, face, neck, right shoulder, left shoulder, chest, upper back, lower back, right arm, left arm, right hand, left hand, right buttock, left buttock, right hip, left hip, abdomen, pelvis, right leg, left leg, right foot, and left foot). Pain intensity (average, worst) within the past week was rated on the conventional 11-point Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain).

Pain duration. Patients were asked to report the date of initial pain onset.

Neuropathic pain characteristics were assessed using the interview version of the Douleur Neuropathique 4 Questions (DN4) which includes seven items (burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching) [22]. It is a commonly used and reliable and valid measure of neuropathic pain [23]. As a physical examination for the three additional items was not possible, patients were asked whether they experienced decreased sensitivity (hypoesthesia) to touch, pinprick, or pain caused or increased by brushing the painful area. This approach has been used previously [24]. A positive item answer results in a score of one, and a negative answer in a score of zero. A total sum of the 10 items ≥ 4 is suggestive of neuropathic pain.

Patient-perceived cause of pain was assessed by the open question: What do you perceive to be the cause of your pain?

Physical functioning, activities of daily living, psychological distress, and quality of life

In addition, all patients were asked questions about their physical functioning, ADL performance, psychological distress, and QoL:

Physical functioning was measured by basic questions on mobility (range 0–6) and arm function (Brooke Upper Limb Scale, range 0–6) [25]. A score of 0 indicates, respectively, inability to use a wheelchair (can only lie down) and inability to use hands. A score of 6 indicates, respectively, ability to walk independently more than 1 km outdoors and full circular motion of hands above the head.

ADL performance was measured using the Barthe]20 Index, which contains questions about bowels, bladder, grooming, toilet use, feeding, transfer, mobility indoor, dressing, stairs, and bathing [26]. The total score ranges from 0 to 20, and the lower the score, the more dependent on help. Self-reports on the Barthel-20 Index have been found reliable and valid.

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), a valid and reliable questionnaire for estimating anxiety and depression [27,28]. The scale consists of seven questions for depression and seven for anxiety [29]. Each answer is scored on a four-point scale (0–3). A total
score is calculated for anxiety and depression separately. A score of 8 or more is generally considered the cut-off score for anxiety and depression with a score of 8–10 suggestive of mild anxiety/depression, 11–14 moderate anxiety/depression, and 15–21 severe anxiety/depression.

Pain catastrophizing was measured using the validated Pain Catastrophizing Scale (PCS) [30,31]. The questionnaire consists of 13 questions divided into three factors: rumination, magnification, and helplessness. An overall score of pain catastrophizing was also obtained. A higher score corresponds to greater pain catastrophizing.

QoL was measured using the 36-Item Short Form Health Survey (SF-36) version 1.0 which consists of eight validated subscales: physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, bodily pain, and general health [32,33]. A higher score indicates better QoL.

Outcomes
The primary outcome of the study was the presence of persistent chronic pain in the patients as defined by “constant pain” or “pain every day, but not all the time” for a duration of 3 months or more. Secondary outcomes were pain descriptors, including number of pain problems, pain intensity, pain location, the presence of neuropathic pain characteristics, and the patient-perceived cause of pain. The third outcome was the interference of pain with daily activities, QoL, and the physical and psychological health of patients. The fourth outcome was predictors of persistent chronic pain.

Statistical methods
Data were analyzed using STATA IC version 16.0 (College Station, TX) and IBM SPSS Statistics 27 (Armonk, NY). Descriptive information is presented as numbers and percentages for categorical variables and as mean and standard deviation (SD) for normally distributed continuous variables. Group comparisons were made using t-test or one-way analysis of variance (ANOVA) followed by a Bonferroni post hoc test. Group comparisons for categorical data were analyzed using chi-square. Continuous data which were not normally distributed are reported as median and interquartile range (IQR), and groups compared using Mann–Whitney U-test or Kruskal–Wallis test and a post hoc Dunn test.

To evaluate data about pain intensity, a mean of the average pain intensity and mean of the worst pain intensity were calculated across all pain locations for each patient.

For pain locations, preliminary analyses were performed to see if they differed between patients with persistent chronic pain and patients with less persistent chronic pain. As these analyses were not significant, data for the two groups are presented collated for pain location. Pain locations of sites with symptoms suggestive of neuropathic pain did also not differ between the two chronic pain groups and are thus also presented together.

To calculate the frequency with which a believed cause of pain was reported for a given pain problem, we divided the number of times a cause was reported with the total number of pain problems. This was done collated for all patients with chronic pain.

A logistic regression was performed to assess factors which may predict persistent chronic pain. The following factors were included: age, sex, time since LGMD diagnosis, type of LGMD, mechanical ventilation use (day/night), mobility, arm function, and Barthel-20 Index score. Factors were included based on clinical relevance and whether there was enough data to allow inclusion in the analysis. The sample size was not large enough to perform multiple regression.

Analyses were based on available data, and missing data were not treated as expected values but excluded from the analyses. The exact number of patients who answered each question is displayed in the tables. Results were considered significant at p < 0.05.

Results
Study population
Table 1 presents characteristics of the patients responding to the questionnaire. The mean age of respondents was 50.0 (range 19–86) years. More than half of the patients were between 40 years and 60 years of age (53.7%), and there were slightly fewer men than women (44.6% and 55.4%, respectively). Half of the patients (49.6%) had LGMD recessive type and far less LGMD dominant type (7.4%). The remainder were unaware of their LGMD type. Mean time since LGMD diagnosis was 19.0 years (range 0.25–55.0). Around one-fourth of the patients (24%) used mechanical ventilation – night only, and only a small proportion (3%) of patients had received back surgery.

Pain
Of the 121 patients, 84 patients (69.4%) reported pain within the last week. Almost one-third of the total sample (31.4%) reported "pain everyday, but not all the time", 23.1% reported "pain, but not everyday" and fewer patients (14.9%) reported "constant pain". Thirty-seven patients (30.6%) reported no pain.

Prevalence of persistent pain
Seven patients did not provide data on pain duration, making it impossible to evaluate whether their pain was persistent or not and they were thus excluded from further analyses.
Fifty-one patients (44.7% of the remaining sample) fulfilled the criteria for persistent chronic pain defined as “constant pain” or pain occurring “every day, but not all the time” lasting more than 3 months (persistent pain group). Twenty-four patients (21.0%) experienced chronic pain that was less frequent (not daily), but with a duration of more than 3 months (less persistent pain group). Two patients (1.8%) had experienced pain for less than 3 months (acute pain) and were thus also excluded from further analyses.

Pain had lasted for close to two decades (18.0 years (IQR 10.0–24.0)) for patients with persistent pain which was significantly longer than for patients with less persistent pain (9.0 years (IQR 4.3–15.0), p < 0.001).

The persistent pain group did not differ from patients with less persistent pain and no pain in terms of time since LGMD diagnosis (M (SD)=17.3 years (12.7) vs. 16.5 years (13.0) vs. 21.8 years (14.7), p = 0.216).

A higher proportion of patients with persistent pain consumed analgesics daily than patients with less persistent pain (18 patients (35.3%) vs. three patients (12.5%), p = 0.034). The percentage of patients who reported the use of other forms of treatments for their pain did not differ between the two chronic pain groups (persistent pain: 29 patients (57%) vs. less persistent pain: 12 patients (50%), p = 0.378). See an overview of types of pain treatments in supplementary material.

Pain intensity and number of pain problems
Patients with persistent pain reported pain in the moderate range both for their average and worst pain. This was significantly greater than the pain experienced by patients with less persistent pain (p < 0.001) (Table 2).

Most patients with chronic pain experienced three or more pain problems, and patients with persistent pain reported more pain problems than patients with less persistent pain (Table 2).

Pain location and characteristics
The patients were asked to report the location of up to three of their worst pain problems. As stated earlier, pain locations were similar for patients with persistent pain and less persistent pain and are thus presented together.

Pain in the lower back was the most frequently reported pain location appearing in 57% of the patients (see Figure 1). Neck pain was present in almost half of the patients. Pain in the shoulders, hips, and legs were also common (>30%). Pain at these sites was sometimes accompanied by symptoms suggestive of neuropathic pain (Figure 1). Pain at distal sites such as hands (2.7%) or feet (6.7%) were rare and when present often accompanied by symptoms suggestive of neuropathic pain.

Patient-perceived cause of pain
Patients described what they believed to be the cause of their pain for each of the pain problems they reported (up to three pain problems) (see Table 3). The most frequently stated cause of pain was muscle weakness/atrophy (31.2% of pain problems). Other common causes were overexertion, muscle tension, and immobility (9.8–12.7%). Less common causes were trauma (5.9%), movement (incl. abnormal gait) (5.4%), poor posture (3.4%), nerve compression (2.4%), scoliosis (2.0%), surgery (2.0%), and referred pain (2.0%). Pain arising from contracture was rarely reported.

Pain interference
Patients with persistent pain generally rated pain interference with daily activities on the BPI to be in the moderate range (see Table 2). For each of the daily activities, this was significantly greater than the interference rated by patients with less persistent pain who generally reported low interference (p < 0.05).

Physical functioning, ADL, psychological distress, and QoL
Physical functioning and ADL performance
No differences between the patients with persistent pain, patients with less persistent pain and patients with no pain were found for mobility (respectively M (SD)=4.3 (1.30) vs. 4.25 (1.48) vs. 4.16 (1.30), p = 0.869), arm functioning (4.35 (1.74) vs. 4.33 (1.61) vs. 4.08 (1.96), p = 0.761) or ADL performance (M (SD)=15.46 (5.50) vs. 15.0 (5.45) vs. 13.92 (5.53), p = 0.432).

Anxiety and depression
Patients with persistent pain reported more symptoms of anxiety and depression on the HADS than patients with no pain but did not differ from patients with less persistent pain (Figure 2).

Looking at individual scores, 19 patients (38%) with persistent pain fulfilled criteria for a possible case of anxiety. Of these, nine patients (18%) experienced symptoms suggestive of mild anxiety, eight patients (16%) moderate anxiety, and two patients (4%) severe anxiety. For patients with no pain, five patients (13.5%) fulfilled criteria for anxiety, all mild. Of the patients with less
persistent pain, six patients (26.1%) fulfilled criteria for possible anxiety with three patients (13.0%) experiencing symptoms suggestive of mild anxiety and three patients (13.0%) severe anxiety. The proportion of patients with persistent pain who fulfilled criteria for a possible case of anxiety was greater than for patients with no pain \( (p = 0.012) \) and similar to the proportion of patients with less persistent pain \( (p = 0.319) \).

For depression, 15 patients (30.0%) with persistent pain fulfilled criteria for a possible case of depression with six patients (12%) experiencing symptoms indicating mild depression, eight patients (16%) moderate depression and one patient (2%) severe depression. This was also a greater proportion than for patients with no pain \( (p = 0.032) \) and similar to the proportion of patients with less persistent pain \( (p = 0.254) \). For patients with no pain, four patients (10.8%) reported symptoms suggestive of depression with two patients (5.4%) reporting symptoms consistent with mild depression, one patient (2.7%) moderate depression and one patient (2.7%) severe depression. For patients with less persistent pain, four patients (17.4%) experienced symptoms suggestive of depression, all mild. The proportion of patients experiencing symptoms suggestive of anxiety \( (p = 0.306) \) and depression

### Table 3. Patient-perceived causes of pain.

| Perceived cause                  | Number and proportion of total pain problems reported, \( n (\%) \) |
|---------------------------------|---------------------------------------------------------------|
| Muscle weakness/atrophy         | 64 (31.2)                                                     |
| Overexertion                    | 26 (12.7)                                                     |
| Muscle tension                  | 23 (11.2)                                                     |
| Immobility (wheelchair use/sitting/lying down) | 20 (9.8)                                                     |
| Trauma                          | 12 (5.9)                                                      |
| Movement/abnormal gait          | 11 (5.4)                                                      |
| Wear and tear                   | 7 (3.4)                                                       |
| Poor posture                    | 7 (3.4)                                                       |
| Nerve compression               | 5 (2.4)                                                       |
| Scoliosis                       | 4 (2.0)                                                       |
| Surgery                         | 4 (2.0)                                                       |
| Referred pain                   | 4 (2.0)                                                       |
| Exercise/sport                  | 3 (1.5)                                                       |
| Contracture                     | 3 (1.5)                                                       |
| Disc protrusion                 | 2 (1.0)                                                       |
| Other (equinus of the foot, cramps) | 2 (1.0)                                                       |
| Do not know                     | 14 (6.8)                                                      |
| Answers missing                 | 3 (1.5)                                                       |

A total of 205 pain problems were reported. Some patients reported more than one cause for each pain problem. Data are combined for patients with persistent pain and less persistent pain.
Psychological distress

Pain catastrophizing

Quality of life

Predictors of persistent pain

Discussion

None of the factors entered into the regression (age, sex, time since LGMD diagnosis, type of LGMD, mechanical ventilation use (day/night), mobility, arm function, and Barthel-20 Index score) could predict persistent pain.

Discussion

To our knowledge, this is the first study to investigate the prevalence of chronic pain in a national cohort of LGMD-patients. We found a high prevalence of chronic pain with a total of 65.7% of patients experiencing chronic pain (44.7% persistent, 21% less persistent). This is considerably higher than the 16% rate of chronic non-cancer pain estimated in the general population [34]. Tiffreau et al. [13] found chronic pain lasting more than 3 months in 50% of their small sample of 15 LGMD-subjects which is in line with our findings. To our knowledge, no additional studies have taken into consideration pain chronicity when investigating pain in LGMD only. Nonetheless, studies of pain in general have found pain to be frequent in LGMD ranging from 55% to 64% [10,11]. Thus, pain should be considered a common and potentially chronic aspect of LGMD. As in the study by Tiffreau et al. [13], pain was rated as moderate by patients with persistent pain.

The majority of our chronic pain patients experienced pain at multiple body sites, most frequently in the lower back followed by pain in the neck, shoulders, hips, and legs. These pain locations are consistent with findings in previous studies [11–13], although Jacques et al. [12] found pain in the shoulders, hips, and
legs to be more frequent than pain in the lower back. Such differences may be explained by sample differences. Jacques et al. [12] included only males and they were slightly younger than our participants. More importantly, they looked at pain within the past three months without distinguishing between acute and chronic pain.

The locations and causes of chronic pain mentioned by the patients in our study primarily point toward a musculoskeletal origin of pain. To the best of our knowledge, no previous studies have investigated the cause of pain in patients with LGMD. Nociceptive pain may arise as a result of muscle, bone, and joint damage [35] and thus possibly plays a role for the pain related to muscle atrophy, overexertion, muscle tension, trauma, poor posture, movement, and wear and tear. In support of this, these causes are considered common contributors to chronic musculoskeletal pain conditions such as chronic myofascial pain [36]. Furthermore, neck and trunk muscle weakness may cause spinal deformities including scoliosis [8,37] which have been linked with pain in other NMDs [35,38,39]. Prolonged immobilization may also cause degenerative changes in connective tissues, bones, and joints and, hence, nociceptive pain as is seen in amyotrophic lateral sclerosis [40].

One may speculate whether central sensitization caused by nociceptor input from strained or damaged joints or muscles may contribute to amplification and chronification of pain in LGMD. Muscle afferents or damage to muscle or joints are known to be able to produce central sensitization [41]. Nerve involvement may also play a role as symptoms suggestive of neuropathic pain was seen at some sites in our chronic pain patients. This has also been documented in other types of NMDs [35]. Neuropathic pain may arise from trauma or surgery or nerve entrapment from overuse activity [42,43]. It is unknown whether pathophysiological mechanisms of LGMD directly contribute to neuropathic pain. Future studies should assess the pathophysiological mechanisms of pain in LGMD.

Interestingly, patients with chronic pain and no pain did not differ in terms of time since LGMD diagnosis, physical functioning, or ADL functioning, arguing against the contribution of progressive muscle weakness to chronic pain. Jacques et al. [12] also failed to find an association between pain and functional scales, suggesting that pain at the whole-body level may not be related to functional impairments or disease progression. It is interesting that patients with persistent pain reported that pain had a greater impact on all daily activities measured by the BPI than patients with less persistent pain which suggests that activity limitations may be a result of pain rather than vice versa. These results are consistent with a previous study [11].

Patients with persistent pain also reported more psychological distress and a poorer QoL which is similar to findings in the wider pain literature [44] and studies of pain in other types of NMDs [45,46]. The rates found in our study are high seen in the light of rates of anxiety and depression in the general population (total anxiety disorders 10%, depression 2–3%) [47,48]. The only other study of chronic pain in LGMD [13] also found positive associations between pain and anxiety and depression, indicating that pain may contribute to psychological distress in LGMD. It is possible that pain and psychological distress may feed into one another and worsen both pain and psychological distress [49–52] and influence the success of pharmacological and psychosocial treatments of chronic pain [53–56]. Thus, it may be advantageous to address the psychological distress of LGMD-patients in a rehabilitation intervention. This could potentially alleviate both pain and psychological challenges.

The findings highlight the importance of addressing pain in the clinic and rehabilitation setting within a biopsychosocial framework. In the light of the high rates of anxiety and depression, it is surprising that none of the patients reported psychological treatment. We can probably not make any firm conclusions about this as patients may not have considered psychological interventions a pain treatment per se. A multidisciplinary approach is the recommended treatment of choice for chronic pain by the International Association for the Study of Pain [57] which fits well with current treatment guidelines for patients with LGMD [58]. However, current treatments of LGMD would benefit from a greater focus on chronic pain as an additional disabling aspect.

Besides psychosocial pain management such interventions should aim to protect against muscle damage, overexertion, trauma, movement-induced pain, wear and tear, and poor postures. In line with the current treatment guidelines for LGMD, a range of assistive devices may be considered and should be carefully fitted for adequate postural support. Patients should be monitored for spinal deformities so this can be managed in due course [58]. Physiotherapy that includes supervised submaximal strengthening and aerobic fitness training may protect against inactivity and the contribution of inactivity to muscle loss beyond that caused by the LGMD itself [58]. However, there may be some risk of exercise-induced muscle damage following high-intensity exercise [58]. Furthermore, daily passive and active-assisted range of motion exercises is believed to be helpful in preventing pain from immobilization [59]. Some of our patients reported making use of physiotherapy and massage for pain treatment. This should be tailored individually to the patients as some patients reported a worsening of pain in response to physiotherapy in another study [38].

Paracetamol was the most commonly used analgesic in the present study and a study of youth with NMDs including LGMD [10]. Nonsteroidal anti-inflammatories were also commonly used [10,13], and more often than paracetamol, in the only other study of chronic pain in LGMD [13]. The effectiveness of analgesics in LGMD have not been investigated in randomized controlled trials. Rehabilitation efforts would benefit from studies that seek to gain greater insights into mechanisms, prevention and treatment of pain in LGMD. Our study is the only study that has looked at predictors of chronic pain in patients with LGMD and we were unable to find any.

Strengths and limitations

A strength of the study is the large number of LGMD-patients who answered the questionnaire (121 patients) which is close to 60% of our national population of adult LGMD-patients. Previous studies have pooled different NMD diagnoses for analyses and included small sample sizes of LGMD [10–14]. Furthermore, we took into consideration pain duration when identifying chronic pain using the officially recognized criterion of more than 3 months [60]. Nonetheless, we cannot exclude that recall bias and selection bias may have contributed to the results as it was a retrospective study based on subjective patient reports and patients needed to actively decide to fill in the questionnaire. Patients with the most resources may have been more likely to answer the questionnaire. On the other hand, patients with pain may have been most interested in participating. Irrespective of this, clear differences emerged between patients with persistent chronic pain and those with less persistent pain or no pain that correspond well with former studies. Future studies should
Conclusions

The present study showed that chronic pain is common in patients with LGMD. Pain should thus be considered an important component of LGMD that contribute to psychological distress and reduced QoL. Clinicians need to systematically ask patients about pain and take pain complaints seriously so these can be adequately addressed and managed from a biopsychosocial perspective. Our results indicate that chronic pain is not purely a result of progressive muscle weakness. More research into the mechanisms and predictors of pain in LGMD need to be performed. We were unable to find any predictive factors for chronic pain in patients with LGMD.

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ORCID

Rikke Nicoline Stokholm http://orcid.org/0000-0001-8618-4944
Charlotte Handberg http://orcid.org/0000-0002-1378-2449
Lone F. Knudsen http://orcid.org/0000-0001-7989-4884

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