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Nociceptive pain in neuromuscular disorders – a low interventional pilot study to assess musculoskeletal pain in neuromuscular diseases

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Anna Elena Sagerer

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Contents

Abbreviations

6MWT	Six-minute-walk-test
BDI-FS	Beck depression inventory – fast screen
BPI	Beck pain inventory
DASS	Depression, Anxiety and Stress Scale
DGM	Deutsche Gesellschaft für Muskelkranke
DM1	Myotonic dystrophy type 1
DM2	Myotonic dystrophy type 2
FSHD	Facio-scapulo-humeral muscle dystrophy
GPQ	German Pain Questionnaire
IBM	Inclusion Body Myositis
LOPD	Late Onset Pompe Disease
MFHW	Marburg Questionnaire
NMD	Neuromuscular diseases
PROM	Patient reported outcome measure
QoL	Quality of Life
QMFT	Quick motor function test
SMA	Spinal muscular atrophy
SMA3	Spinal muscular atrophy type 3 (walkers)

Publications

Publication I [1]

Nociceptive pain in adult patients with 5q-spinal muscular atrophy type 3: a cross-sectional clinical study

Elena Sagerer, Corinna Wirner, Benedikt Schoser, Stephan Wenninger

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Publication II [2]

Nociceptive pain in patients with neuromuscular disorders - a cross-sectional clinical study

Elena Sagerer, Corinna Wirner-Piotrowski, Marko Mijic, Marcela Arndt, Natalia Garcia- Angarita, Benedikt Schoser and Stephan Wenninger

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155th place out of 313 in the category Neurosciences (Scie) (rank 58.9%) for 2023

Introduction

Many studies aimed to identify components that are associated with pain in neuromuscular diseases. Psychological and emotional components (e.g. psychological functioning), decreased quality of life, and female gender have been frequently mentioned in various studies. However, numerous other factors that may be associated with pain perception should not be neglected, for example, the number of pain locations, disturbed role or social functioning, low levels of general health, activity in daily life, inability to cope with stress adequately, the BMI, sleep disturbances, leisure, work or general mobility. [3-9]

Background

While nociception describes the neuronal coding of noxious stimuli, the IASP (International Association for the Study of Pain) [10] defines pain as an unpleasant sensory and emotional experience that can be caused by actual tissue damage or just be interpreted as such [11]. In this context, interpretation i.e., subjective cortical evaluation is essential for experience of pain: pain cannot arise from nociceptive afferents alone [10, 12].

The individual's perception of pain is very heterogeneous and based on an interaction of exogenous and endogenous influences. Some factors may have a direct influence on pain, for example, genetic and epigenetic factors that interact with the expression of biological signaling pathways [13]. However, a variety of other factors, including age or ethnicity, merely modify the perception of pain [14, 15].

The role of gender in the perception of pain is also widely discussed. The prevalence of common forms of pain is higher in women than in men [3, 8, 14]. Regarding sex differences in the research of pain perception, potential etiological factors for the origin of pain, such as the influence of sex hormones, endogenous opioid structures, pain coping factors, cognitive factors and stereotypical gender roles, have been mentioned [8, 9].

According to a biopsychosocial model by John D. Loeser [7, 16, 17], individual pain perception is additionally influenced by four psychological processes: attention (distraction from or focus on pain), cognitive setting (catastrophizing, negative or positive thoughts, expectations), emotions (anxiety, depression, stress, positive feelings), and coping strategies (e.g., avoidant behavior). A biopsychological model as the most comprehensive explanation behind the etiology of pain is needed to understand pain, emphasizing the importance of biological, psychological and sociological factors [17]. All these factors together form a complex, mutually influencing system that is far from being understood.[15].

Study objectives and study setting

The explorative, cross-sectional clinical pilot study intended to identify possible differences in prevalence, localization, severity and characteristics of muscle pain across the spectrum of the examined neuromuscular diseases. The second main objective was to find out whether gender, muscle strength and psychological factors, especially the emotional component, affected the patients` nociceptive pain. Another secondary objective was to determine whether changes in muscle frequency, stiffness, relaxation and creep are related to muscle pain.

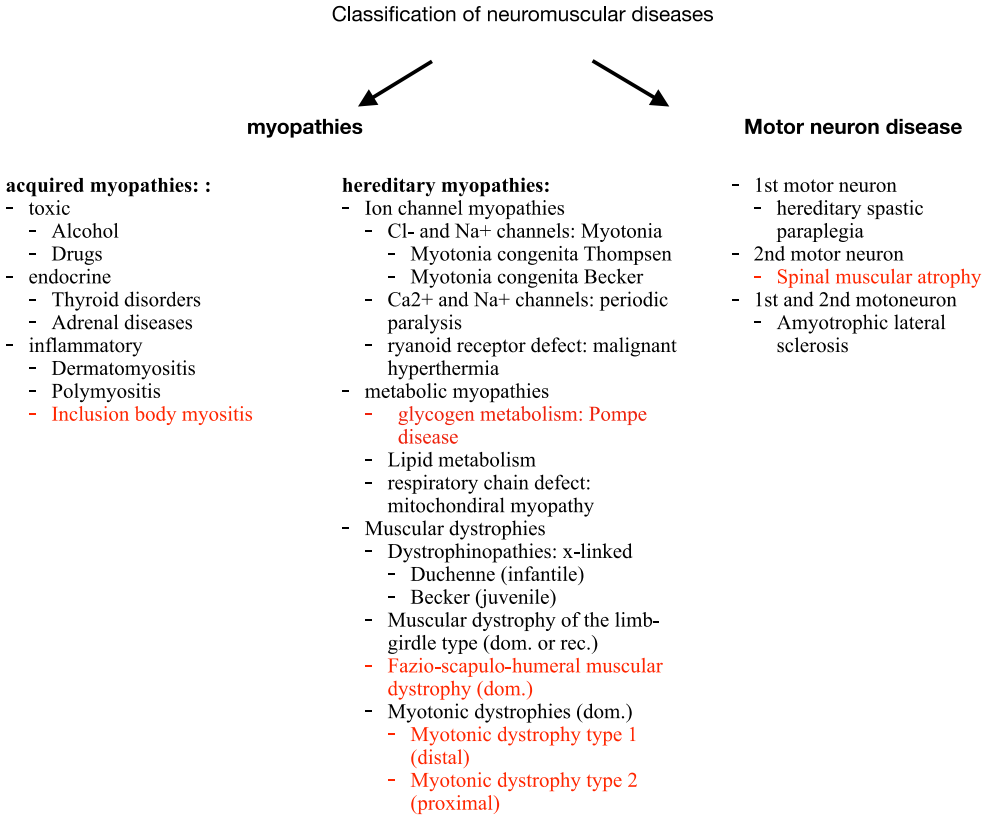

Figure 1 Classification of disease patterns

Only patients with genetically or histologically confirmed diseases have been chosen to participate in the study (marked red in figure 1). Summarized, 81 patients have been enrolled for this study: 12 patients with genetically confirmed myotonic dystrophy type 1, 12 patients with genetically confirmed myotonic dystrophy type 2, 13 patients with Pompe disease, 20 patients with spinal muscular atrophy type 3 (walkers),12 patients with facioscapulohumeral muscular dystrophy and 12 healthy participants for the control group. We expanded the SMA subgroup to 20 patients because we presented interim results concerning nociceptive pain in SMA patients in our first publication.

25 subjects had an excessively high score on the BDI-FS at screening. As the presence of major depression is possible in these patients and my affect the perception of nociceptive pain negatively, they were excluded from participation in this study. We also planned to include 12 patients with histologically confirmed inclusion body myositis, but lack of interest in the study and willingness to participate resulted in the enrollment of only 4 patients. Furthermore, the mean age of the IBM patients would have been much higher than the mean age of the other subgroups, so the comparison would be difficult to make (the mean age of the IBM group would be approximately 80-90 years, the mean age of the other groups between 39 and 49 years). So, after examination of 4 IBM patients, we decided to exclude them from the study.

All patients underwent the study protocol (figure 2). Inclusion and exclusion criteria, a description of methods and all performed tests are described in our first publication in detail [1]. In brief, patients first underwent a screening for depression using the BDI-FS, suggesting that a manifest depression would cause bias in the exploration of pain perception. We excluded 22,5% (25 subjects) of all screened patients due to a score ≥4 at screening. All patients completed pain-, fatigue- or quality of life-related questionnaires, including questions about depression, anxiety and stress. The clinical examination consisted of an evaluation of muscle strength (MRC grading and dynamometry including hand-held dynamometry), motor function (QMFT), pressure pain threshold (PPT), myotonometry and a 6MWT (including PPT testing of the legs before and after conduction of the 6MWT). The detailed study setting is shown in figure 2.

In the first publication, we presented interim results of the study about a group of 20 SMA patients. We focused on the first objective of the study: pain prevalence, localization, duration and characteristics of the patients were described in detail. Because of the great differences between female and male patients, results were divided by gender. We also showed a significant correlation between muscle pain in different body regions and decreased muscle strength by performing a linear regression analysis.

All 81 patients of the study were included in the second publication. As in the first publication, we described pain characteristics in detail but are now categorized by disease rather than by gender. Based on the results of our interim publication, we used multiple regression analyses to show a significant correlation between patients' musculoskeletal pain and muscle strength. Based on the literature review, we also included gender and psychological components in these analyses. We additionally analyzed the MyotonPro® values and their correlation with the PPT values of the neck muscles of all patients.

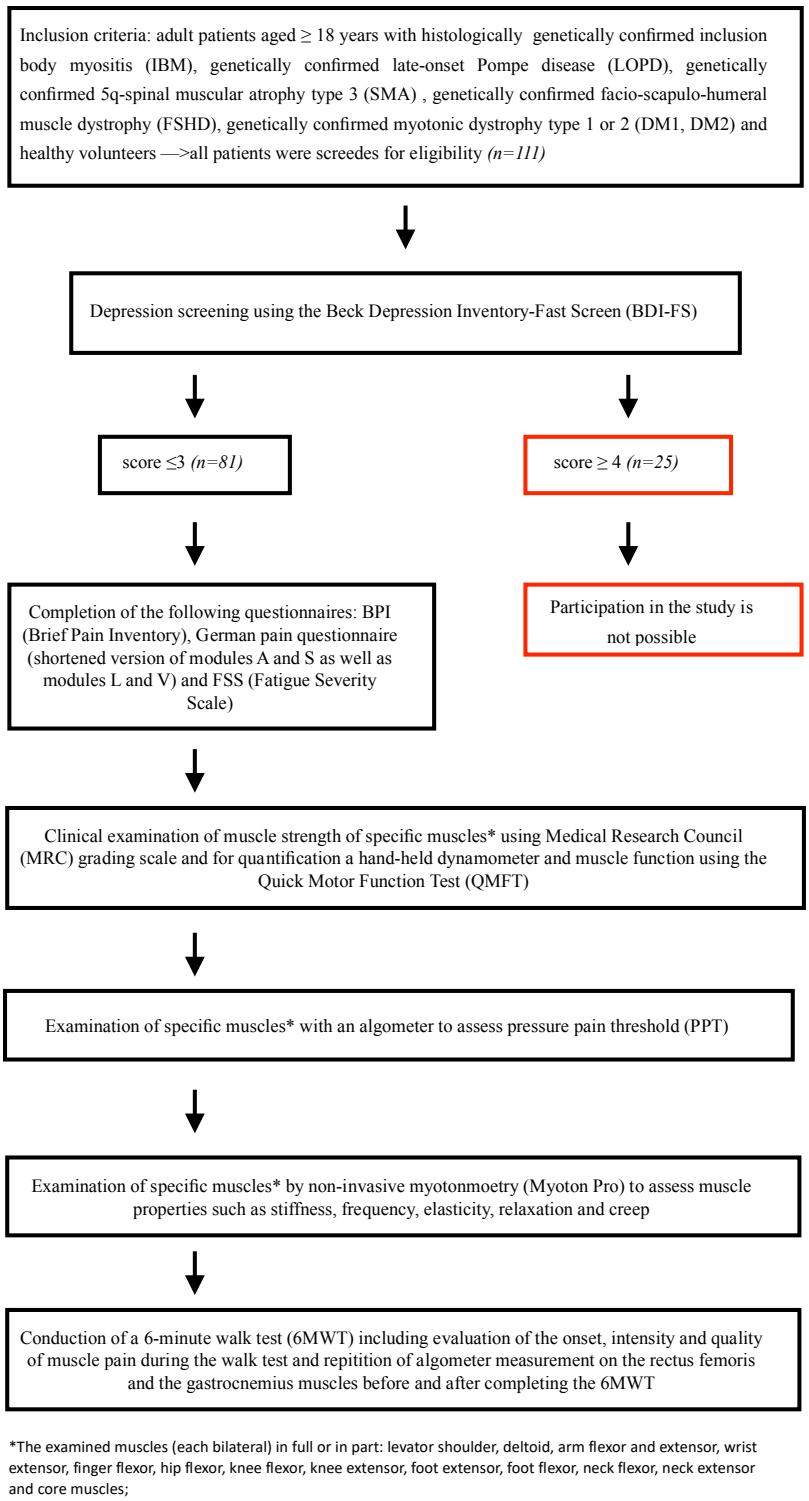

Figure 2 Study setting with inclusion criteria

Limitations and discussion of the methods

A method-critical part supplements the discussion. As the study is a pilot study, a method-critical part is useful to improve the quality of data collection for further or similar studies.

The advantage of the study was certainly that I had seen and examined each of the patients myself. So, there was no bias due to many investigators. A precise planning of the procedure turned out to be essential for the study (figure 2). At the beginning of the data collection, I carried out some test runs with healthy test subjects and employees of the Friedrich-Baur Institute to familiarise myself with the methodology. I did not include these runs in the study. The case report form (appendix) shows the order in which I carried out the tests.

It made sense to collect the demographic data and questionnaires at the beginning of the study. This usually took more than an hour, often accompanied by problems such as language barriers and general comprehension problems. The physical examinations then took a further two hours. The muscle strength exercises were strenuous for the patients, so it made sense to give them a "break" while performing the myotonometry. It also helped to perform the 6MWT at the end of the procedure, because it was most exhausting for the patients. To improve the quality of the study, I can only suggest shortening the entire study to a maximum of two hours. The patients' attention and energy levels decreased towards the end of the study, which is likely to affect the data quality. Another rationale for administering the questionnaires at the beginning of the study were the inclusion criteria. Due to the criteria, patients with a BDI FS >4 were excluded from participation in the study, as the presence of severe depression could not be ruled out. I conducted this test initially to avoid examining patients who were not eligible for study participation. I invited some patients via the DGM central register for myotonic dystrophies: after completion of the BDI-FS, some of them were found to be ineligible to take part in the study. Unfortunately, some of these patients had travelled several hours. I would therefore recommend sending the BDI-FS by email in advance for future studies in order to check the inclusion criteria and avoid patients travelling unnecessarily. I implemented this later during the study, but some patients, particularly older patients, faced difficulties with the mailing and uploading of the BDI-FS due to their limited technical knowledge, which could cause a potential bias.

Most of the time, the strength exercises and myotonometry worked without problems. I had to pay attention to the correct posture: I always examined certain muscles in the prone position, others always in the supine or sitting position. The problem arose that some patients developed breathing problems in the prone position and could only lie on their stomachs for a short time or not at all. Extreme obesity was also a problem here. It was important to ensure that the patients completely relaxed their muscles, as otherwise, the results would have been distorted and were not comparable. Measurements had to be taken very carefully at the same measurement point of the muscle and at the same angle (figure 1). Apart from the fact that the patients were

sometimes very ticklish during myotonometry, this examination was very reliable, quick and easy to carry out.

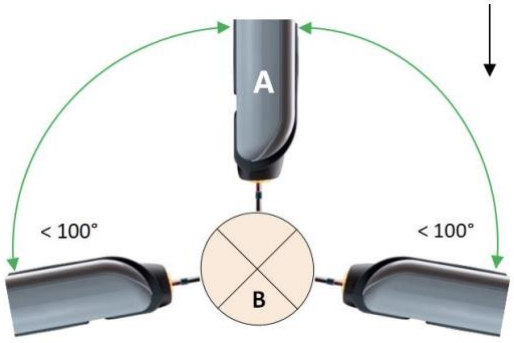

Figure 1 The range of measurement axis of the Myoton Pro [18]
The angle of measurement exceeding 1000 from the vertical position must be avoided

Attention also had to be paid to the acceleration curve result (figure 2) immediately after the test was carried out, as otherwise, the examination of the corresponding muscle had to be repeated. I had to ensure that the result of each measurement was a “soft tissue oscillation acceleration signal” with at least three positive peaks and that measurements were not distorted by short-term disconnection to the tissue or dysfunction of the device. For future studies with the MyotonPro®, I recommend a sufficient training period with the device.

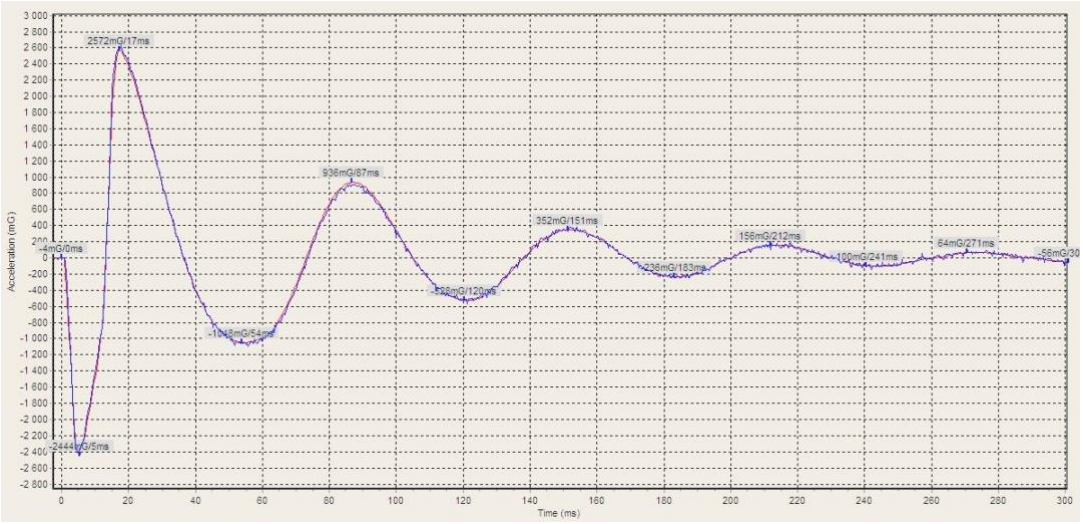

Figure 2 Soft tissue oscillation acceleration signal [18]

The measurements with the algometer also worked without any problems for the most part. However, I recommend going through one or two test exercises with the patient first. Some had

difficulties understanding what exactly was meant by the pressure pain threshold. The misunderstanding with some patients was that they did not report when the pressure was perceived as painful, but when it became unbearable. Therefore, it makes sense to carry out a few test exercises first to ensure the patient has understood their task. As I always carried out each algometer measurement three times per muscle and averaged the results, I can also say that the measurement of the pressure pain threshold works very accurately, as there were hardly any outliers in most patients. Here, I can confirm the reliability of the algometer [19]. In addition, the algometer measurement was very strenuous for me as the person examining due to the constant pressure. This naturally leads to a bias in the process. I solved this by not carrying out the algometer measurement for each muscle three times in a row, but three times for the entire algometer measurement procedure. This aimed to ensure that I did not have less strength in certain muscle groups, e.g., always in the leg muscles.

The QMFT was also easy to perform. A standing jump was one of the "exercises" to be performed as part of this test. Some patients wanted to try this test, although they seemed too unstable and muscularly weak for this exercise. I sometimes omitted this exercise as I didn't want to endanger any patient.

The 6MWT was overall easy to perform. However, it should be mentioned here that some patients' diseases were already very advanced, meaning that they already had very limited muscle strength. I included some patients in the study during their stationary stay at the LMU clinic. As the 6MWT took place in the outpatient clinic, the journey from the ward to the outpatient clinic alone was exhausting for many patients and would have falsified the results of this exercise test. I can therefore recommend that patients who are still able to walk should also be transported to the route for the 6MWT in a wheelchair so that they do not overexert themselves before the test begins. Before and after the 6MWT, I measured the pressure pain threshold of the leg muscles using the algometer. This revealed a problem with the patient's clothing. Some patients wore short sports trousers, and some wore thicker pants, especially in cold temperatures. During the examination, I always continuously measured the pressure pain threshold directly on bare skin. Of course, the measurement through clothing can hardly be compared with the measurement on bare skin. As the 6MWT was the last test to be carried out, patients were often unwilling to change their clothes for it. The idea of going into an examination room directly before and after the test to carry out the algometer measurements also failed due to logistical problems. There was often no free room available, or the journey to such a room was too far and too strenuous for the patients. This meant that algometer measurements before and after the 6MWT could be compared, but not between different patients.

When carrying out the questionnaires, very precise attention was paid to descriptive elements of pain to differentiate between neuropathic and nociceptive pain, as can be seen in the results [1, 2]. The majority of the pain was not clearly attributable to nociceptive or neuropathic pain. By measuring the pressure pain threshold in different muscles, however, the patients' muscle pain,

i.e., the nociceptive pain, was measured specifically. The algometer measurement is a reliable and objective method to determine local pain [14].

Publication I

The first publication [1] investigated nociceptive pain in 20 patients with longstanding spinal muscular atrophy type 3 (walkers) in comparison with a control group (12 participants).

Fatigue was present in 50% of the SMA cohort and pain in 55%. This study investigated pain characteristics in these patients in detail: patients reported pain in high variability in intensity and localization (lumbar spine, legs and neck), mostly suffering from pain attacks (81,8%) with a duration of minutes or seconds. Patients described the pain as pulling and oppressive. Women with SMA 3 reported musculoskeletal pain significantly more often (31% of men and 100% of women, p=0.003) and in more body regions than male patients (3.9 ± 2.6 vs 1.5 ± 0.6). Whereas the pain severity score was higher in women than in men (4 ± 3.8 vs 2.8 ± 1.3), pain interference score was higher in men (11.5 ± 13.9 vs 7.1 ± 9.8), especially in the categories walking, work and enjoyment of life. All patients received nusinersen as SMA specific treatment, but none of them reported an impact on pain perception. The study also investigated pain triggers (especially physical exertion) and pain relievers (especially relaxation and specific physical exercises such as physiotherapy). This is particularly interesting because muscle training seems to be both a potential pain trigger and reliever. Specific exercises in combination with physiotherapy seem to be beneficial for pain relief but overstressing of muscles due to too much exercise seems to be detrimental. According to the results, physical training is beneficial if it is related to specific exercises and the muscles are not overloaded.

I performed a linear regression analysis to examine the correlation between muscle strength and nociceptive pain. Therefore, I summarized the PPT dynamometer scores for four different body regions: the arm, leg, shoulder/neck and trunk region. According to the linear regression model, lower scores in PPT (reflecting a higher sensitivity of the muscles on pressure) correlate with lower scores in dynamometry (reflecting lower muscle strength). The linear regression analysis was significant for the arm (p = 0.041*) and leg region (p = 0.024*), but not for the shoulder/neck region or the trunk region. A lower score in dynamometry is associated with lower scores in PPT in the arms and legs. This reflects a higher sensitivity of the muscles of the arm and leg region to pressure pain.
Although women reported experiencing pain more frequently and with greater severity than men, they exhibited higher levels of habitual well-being and lower scores for depression, anxiety, and stress (according to patient-reported outcome findings). These findings suggest that these psychological comorbidities do not influence the heightened perception of pain in women.

I assessed PPT values of the gastrocnemius and rectus femoris muscles before and after performing the 6MWT. The pre-post difference was only statistically significant for male patients' rectus femoris muscle on the right side (p = 0.034). In summary, changes in the PPT before and after the 6MWT did not indicate clinically meaningful results, such as induction of muscle pain.

There were no significant correlations between PPT values and MyotonPro measurements, suggesting that nociceptive pain in SMA3 is primarily due to muscular weakness rather than changes in muscle properties like stiffness, frequency, decrement, relaxation, or creep.

Publication II

The second publication aimed to extend research in patients with other neuromuscular diseases. Therefore, patients with late-onset Pompe disease (LOPD), myotonic dystrophy type 1 (DM1), myotonic dystrophy type 2 (DM2), and facio-scapuloo-scapular-humeral muscle dystrophy (FSHD) were additionally included in this second study.

According to pain characteristics, we found highly significant results. Patients with DM2 and FSHD had a significantly higher prevalence of pain. FSHD patients reported pain mainly in the shoulders and neck, and DM2 patients, especially in the thighs, calves, and gluteal muscles. We also found significantly higher values of impairment of pain in daily life and levels of fatigue in DM2 patients when compared to the other examined NMDs and the healthy control group.

The objective of the study was to identify variables influencing nociceptive pain in NMD patients. Results of the linear regression model in the first publication about the SMA cohort showed an association of pressure pain sensitivity (assessed by PPT) with female gender and decreased muscle strength. Psychological facts did not significantly correlate with nociceptive pain in women in this cohort. Thus, in literature, there is much evidence that psychological aspects influence pain [17]. I conducted a multiple regression analysis based on the literature and our previous research in the first publication. As the dependent variable, I determined PPT sum scores of the four body regions to reflect nociceptive pain. As the independent variables, I chose QMFT/MRC, FSS points and gender. To represent patients' muscle strength and motor function, I chose the QMFT as the representing variable because it showed strong Pearson correlations with the 6MWT, the dynamometer of the leg region, the dynamometer of the arm region and the MRC sum scores. So, the assumption of multicollinearity could be excluded by just including the QMFT as the independent variable. I included gender as a dummy variable in the multiple regression analysis. To include psychological and emotional aspects of pain, I used data from the patient-reported outcome measures (questionnaires about fatigue, anxiety, depression, stress and the MFHR about general well-being).

To avoid multicollinearity as a potential source of bias, I chose the FSS score to represent psychological aspects: The FSS showed strong Pearson correlations with the scores of the DASS and the MFHR. Detailed statistical methods for the multiple regression analysis are explained in our publication [2]. I performed three multiple regression analyses for each of the leg, arm and shoulder/neck regions to identify regression coefficients and their significance in the prediction of PPT values (dependent variable). In the model for the leg region (significance of the regression model: <0.001**; f^2 Cohen: 0.302, assuming a medium effect;), the QMFT (0.004**) and gender (0.031*) of the participants were highly significant variables. In the regression model for the arm region (significance of the regression model: <0.001**, f^2 Cohen: 0.4388 assuming high effect), the QMFT (0.005**), the patient's gender (<0.001**) and the FSS points (0.03*) were significant. In the regression model for the neck/shoulder region (significance of the regression model: <0.001**, f^2 Cohen: 0.289 assuming medium effect), MRC of the neck muscles (0.028*), gender (0.005**) and FSS points (0.006**) were significant variables. In summary, the results of these three multiple regression analyses show that patients who have more muscle strength in the extremities are likely to experience less muscle pain in these regions.

In contrast, muscle strength of the neck muscles showed a negative correlation (correlation coefficient: -1.44, p=0.028*), assuming that higher muscle strength of the neck muscles is correlated to a heightened sensitivity to pressure. Over all three analyses, the female gender is associated with lower values of pain pressure threshold, which is consistent with literature [3, 7-9, 14]. The FSS showed a significant correlation for the arm region (correlation coefficient: -1.02, p=0.03*) and for the neck/shoulder region (correlation coefficient: -1.96, p=0.006**). So, higher fatigue levels correlate with lower PPT scores (higher sensitivity to pressure) in these regions. These findings emphasize the importance of emotional components in the perception of pain [16, 17]. Psychological therapy approaches should, therefore, not be neglected when dealing with muscle pain, especially in female patients.

The second objective of this study was to determine the influence of muscle properties on patients' musculoskeletal pain. Therefore, non-invasive myotonometry by the MyotonPro was used to identify stiffness, frequency, relaxation, elasticity and creep of the neck extensor muscles of all 81 examined patients. I performed eight correlations between PPT values of the neck and the corresponding muscle properties. After Bonferroni correction, I found significant positive correlations with frequency (muscle tone of the neck muscles) (p=0.003**) and stiffness (resistance of the muscles to external deformation) (p=0.004**) and significant negative correlations with relaxation (time of recovery after deformation) (p=0.005**) and creep (p=0.002**). In summary, decreased pressure sensitivity (high PPT) is associated with high muscle tone, high resistance and short recovery time of the neck muscles. These findings suggest that muscle properties of the neck muscles play an important role in neck pain in patients with NMDs.

Outlook

The presentation of pain characteristics among the different NMD groups in this pilot study contributes to a greater overview and better comparability of the symptomatology in NMDs. It also highlights the variety, complexity and diversity of factors in the development and perception of muscle pain. More research in this area will be needed in the future to better understand influences on muscle pain and to develop therapeutic options as well as individualized and interdisciplinary approaches for its treatment.

Contributions

I, Anna Elena Sagerer, am the first author and principal investigator of both publications of this cumulative dissertation. No shared first authorships were applied.

The project was conceived by Prof. Dr Benedikt Schoser, PD Dr Stephan Wenninger, Marcela Arndt and Natalia Garcia-Angarita. PD Dr. Stephan Wenninger conceptualized the study, wrote the study protocol and received positive approval to conduct the study from the ethics committee of the Medical Faculty of the Ludwig-Maximilians-University Munich on 14.01.2021. The research project was funded by the DGM. Prof. Dr Benedikt Schoser supervised the project throughout its entire duration.

Recruitment of the patients began in January 2021. As part of the structured doctoral programme at LMU Munich, I worked full-time on the project from February 2021 to October 2021 for 8 months. A large part of the data recruitment took place during this time. I managed patient recruitment, study organization, data collection (interviews, motoric tests such as the QMFT and the 6MWT, questionnaires, tests with a PPT algometer and MyotonPro) and data entry. This consisted of selecting and contacting suitable patients, making appointments and carrying out the study procedures, which took 3-4 hours per patient. At the beginning of the data collection, Corinna Wirner-Piotrowski introduced me to the study's methodology. I saw all the patients of this study and conducted all the data collection myself. During this time, I was independently responsible for the project.

I carried out the literature search, literature review, statistical analysis, interpretation and discussion of the results, tables, figures, first and final manuscript drafts, editing, submission process, and revisions independently.

PD Dr Stephan Wenninger supported the critical revision of the manuscripts, the discussion of results, and the revision process and was supervised by Prof. Dr Benedikt Schoser.

Summary

Nociceptive pain significantly impacts patients with NMDs and severely diminishes their quality of life. This cumulative dissertation comprised two publications about one pilot study, including one publication about 20 patients with SMA3 [1] and another publication about 81 patients with various NMDs, including SMA3, LOPD, FSHD, DM1, DM2 and a healthy comparison group [2]. This study evaluated patient-reported outcomes, motor function and muscle strength (using dynamometry and the Quick Motor Function Test [QMFT]), nociceptive pain (using Pressure Pain Threshold [PPT]), and muscle properties through non-invasive myotonometry.

This clinical study intended to identify variations in pain prevalence and characteristics among the six NMDs compared to a healthy control group and to determine whether gender, muscle strength, and emotional factors influence patients' nociceptive pain. Among SMA patients, significantly more women than men experienced musculoskeletal pain [1]. The findings also highlight the role of muscle weakness in nociceptive pain: nociceptive pain in SMA patients seems to be associated with a dysbalanced muscular system because of decreased muscle strength. In the broader NMD cohort [2], pain prevalence varied significantly, with DM2 and FSHD patients experiencing higher pain levels than other NMD subgroups and the control group. Factors such as female gender, high fatigue levels (indicative of depression, anxiety, stress, and impaired quality of life), and low QMFT scores (indicating decreased muscle strength) showed a significant association with heightened pressure pain sensitivity in the arms and legs.

A secondary aim was to investigate whether muscle properties like frequency, stiffness, relaxation, and creep (assessed by myotonometry) are related to muscle pain. For SMA3 patients, muscle pain was connected to muscle weakness but not to changes in muscle properties [1]. In the cohort with more NMDs [2], findings were different: higher muscle tone, higher stiffness, and shorter relaxation time in muscles of the neck correlated significantly with reduced pain, emphasizing the importance of intrinsic muscle tone for pressure pain sensitivity in the neck muscles.

In conclusion, a review of this pilot study in conjunction with a literature search indicates that the influence of emotional and psychological factors such as anxiety, stress, depression and fatigue should not be overlooked. This expanded understanding of the origin of pain demonstrates the necessity for an interdisciplinary approach to its treatment, in addition to physical treatments, particularly in female patients with NMDs.

Zusammenfassung

Nozizeptive Schmerzen beeinträchtigen Patienten mit NMDs erheblich und schränken ihre Lebensqualität stark ein. Diese kumulative Dissertation umfasste zwei Veröffentlichungen im Rahmen einer Pilotstudie, darunter eine über 20 Patienten mit SMA3 und eine weitere über 81 Patienten mit verschiedenen NMDs, darunter SMA3, LOPD, FSHD, DM1, DM2 und eine gesunde Kontrollgruppe. In dieser Studie wurden die von den Patienten berichteten, subjektiven Wahrnehmungen über Schmerzen und Lebensqualität, deren motorische Funktion und die Muskelkraft (mit Hilfe der Dynamometrie und des Quick Motor Function Test [QMFT]), die nozizeptiven Schmerzen (mit Hilfe des Pressure Pain Threshold [PPT]) und die Muskeleigenschaften mit Hilfe der nicht-invasiven Myotonometrie untersucht.

In der klinischen Studie sollten die Unterschiede in der Schmerzprävalenz und -charakteristik der sechs NMD-Untergruppen im Vergleich zu einer gesunden Kontrollgruppe ermittelt werden. Außerdem sollte festgestellt werden, ob Geschlecht, Muskelkraft und emotionale Faktoren die nozizeptiven Schmerzen der Patienten beeinflussen. Unter den SMA-Patienten litten deutlich mehr Frauen als Männer unter Schmerzen des Bewegungsapparats. Die Ergebnisse unterstrichen auch die Rolle der Muskelschwäche bei nozizeptiven Schmerzen: Nozizeptive Schmerzen bei SMA-Patienten schienen mit einer gestörten Muskelbalance als Folge einer verminderten Muskelkraft verbunden zu sein. In der breiteren NMD-Kohorte variierte die Schmerzprävalenz erheblich, wobei DM2- und FSHD-Patienten eine höhere Schmerzprävalenz und -intensität aufwiesen als andere NMD-Untergruppen und die Kontrollgruppe. Faktoren wie das weibliche Geschlecht, ein hohes Maß an Fatigue (das auf Depression, Angst, Stress und eingeschränkte Lebensqualität hinweist) und niedrige QMFT-Werte (die auf eine verminderte Muskelkraft hindeuten) zeigten einen signifikanten Zusammenhang mit einer erhöhten Druckschmerzempfindlichkeit in Armen und Beinen.

Ein sekundäres Ziel war es, zu untersuchen, ob Muskeleigenschaften wie Frequenz, Steifheit, Relaxation und Creep (Verhältnis von Relaxation und Deformationszeit) mit Muskelschmerzen in Verbindung stehen. Bei SMA3-Patienten standen die Muskelschmerzen in Zusammenhang mit der Muskelschwäche, nicht aber mit Veränderungen der Muskeleigenschaften [1]. In der Kohorte mit allen NMDs verhielten sich die Ergebnisse anders: ein höherer Muskeltonus, eine höhere Steifheit und eine kürzere Entspannungszeit in den Nackenmuskeln korrelierten signifikant mit geringeren Schmerzen, was die Bedeutung des intrinsischen Muskeltonus für die Druckschmerzempfindlichkeit in den Nackenmuskeln unterstreicht [2].

Zusammenfassend zeigt eine Überprüfung der Studie in Verbindung mit einer Literaturrecherche, dass der Einfluss emotionaler und psychologischer Faktoren wie Angst, Stress, Depression und Fatigue nicht unterschätzt werden sollte. Dieses erweiterte Verständnis der Entstehung von Schmerzen zeigt die Notwendigkeit eines interdisziplinären Ansatzes bei der Schmerzbehandlung von Patienten mit NMDs, insbesondere bei Patientinnen.

Publication I

Nociceptive pain in adult patients with 5q-spinal muscular atrophy type 3: a cross-sectional clinical study [1]

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ORIGINAL COMMUNICATION

Nociceptive pain in adult patients with 5q-spinal muscular atrophy type 3: a cross-sectional clinical study

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Abstract

Background Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by mutations in the SMN gene, leading to progressive muscular weakness, atrophy and so far neglected musculoskeletal pain. This study is the first to characterize nociceptive pain in patients living with SMA type 3 by assessing whether muscle pain is associated with alterations in muscle strength, function, stiffness, frequency, decrement, relaxation, or creep.

Methods We performed a cross-sectional pilot study on 20 SMA3 patients. We evaluated motor function and muscle strength (dynamometry, quick motor function test and 6-min-walk test), nociceptive pain (pressure algometer evaluating muscular pressure pain threshold (PPT)) and non-invasive measurement of muscle stiffness, frequency, decrement, relaxation, or creep (myotonometry with the MyotonPro®). For statistical analysis, we used *t* tests, Mann–Whitney *U* tests and linear regression.

Results Significantly more women than men reported musculoskeletal pain ($p = 0.003$). A lower score in dynamometry was associated with lower scores in PPT in all extremities reflecting a higher sensitivity of these muscles to pressure. We did not find significant correlations between the PPT values and the MyotonPro values in the corresponding muscles. Assessments of PPT before and after the 6-min walk test did not show clinical meaningful changes. Besides nociceptive pain, fatigue was prevalent in 50% and pain in 55% of the patients.

Conclusions Muscle pain in SMA3 is associated with muscular weakness in the arms and legs, but not with changes in muscular stiffness, frequency, decrement, relaxation, or creep. This shows that muscle pain in SMA3 is mainly caused by changes in the dysbalanced musculoskeletal system due to muscle weakness.

Keywords Nociceptive pain · Spinal muscular atrophy · SMA3 · Clinical outcome · Pain pressure threshold · Myotonometry

Introduction

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder caused predominantly by a homozygous deletion [24] of the SMN1 gene on chromosome 5q13 [11] with the absence of SMN1 in exon 7 [4]. The number of compensatory increased SMN2 copies influences the clinical phenotypes, formerly classified as types 0–4 [17]. Since 2017, three specific therapeutic agents have been approved, including nusinersen, onasemnogene abeparvovec (only for SMA type 1), and risdiplam [7, 13]. As a result of novel specific therapies, the new classification was necessary to reflect the clinical phenotypes more appropriately and now subdivided into "non-sitter", "sitter" and "walker" [12]. In SMA type 3 or walkers, patients develop a slowly progressive proximal muscle weakness and muscular atrophy to a variable degree and rarely restrictive respiratory insufficiency.

The prevalence of pain and fatigue is estimated between 30 and 90% in all types of neuromuscular diseases [6]. Musculoskeletal pain may appear to variable degrees as a primary symptom, but also evolve frequently with the progression of the disease. It is unclear whether the pain is caused by the disease itself or whether ancillary factors such as muscular imbalance or increased muscle tension contribute to amplified pain perception. Nevertheless, pain has a considerable impact on quality of life and disease burden and is often treated negligibly. In SMA type 3 or walkers,

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with the progression of muscular weakness, nociceptive pain occurs in some patients, but clinical studies on pain in these SMA patients are rare. Few recommendations have been published, mainly focusing on pain caused by skeletal deformities and orthopedic corrections [18]. Besides, some surveys have included questions regarding pain in different SMA phenotypes [2, 5, 10]. This is the first clinical study evaluating nociceptive pain in SMA type 3 (walkers).

Methods

Study setting and patient population

This explorative, cross-sectional clinical study aimed to characterize the prevalence, quality, intensity and distribution of musculoskeletal nociceptive pain, and fatigue in adult patients with longstanding SMA3. The second objective was to assess whether muscle pain severity and distribution are associated with alterations in muscle function, muscle strength and muscle stiffness or elasticity. Only adult patients aged ≥ 18 years with genetically confirmed 5q-SMA, clinically type 3/walkers and ability to perform study-related functional tests were enrolled in this study. Because of possible interference between depressive symptoms and pain, patients with a Beck Depression Inventory-Fast Screen score > 3 were excluded from study participation. Other exclusion criteria were participation in another clinical study, use of an investigational treatment, or inability (in the investigator's opinion) to adhere to the requirements of the study. All patients were enrolled at the neuromuscular expert center Friedrich-Baur-Institute at the LMU Munich, Germany. The study was approved by the ethics committee of the LMU Klinikum, Project No. 20–0980, and the protocol was registered on a public clinical trials registry (ClinicalTrials.gov Identifier NCT04907162).

Examinations and methods

Musculoskeletal strength was assessed by the MRC scale (Medical Research Council scale) and dynamometry. Muscle strength was assigned an MRC score with a range from 0 (no movement possible) to 5 (maximum force) for each muscle [3]. Dynamometry was used to document maximum force in kg as the best of three attempts to ensure a high level of objective and precise results. The neck flexor and extensor, shoulder abductor, elbow flexor and extensor, hand extensor, finger flexor, hip flexor, knee flexor and extensor, and foot flexor and extensor, each on the left and right sides were examined.

A pressure algometer was used as a reliable method to quantify local pain by measuring the musculoskeletal pressure pain threshold (PPT) in different muscles. The algometer was placed onto the muscles with a contact area of 1 cm^2 and the stimulus intensity was increased until the patient felt any sensation of pain. The result was taken in kg as the arithmetic mean of three repeats and was recorded on both sides of the trapezius, deltoideus, supraspinatus, biceps brachii, rectus femoris, tibialis anterior and gastrocnemius muscles, as well as the erectors spinii and the neck extensor muscles.

A 6-min walk test (6MWT) and a Quick Motor Function Test (QMFT) were performed to examine the physical function and muscular endurance. The 6MWT [1] was adapted for this study by adding algometer measurements at the lower limbs (*M. rectus femoris* and *M. gastrocnemius*) before and after the 6MWT and evaluating pain symptoms during the test. The QMFT is widely used in assessing neuromuscular diseases, delivering a score of movement and muscle function from 0 to 64 points [22].

For the non-invasive measurement of muscle stiffness, muscle tone, muscle relaxation and viscoelasticity, myotonometry was performed using the commercially available MyotonPro®. The tip of the MyotonPro® is placed perpendicular to the underlying muscle. A slight pressure with a constant preload induces an oscillation, which leads to a short-term deformation of the underlying muscle. An acceleration sensor now analyzes the vibration behavior of the muscle and the viscoelastic stiffness is calculated. The calculation is based on the stiffness of the muscle (in N/m), the elasticity (the ability of the muscle to return to its initial shape) and the duration required for this. Values of the MyotonPro were assessed for the neck extensor muscles, the trapezius, supraspinatus, deltoideus, biceps brachii, erectors spinii, rectus femoris, tibialis anterior and gastrocnemius muscles on both sides. The MyotonPro® was rated as having an excellent test–retest reliability for most muscles [3], but was hardly described in any neuromuscular disease.

Disease-related history and pain profile

The characteristics of both pain types were explained to the patient to differ between nociceptive and neuropathic pain. Pain that could not be assigned to nociceptive pain (i.e., mixed pain, often experienced in the back) was also captured in the study. Before the clinical examination, disease-related history, medical history and disease- and quality-of-life-related questionnaires (FSS, BPI and German Pain Questionnaire) were obtained. Historical data were collected with a focus on the intensity, frequency, and quality of nociceptive pain and previous and current drug use or non-drug therapy methods (physiotherapy, manual therapy) and surgery influencing the myalgia. The Fatigue Severity Scale (FSS) includes nine questions and evaluates the severity of fatigue, i.e., physical and mental exhaustion and its influence on the quality of life. The FSS total score is the

average of the nine-item scores and ranges from 1 ("no signs of fatigue") to 7 ("most disabling fatigue"). For this study, a cutoff value greater than four was chosen for evaluating the presence of fatigue [20]. The FSS was originally designed for people with multiple sclerosis or systemic lupus erythematosus [9] and is also currently used for the evaluation of fatigue in various neuromuscular diseases such as Pompe disease [8], spinal muscular atrophy type 2 and congenital myopathies [23]. The Brief Pain Inventory is a questionnaire on the severity of pain and impairment of function caused by the pain in the past 24 h. The questionnaire consists of a map of the human body on which the patient should mark the distribution of the nociceptive pain. Furthermore, the results of the BPI are two scores [16]. The pain intensity score is calculated using four items on pain intensity (strongest pain, lowest pain, average pain, pain at the moment). Each item is rated by the patient from 0 (no pain) to 10 (worst imaginable pain) and contributes with the same weighting to the final score (0–40 points). For a pain interference score, seven subpoints (general activity, mood, ability to walk, normal gait, relationships with other people, sleep and quality of life) are rated from 0 (not disruptive) to 10 (completely disruptive) and contribute with the same weighting to the final score (0–70 points). The BPI is a widely used questionnaire on pain [16] and is internationally recommended for the assessment of chronic pain in various clinical trials [21].

A detailed description of pain was evaluated with the German Pain Questionnaire (GPQ), including pain sites, duration, intensity, pain-relieving and -aggravating conditions and subjective pain perception [14]. The GPQ is based on a bio-psycho-social pain model and therefore includes questions regarding the prevalence of depression, fear and stress, comorbidities, social situation and disease-related quality of life. The GPQ has been developed and validated by the Taskforce on "Standardization and Economy in Pain Management" of the German Chapter of the International Association for the Study of Pain (DGSS) [19].

The DASS (Depression, Anxiety and Stress Scale) is a brief and reliable questionnaire [15]. The questionnaire contains 21 questions, 7 items each for depression, anxiety and individual stress. In comparison to the BDI, which was designed for a psychiatric assessment of depression, the questions are worded less drastically, so patients are less deterred by them. Therefore, sensitivity to weaker psychiatric disorders is higher on the DASS. For each of the three scales, cutoff values were set for an increased likelihood of the presence of depressive disorder (cutoff: > 10 points), anxiety disorder (cutoff: > 6 points) or increased stress load (cutoff: > 10 points).

The Marburg Questionnaire (MFHW) was used to assess habitual well-being in relation to perceived pain. It consists of seven questions regarding mental, physical and emotional well-being and performance despite the experienced pain. It provides additional information compared with the DASS by addressing positive abilities of the patients. The maximum score is 35 points, indicating a particularly high level of well-being. A score of ten points and below is a low value of habitual well-being in pain patients.

A detailed description of pain was evaluated with the German Pain Questionnaire (GPQ), including pain sites, duration, intensity, pain-relieving and -aggravating conditions and subjective pain perception [14]. The GPQ also included questions regarding the prevalence of depression, fear and stress, comorbidities, social situation and disease-related quality of life.

Statistical analysis

SPSS Statistics® Version 27 and Microsoft Excel® 2016 were used for the analysis. For the illustrations of the human body, BioRender® was used. All data were graphically checked for normal distribution. For all metric, normally distributed values, we performed an unpaired, two-sided *t* test. For all non-parametric values, we performed a Mann–Whitney *U* test. For the change in PPT values before and after the 6MWT, we performed a paired two-sided *t* test or a Wilcoxon rank test. The significance level (alpha) was set at ≤ 0.05.

Results

All patients gave written informed consent before the first assessment. Of 25 patients screened for eligibility, 20 patients were enrolled in the study. Two patients declined to participate after study information, and three patients were not eligible due to a score of ≥ 4 in BDI-Fs at screening. Because of the significantly different perceptions of pain in men and women (Table 1), we divided the SMA patients into a male and a female subgroup to identify different sex-dependent pain patterns.

Baseline demographics and characteristics

Baseline demographics are provided in Table 1. All 20 patients (13 male, 65%) had genetically confirmed 5q spinal muscular atrophy. At baseline, the median age was 40.5 years, age at first symptom 11 years and age at diagnosis 16 years. No statistically significant differences were found between men and women regarding baseline demographics, reflecting an equal distribution. Four men (31% of the male cohort) and all seven women reported pain ($p = 0.003$). Two patients (26.8%) took pain medication irregularly as needed due to muscle pain. The pain was chronic (experienced for longer than 6 months) in ten patients. The pain was only nociceptive in six patients and

Table 1 Demographic characteristics of the enrolled 5Q-SMA3 patients

	Male	Female	Total	*p* value
Number (percent)	*N* = 13(65%)	*N* = 7(35%)	*N* = 20	0.18
Age at baseline (years)				
Mean (± SD; min; max)	40.15 (± 12.48; 20; 57)	34.71(± 14.74; 20; 54)	38.25 (± 13.19; 20; 57)	0.39
Age at first symptom (years)				
Mean (± SD; min; max)	12.54 (± 9.85; 2; 40)	7.29 (± 4.68; 2; 14)	10.70 (± 8.65; 2; 40)	0.20
Age at diagnosis (years)				
Mean (± SD; min; max)	18.15 (± 13.2; 4; 51)	18.57 (± 15.43; 5; 48)	18.30 (± 13.64; 4; 51)	0.95
Disease duration (years)				
Mean (± SD; min; max)	27.62 (± 13.05; 9; 53)	27.43 (± 13.35; 11; 49)	27.55 (± 12.80; 9; 53)	0.938
SMN2 copies				
Mean (± SD; min; max)	3.77 (± 0.44; 3; 4)	3.71 (± 0.49; 3; 4)	3.75 (± 0.44; 3; 4)	0.80
BMI*				
Mean (± SD; min; max)	24.24 (± 5.01; 17.5; 35.5)	25.26 (± 4.27; 20.5; 31.2)	24.60 (± 4.68; 17.5; 35.5)	0.66
Mobility				0.154
Ambulant	*N* = 7 (54%)	*N* = 6 (86%)	*N* = 13 (65%)	
Non ambulant	*N* = 6 (46%)	*N* = 1 (14%)	*N* = 7 (35%)	
Disease-specific therapy				
Nusinersen	*N* = 13 (100%)	*N* = 7 (100%)	*N* = 20 (100%)	
Therapy since (years)	3.07 (± 0.65; 2; 4,1)	3.05 (± 0.57; 2.5; 4.1)	3.06 (± 0.61; 2; 4.1)	0.877
Start at age	37.0 (± 12.4; 18; 54)	31.3 (± 15.5; 16; 52)	35 (± 13.5; 16; 54)	0.241
Report of pain (historical)	*N* = 4 (31%)	*N* = 7 (100%)	*N* = 11 (55%)	**0.003***
Nociceptive	*N* = 2	*N* = 4	*N* = 6	
Mixed	*N* = 1	*N* = 4	*N* = 5	
Chronic pain (> 6 months)	*N* = 4 (31%)	*N* = 6 (86%)	*N* = 10 (50%)	
Pain during 6MWT	*N* = 0 (0%)	*N* = 2 (28.6%)	*N* = 2 (10%)	0.202
Pain-specific therapy**	*N* = 0 (0%)	*N* = 2 (28.6%)	*N* = 2 (28.6%)	0.060
Number of body parts affected by pain	1.5 ± 0.6	3.9 ± 2.6	3 ± 2.4	
FSS points***	3.955	4.114	4.011	0.699
Presence of fatigue***	*N* = 6 (46%)	*N* = 4 (57%)	*N* = 10 (50%)	0.64
QMFT				
Mean (± SD; min; max)	27.23 (± 15.09; 5; 56)	34.83 (± 14.13; 10; 53)	29.63 (± 14.85; 5; 56)	0.313
MRC sum score****				
Mean (± SD; min; max)	82.5 (± 16.3; 51; 108.5)	91.4 (± 11.24; 77; 105.5)	85.63 (± 15.07; 51; 108.5)	0.215

*BMI = weight[kg]/(height [m])^2; **All patients took ibuprofen 600 mg one to four times a month as pain-specific treatment. ***Points in the Fatigue Severity Scale (1–7 points); for the presence of fatigue, a cutoff > 4 points was chosen; ****MRC sum score was calculated by summing MRC of 12 muscles or regions (both sides), ranging from 0 (complete paralysis) to 110 (normal strength): neck flexors and extensors, deltoid, biceps brachii, triceps brachii, hand extensors, finger flexors, iliopsoas, knee flexors and extensors as well as foot flexors and extensors, each of them ranged from 0 (complete paralysis) to 5 (normal strength)

All significant values are bold

mixed in five patients. All patients received nusinersen as a specific disease treatment. 13 (65%) patients were ambulant and could perform the 6MWT. In seven (35%) patients who were either wheelchair dependent or only able to walk a few steps, the 6MWT was not performed. There was no significant difference between men and women in any category regarding muscle strength, muscle function (assessed by the QMFT) or fatigue.

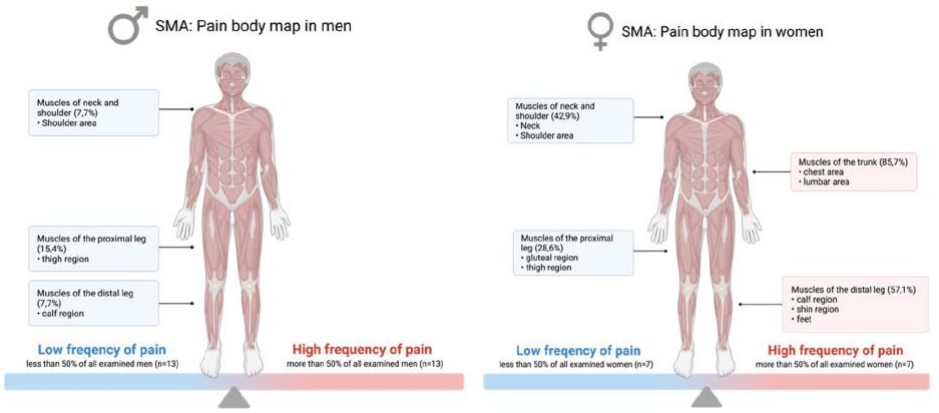

Fig. 1 Frequency of pain in all examined men ($N=13$) and women ($N=7$)

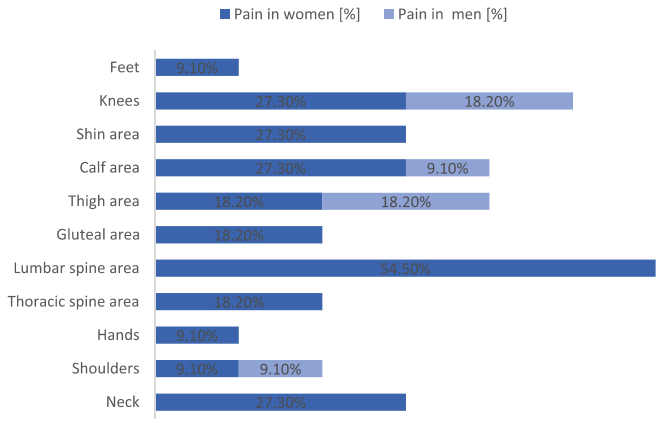

Fig. 2 Location of perceived pain in all patients reporting pain ($n=11$). Percentage of patients experiencing pain in different locations of all 11 patients reporting pain

Fatigue

Prevalence of fatigue (FSS score > 4) was high within the cohort (50% of all patients) and was present in six male (46%) and four female (57%) patients.

Pain frequency and distribution

55% ($n=11$) of the SMA patients reported nociceptive or mixed pain with a high localization and strength variability, visualized in Figs. 1 and 2. Most of the patients reporting pain suffered from pain attacks ($n=9$, 81.8%), and only two patients reported permanent pain (18.2%). Overall, the pain was perceived in declining frequency in the lumbar spine region (54.5%), the legs, especially in the knees (45.5%) and in the neck (27.3%).

Women with SMA experienced pain significantly more often ($p=0.003$; Table 1), and the distribution of pain differed between men and women (Figs. 1 and 2). In women, the pain was reported most frequently in the trunk/chest muscles, lumbar region, distal leg muscles, and less frequently in the shoulder and neck muscles and proximal leg muscles. Men reported pain less regularly and only in the shoulders and legs (proximal and distal). Furthermore, women experienced pain in a higher number of various

regions of their body (3.9 ± 2.6 different locations in women versus 1.5 ± 0.6 other locations in men; Table 1).

Pain quality and intensity

Pain characteristics are reported in Table 2. Most frequently, the pain was described as pulling, oppressive and dull. In 81.8%, the pain was described as pain attacks with a duration of minutes (45.5%) or seconds (18.2%). In 54.5%, no daily dependency was reported. Pain severity was rated as mild to moderate on a scale from 0 to 10: Within the last 4 weeks, the maximum pain severity evaluated by the numeric rating scale (NRS) was 3.91 (SD ± 2.12), and the mean pain score was 1.73 (SD ± 1.19). The pain severity score in the last 48 h, evaluated by BPI, was higher in women (4 ± 3.8) than in men (2.8 ± 1.3), whereas the pain interference score was higher in men (11.5 ± 13.9) than in women (7.1 ± 9.8). There were also differences in the categories of interference that were most affected by the pain (on an interference scale from 0 to 10; 0 = no interference, 10 = high interference). In women, enjoyment of life (1.43), activity (1.43) and general mood (1.29) were most affected by pain. In men, interferences with walking (3), work (2.25), enjoyment of life (2), relationships (1.5) and sleep (1.5) were most affected.

Physical and mental comorbidities

Comorbidities and habitual well-being are presented in Table 3. Although women experienced pain significantly more often and with a higher severity, women experienced higher habitual well-being than men (27.4 ± 6.3 vs 21 ± 11). Results of the DASS showed lower values for depression and stress disorders and equal values for anxiety disorders in women with pain compared to men with pain. However, men without pain reported the lowest values for depression, stress and anxiety. Comorbidities were more common in men than in women, especially cardiovascular and gastrointestinal disorders. One male and two female patients with nociceptive pain had scoliosis, and two women reported cervical spine stenosis. 100% of the women regularly attended physical therapy, compared to 75% of the men with pain and 56% of the men without pain.

Pain triggers and relievers

Pain triggers are summarized in Table 4. Most frequently, the pain was triggered by doing too much exercise or physical exertion, such as running or walking for too long (63.6%; $N = 7$). To relieve the pain, most patients chose relaxation, for example, going for a walk or resting (72.7%; $N = 8$). In general, movement and exercises were associated with pain triggers and pain relievers. Two female patients used pain-specific treatment: both took ibuprofen 600 mg as needed up to four times a month. One female patient tried massage and hot baths for pain relief, but with only minimal benefit.

SMA-specific treatment

All patients received nusinersen as disease-specific treatment at baseline (starting at age 35 with a mean therapy duration of 3.06 years; Table 1). None of the patients reported an impact on pain or fatigue occurrence, neither a change in frequency, intensity, characteristics or fluctuation of pain.

Objective assessments: PPT, dynamometry and MyotonPro® results

Pain pressure threshold values and muscle strength

Pain pressure threshold (PPT) was lower in women than in men in nearly all muscles (Fig. 3). However, the differences between men and women were only slightly statistically significant in the M. rectus femoris on the left side ($p = 0.037$; Supplements Table 1), which was no longer evident after Bonferroni correction (significance level was set at alpha = 0.003). Figure 3 highlights the force needed to induce pain in men compared to women, displayed for nine different muscles.

For a linear regression model, we summarized PPT values of four body regions: the arms (deltoid and biceps brachii), legs (rectus femoris, tibialis anterior and gastrocnemius muscles), shoulder and neck region (supraspinatus, trapezius and neck extensor muscles) and trunk (erector spinii muscles) (Table 5). We also summarized the dynamometer scores for an arm (dynamometer values for the biceps brachii, the triceps brachii and the deltoid muscles) and a leg region (hip flexion, knee extension and knee flexion, foot extension and foot flexion). Because the legs were particularly affected in the patients, we divided the leg region into a proximal and a distal part. Data were visually scanned for autocorrelation and homoscedasticity. Pressure pain threshold values show a positive regression for the arm ($p = 0.041$*) and the leg region ($p = 0.024$*), especially for the distal part ($p = 0.022$*), but not for the shoulder and neck region or for the trunk region (Table 2). A lower score in dynamometry was associated with lower scores in PPT in the extremities, reflecting a higher sensitivity of these muscles to pressure.

Parameters of the MyotonPro

Correlation with the parameters of the MytonPro® are presented in Table 6. In a Kendall's Tau correlation for the PPT of each muscle and their corresponding MyotonPro® parameter, such as frequency, stiffness, decrement, relaxation and creep, only the PPT of the rectus femoris on the right

Table 2 Pain characteristics

Pain characteristics	Pain in women ($n=7$)	Pain in men ($n=4$)	Pain in men and women ($n=11$)
Pain severity score mean (last 48 h) (0–40)	4 ± 3.8	2.8 ± 1.3	3.5 ± 3.1
Pain interference score mean (last 48 h) (0–70)	7.1 ± 9.8	11.5 ± 13.9	87 ± 11
Pain severity score mean (last 4 weeks)			
Highest score	4.29 ± 1.89	3.25 ± 2.63	3.91 ± 2.12
Mean score	2.00 ± 0.58	1.25 ± 1.89	1.73 ± 1.19
Pain characteristics			
Emotional characteristics	57%	25%	46%
Dull	71%	50%	64%
Oppressive	86%	50%	73%
Throbbing	43%	25%	36%
Knocking	29%	25%	27%
Stabbing	57%	25%	36%
Pulling	86%	100%	91%
Hot	14%	0%	9%
Burning	29%	50%	36%
Impairment (score from 1 to 10) of			
Ability to walk	1.00 ± 1.92	0.92 ± 2.25	1.73 ± 2.61
Normal gait	1.00 ± 1.67	0.69 ± 1.70	1.45 ± 1.86
Sleep	1.00 ± 1.53	0.46 ± 1.66	1.18 ± 2.04
Enjoyment of life	1.43 ± 2.94	0.62 ± 1.50	1.64 ± 2.62
Relationships with other people	0.00 ± 0.00	0.46 ± 1.39	0.55 ± 1.51
General activity	1.43 ± 2.15	0.15 ± 0.38	1.09 ± 1.76
Mood	1.29 ± 2.98	0.23 ± 0.60	1.09 ± 2.39
Fluctuations and attack durations			
Permanent pain	28.6% ($N=2$)	0%	18.2% ($N=2$)
Pain attacks	71.4% ($N=5$)	100% ($N=4$)	81.8% ($N=9$)
Attack duration			
Seconds	28.6% ($N=2$)	0%	18.2% ($N=2$)
Minutes	14.3% ($N=1$)	100% ($N=4$)	45.5% ($N=5$)
Hours	14.3% ($N=1$)	0%	9.1% ($N=1$)
Up to 3 days	14.3% ($N=1$)	0%	9.1% ($N=1$)
Attack frequency			
Several times daily	14.3% ($N=1$)	25% ($N=1$)	18.2% ($N=2$)
Daily	14.3% ($N=1$)	0%	9.1% ($N=1$)
Weekly	14.3% ($N=1$)	75% ($N=3$)	36.4% ($N=4$)
Monthly	14.3% ($N=1$)	0%	9.1% ($N=1$)
Less often	14.3% ($N=1$)	0%	9.1% ($N=1$)
Daily dependance			
None	28.6% ($N=2$)	100% ($N=4$)	54.5%
In the morning	28.6% ($N=2$)	0%	18.2%
In the evening	14.3% ($N=1$)	0%	9.1%
In the night	28.6% ($N=2$)	0%	18.2%
Time since onset of pain			
< 1 month	14.3% ($N=1$)	0%	9.1% ($N=1$)
1 month to ½ year	0%	0%	0%
1/2 year to 1 year	0%	25% ($N=1$)	9.1% ($N=1$)
1 year to 2 years	14.3% ($N=1$)	0%	9.1% ($N=1$)
2 year to 5 years	28.6% ($N=2$)	0%	18.2% ($N=2$)
> 5 years	42.9% ($N=3$)	75% ($N=3$)	54.5% ($N=6$)

Table 3 Physical and mental comorbidities, physiotherapy and general well-being in women and men with and without pain

	Women with pain ($n=7$)	Men with pain ($n=4$)	Men without pain ($n=9$)
MFHW* (mean ± SD, min; max)	27.4 ± 6.3; 18; 34	21 ± 11; 10; 32	–
Depression score (mean ± SD, min; max)	2.1 ± 1.8; 0; 5	3.3 ± 3.2; 1; 7	1.1 ± 2.4; 0; 7
Anxiety score (mean ± SD, min; max)	2.7 ± 3.9; 0; 11	2.7 ± 1.5; 1; 4	1.9 ± 2.4; 0; 7
Stress score (mean ± SD, min; max)	4.1 ± 4.1; 0; 11	5.3 ± 5.8; 2; 12	2.5 ± 4.4; 0; 13
Physiotherapy	100%	75%	56%
Comorbidities			
Musculosceletal	57% ($n=4$)	25% ($n=1$)	–
Cardiovascular	–	–	22.2% ($n=2$)
Gastrointestinal	–	25% ($n=1$)	11.1% ($n=1$)
Skin	–	25% ($n=1$)	–

Musculoskeletal comorbidities in women with pain: cervical spine stenosis ($n=2$), scoliosis ($n=2$)

Musculoskeletal comorbidities in men with pain: scoliosis ($n=1$); Other comorbidities in men: cardiovascular: hypertension ($n=2$); gastrointestinal: diverticulosis ($n=1$) and reflux disease ($n=1$); skin: psoriasis ($n=1$)

*MFHW (Marburg questionnaire on habitual well-being despite the perceived pain): maximum (35 points) means particularly great well-being

Table 4 Pain-relieving and -aggravating conditions

	Women and men experiencing pain ($N=11$)
Pain-aggravating conditions	
Too much exercise and physical exertion, i.e., running or walking too much	63.6% ($N=7$)
Wrong posture	27.3% ($N=3$)
Falls	18.2% ($N=2$)
Wrong moves	18.2% ($N=2$)
Immobility	9.1% ($N=1$)
Overweight	9.1% ($N=1$)
Pain-relieving conditions	
Relaxation, i.e., going for a walk or resting	72.7% ($N=8$)
Strengthening the muscles by doing specific exercises such as physiotherapy	36.4% ($N=4$)
Warmth	18.2% ($N=2$)
Distraction, i.e., reading a book	18.2% ($N=2$)

side correlated negatively with its decrement ($p=0.044$, $r=-0.349$). The regression model was not significant ($R=0.368$, $R^2=0.135$, $p=0.133$).

6MWT

Results of the adapted 6MWT in 13 patients are shown in Table 7. There was no significant difference in the distance walked between women and men. Only two women experienced pain during the 6MWT. A comparison of PPT values before and after the 6MWT of the rectus femoris and the gastrocnemius muscles showed a slight increase in men, reflecting less pressure pain. In contrast, a slight decrease was found in women. The pre–post difference was only statistically significant for the rise in the right rectus femoris muscle for men ($p=0.034$), and further analysis using Cohen's d suggests a high effect size ($d=0.79$).

Study limitations

Despite the relatively high number of SMA patients regularly seen at the neuromuscular expert centre, only a small number of patients were eligible or consented to participation in this study, making a comprehensive statistical analysis of factors influencing nociceptive pain not reasonable. On the other hand, this is the first study in a sufficient number of patients with longstanding SMA3 evaluating nociceptive pain by combining results from clinical assessments, medical history and pain-related questionnaires.

Discussion

We conducted this pilot study of nociceptive pain in longstanding SMA 3 (walkers) patients, which is the first to our knowledge that combines results from medical history, clinical assessments and pain-specific and health-related patient-reported outcomes. In summary, muscle pain in SMA3 is reported by approximately 50% of the patients and musculoskeletal dysbalance due to regional muscle weakness seems to be the underlying cause. Due to our findings, muscle pain is associated with muscular weakness in the arms and legs, but not with changes in muscular stiffness, frequency, decrement, relaxation or creep.

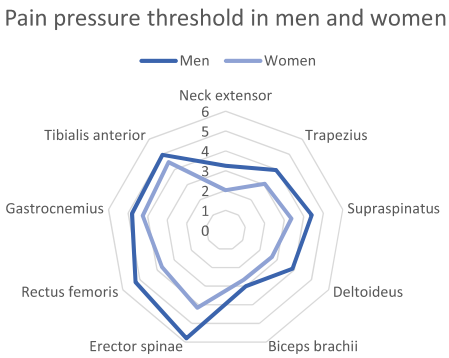

Fig. 3 PPT values [kg] in men ($N=13$) and women ($N=7$). Mean force, displayed in kilogram, needed to induce pain in the muscle. The patients were separated into a female ($n=7$) and a male ($n=13$) subgroup. Nine different muscles were examined on both sides

Measurements of pressure pain threshold (PPT) were lower in women than in men in nearly all muscles, indicating a higher susceptibility of pain perception in women. In healthy volunteers, examinations [7] showed that male sex and higher age are associated with higher PPTs in some muscles. However, differences between men and women were only statistically significant in the rectus femoris muscle on the left side ($p=0.037$; supplements). Besides, we found an association between muscle strength and algometer scores of the arms and legs in the linear regression model (Table 2), especially in distal limbs. A lower score in dynamometry was associated with lower scores in PPT, which reflects a higher muscular sensitivity to pressure in weaker muscles.

Assessments of pressure pain threshold (PPT) before and after the 6-min walk test, which reflects a standard test for muscular endurance in neuromuscular disorders, did not show valuable or clinical meaningful change. Of the cohort, only two women complained of muscular pain after the 6MWT. Besides, patients reported a way of pain relief due to muscle exercise, but also a high number complained about muscle pain after too much exercise and physical exertion. Only two female patients used pain-specific medication. Although conclusions should be made very carefully due to the small sample size, our results do not indicate that muscle endurance activity measured by the 6MWT induces muscle pain or lowers the pain threshold. As reported by patients, muscular endurance exercises may be more beneficial for pain reduction than provoking pain, as long as muscles are not overstressed. Overall, further research is necessary for the efficacy of muscle training in SMA patients to prevent muscle wasting and muscle pain and maintain muscle strength as long as possible.

Table 5 Linear regression for PPT (pressure pain threshold) as a dependent variable

PPT summarized [kg]	Dynamometer arm [kg]	MRC trunk	MRC neck extensor	Dynamometer leg [kg]	p (model)	R	R^2	Adjusted R^2	Regression model
Arm region	**0.041***	–	–	–	**0.041***	0.461	0.213	0.169	11.119 + 0.065 * x
Trunk region	–	0.862	–	–	–	–	–	–	–
Leg region	–	–	–	**0.024***	**0.024***	0.561	0.315	0.266	21.158 + 0.157 * x
Proximal leg region	–	–	–	Proximal leg values: 0.159	–	–	–	–	–
Distal leg region	–	–	–	Distal leg values: **0.022***	**0.022***	0.568	0.323	0.275	13.258 + 0.139 * x
Shoulder and neck region	0.127	–	0.650	–	–	–	–	–	–

A linear regression model was performed to identify a relationship between pressure pain threshold values and muscle strength in different body regions (arm region, trunk region, leg region, shoulder and neck region). Pressure pain threshold were calculated by summarizing PPT [kg] of specific muscles for each body region. To evaluate muscle strength, MRC or dynamometer values were used. For the arm and leg region, muscle strength was evaluated by summarizing dynamometer values [kg] for legs respectively arm muscles. For the neck and trunk region, MRC (Medical Research Council) scale was specified for the neck extensor muscles and the muscles of the trunk by assigning a value from 0 (complete paralysis) to 5 (normal strength)

*Significance at a level ≤ 0.05

All significant values are bold

Table 6 Significance of correlations (Kendall's Tau) between PPT values with their corresponding myoton parameters (frequency, stiffness, decrement, relaxation, creep) in the same muscle

Corresponding PPT and MyotonPro parameters	Frequency	Stiffness	Decrement	Relaxation	Creep
Neck extensor right	0.268	0.140	0.853	0.538	0.712
Neck extensor left	0.891	0.585	1.000	0.750	0.339
Deltoid right	0.342	0.210	0.255	0.224	0.270
Deltoid left	0.618	0.648	0.676	0.835	0.803
Biceps brachii right	0.467	0.423	0.360	0.593	0.674
Biceps brachii left	0.879	0.425	0.380	0.424	0.254
Supraspinatus right	0.433	0.563	0.303	0.563	0.301
Supraspinatus left	0.402	0.483	0.117	0.364	0.386
Trapezius right	0.964	0.752	0.964	1.000	0.822
Trapezius Left	0.116	0.231	0.215	0.200	0.200
Erector spinae right	0.221	0.557	0.442	0.684	0.964
Erector spinae left	0.786	1.000	0.443	0.717	0.588
Rectus femoris right	0.240	0.596	**0.044***	0.289	0.362
Rectus femoris left	0.053	0.240	0.211	0.053	0.069
Tibialis anterior left	0.359	0.342	0.386	0.342	0.277
Tibialis anterior right	0.650	0.155	0.836	0.302	0.252
Gastrocnemius right	0.569	0.791	0.068	0.733	0.543
Gastrocnemius left	0.836	0.741	0.117	0.901	0.967

All significant values are bold

Table 7 6MWT and PPT values before and after physical exertion

	Men ($N=13$)	Women ($N=7$)	Women and men ($N=20$)
6MWT performed	61.5% ($N=8$)	71.4% ($N=5$)	65% ($N=13$)
6MWT meters			
Mean	397.5	443.6	415.23
Median	452.5	466	466
Sensation of pain during 6MWT	0% ($N=0$)	28.6% ($N=2$)	($N=2$)
Rectus femoris muscle:			
PPT before 6MWT right/left [kg]	6.29/6.14	4.22/3.84	5.49/5.25
PPT after 6MWT right/left [kg]	7.03/6.64	3.48/3.52	5.66/5.44
Difference right/left [kg]**	+0.74/+0.5	− 0.74/− 0.32	+0.17/+0.19
Difference right/left [%]	+11.8%/+8.1%	− 17.5%/− 8.3%	+3.1%/+3.6%
p* right/left	**0.034***/0.265	0.051/0.246	0.562/0.530
Cohens D	0.79/-	−/−	−/−
Gastrocnemius muscle:			
PPT before 6MWT right/left [kg]	5.43/5.35	3.82/3.36	4.82/4.58
PPT after 6MWT right/left [kg]	5.45/5.35	3.80/3.22	4.82/4.53
Difference right/left [kg]**	+0.02/+0.00	− 0.02/− 0.14	+0.00/− 0.05
Difference right/left [%]	+0.00%/+0.00%	− 0.00%/− 4.2%	±0.0%/− 1.09%
p* right/left	0.97/1.00	0.936/0.611	1.00/0.812
Cohens D	−/−	−/−	−/−

*Results of PPT were not normally distributed (Shapiro–wilk test); group differences were assessed by a paired t test. Bold values indicate significant difference for $p \leq 0.05$. Gastrocnemius PPT test results were not normally distributed, group differences were assessed by Wilcoxon signed rank test. **Positive higher values reflect less pressure pain

We did not find correlations between the PPT values and the MyotonPro values for frequency, stiffness, decrement, relaxation and creep in the corresponding muscles. The only statistically significant correlation was found between the PPT of the rectus femoris on the right side and the decrement of the right side (Kendall's Tau $p=0.044$, correlation coefficient $=-0.349$; $R^2=0.135$). PPTs of the rectus femoris muscle decrease with higher decrement values equivalent to lower elasticity values (decrement is inversely proportional to elasticity). Elasticity is a measure of the muscle's ability

to recover its initial shape after deformation. The lower elasticity of the muscle, the lower the PPTs.

Although women experienced pain significantly more often and with a higher severity, they experienced a higher habitual well-being and lower scores for depression, anxiety and stress than men experiencing pain. Thus, the higher perception of pain in women does not appear to be affected by these psychological comorbidities. Musculoskeletal comorbidities occurred in both men and women (scoliosis and cervical spine stenosis), but could not explain the high proportion of low back pain in women.

Comparison with results of previous studies is difficult to make, as most of them were questionnaire based and none included objective clinical assessments. A survey from de Groot et al. [5] summarized physical complaints in longstanding SMA type 3 patients and a severe disease course to determine whether new symptoms arise with increased age. The high prevalence of fatigue of 61.4% corresponds to our findings, but the prevalence of muscle pain was significantly higher in our cohort (31.4% vs 55%). Considering the results of both studies, back pain (27.1%) and neck pain (34.3%) were essential complaints of SMA3 patients (Figs. 1and 2). In contrast, a survey from Abresch et al. [2] evaluated pain profiles of various neuromuscular diseases, including 29 patients with SMA3. As the main result of this survey, the prevalence of pain and pain sensitivity evaluated for the SMA type 2 and type 3 group was not significantly different from a US population (30.2% in the SMA group vs 31.8% in the US population reporting good health and no pain). In the SMA group, the pain was affected by gender, which fits the results of our study reporting a higher pain prevalence in female patients.

Even though a potential effect on pain of nusinersen was not a predefined outcome, our data suggest that there is no relevant impact on the occurrence or frequency or intensity of pain, which might be due to a relatively short-term specific therapy in longstanding chronic disease. But further particular studies are needed to evaluate the effect of SMA specific therapies on nociceptive pain.

Overall, muscle pain in SMA type 3 cannot be explained by changes in muscular stiffness, frequency, decrement, relaxation or creep. This shows that muscle pain in SMA type 3 is mainly caused by changes in the dysbalanced musculoskeletal system, caused by (regional) muscular weakness. As our conclusions are based on a relatively small cohort, we suggest evaluating pain in SMA3 in larger cohorts in the future.

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Author contributions ES: statistical analysis and interpretation of data, discussion of results, critical revision of the manuscript for intellectual content, first and final manuscript draft, a guarantor who accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. SW: statistical analysis and interpretation of data, discussion of results, critical revision of the manuscript for intellectual content. CW: data aquisition, discussion of results, critical revision of the manuscript for intellectual content. BS: discussion of results, critical revision of the manuscript for intellectual content.

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Availability of data and material The anonymized participant data presented here are available upon request from the correspondent author (stephan.wenninger@med.uni-muenchen.de).

Declarations

Conflicts of interest All authors report no disclosures regarding this study. Outside of this context, SW has received research grant by the DGM—Deutsche Gesellschaft für Muskelkranke e.V. He has served on advisory boards for Alexion Pharma, CSL Behring and Sanofi Genzyme GmbH. He received funding for travel or speaker Honoraria from Sanofi-Aventis Germany GmbH; SH Glykogenose Gesellschaft; AbbVie Germany GmbH; Recordati Pharma GmbH; CSLBehring GmbH; Alexion Pharma GmbH; Desitin Germany; Akcea GmbH. Outside of this context, BS has served on advisory boards for Alexion, Argenex, Amicus, Astellas, Spark, and Sanofi; he has undertaken contracted unrestricted research for Sanofi and Amicus; and has received honoraria from Kedrion. The other authors have no conflicts of interest to declare.

Ethical approval The study was approved by the ethics committee of the LMU Klinikum, Project No. 20–0980, and the protocol was registered on a public clinical trials registry (ClinicalTrials.gov Identifier NCT04907162).

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Publication II

Nociceptive pain in patients with neuromuscular disorders - a cross-sectional clinical study [2]

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Research Report

Nociceptive Pain in Patients with Neuromuscular Disorders – A Cross-Sectional Clinical Study

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Abstract.
Background: Muscle pain is a common symptom in patients with neuromuscular disorders (NMD) and accounts for severely reduced quality of life. OBJECTIVE: This clinical study aimed to observe possible differences in pain prevalence among distinct NMDs and to determine whether the patients' nociceptive pain is influenced by gender, muscle strength and psychological factors and to examine potential pain-associated alterations in muscle properties.
Methods: The cross-sectional study on nociceptive pain in various NMDs involved patient-reported outcomes, muscle strength evaluations (dynamometry and quick motor function test (QMFT)), nociceptive pain evaluations (muscular pressure pain threshold (PPT)), and non-invasive measurement of muscle stiffness, frequency, decrement, relaxation, and creep (myotonometry).
Results: Involving 81 NMD patients and a control group, the study found high variability in pain prevalence among the subgroups. Patients with DM2 and FSHD had significantly higher levels of pain prevalence compared to other examined NMD subgroups and the control group. Female gender, high fatigue levels (representing factors such as depression, anxiety, stress, and impairment of quality of life), and low QMFT scores (representing reduced muscle strength) showed an association with increased sensitivity to pressure pain in the arm and leg region. As assessed by myotonometry, less pain is experienced in neck muscles with a high muscle tone, high stiffness, and a short relaxation time highlighting the importance of intrinsic muscular tone for their pressure pain sensitivity.
Conclusion: Individualized therapeutic concepts including psychological and physical approaches in the pain management of patients with NMDs, especially in women, should be considered. Further research in this field is necessary to gain a more detailed insight into the perception of muscle pain.

Keywords: Nociceptive pain, neuromuscular diseases, pain threshold, myotonometry, dynamometry

INTRODUCTION

The estimated prevalence of pain and fatigue in patients with neuromuscular disorders (NMD) ranges from 30–90% but without differentiation, whether pain is directly associated with muscle disease or secondary due to muscular-skeletal problems [1]. Results of surveys indicate that pain, as a common secondary problem in patients with NMD, has a major impact on their quality of life [2–5]. In

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some neuromuscular diseases, musculoskeletal pain manifests as one of the initial symptoms, while in others, pain gradually develops as the disease progresses. Findings in pain research are often difficult to compare. The heterogeneity across clinical studies, methods, patient cohorts, and research objectives may explain the substantial variability in pain prevalence, intensity, characteristics, and factors influencing the pain.

Pain perception is individual, very heterogeneous, and based on a complex interaction of exogenous and endogenous influences. Some factors may exert a direct influence on pain. Our previous paper described a correlation between muscle pain and muscle weakness in patients with spinal muscular atrophy (SMA) type 3 [6]. We also found gender differences modifying the perception of pain, which is already described in literature [7, 8]. Surveys conducted by Solbakken et al. in late-onset Pompe disease (LOPD) patients [4] and Moris et al. in facio-scapulo-humeral muscle dystrophy (FSHD) patients [9] also corroborate gender disparities in pain perception within the context of neuromuscular diseases. Individual pain perception is additionally influenced by psychological processes, including cognitive setting, emotions (anxiety, depression, stress, positive feelings), and coping strategies (e.g. avoidant behavior) [10]. Enax-Krumova et al. [11] described a correlation between relevant depression and anxiety symptoms and the intensity of pain in LOPD patients. All these factors contribute to a complex pain perception system that is currently not fully understood.

The aim of this explorative, cross-sectional clinical pilot study was to observe possible differences in prevalence, localization, intensity and characteristics of muscle pain among the various examined neuromuscular diseases. The second objective was to determine whether the patients' nociceptive pain (assessed by pressure pain threshold PPT) is influenced by gender, muscle strength and psychological factors. Further secondary objective was to examine whether muscle pain of the neck muscles is associated with alterations in muscle frequency, stiffness, relaxation, and creep (assessed by myotonometry).

MATERIAL AND METHODS

Adult patients (aged $\geq$ 18 years) with genetically confirmed neuromuscular diseases and the ability to perform study-related functional tests were enrolled in this study. Patients with the following neuromuscular diseases were included in the study: spinal muscular atrophy type 3 (walkers), late-onset Pompe disease (LOPD), myotonic dystrophy type 1 (DM1), myotonic dystrophy type 2 (DM2), and facio-scapulo-humeral muscle dystrophy (FSHD). Healthy participants were examined as a control group. Because of possible interferences between major depression symptoms and pain, patients with a Beck depression inventory- fast screen score >3 at screening were excluded from study participation. Other exclusion criteria were participation in another clinical study or the use of an investigational treatment. Also, patients unable to adhere to the requirements of the study, e.g., inability to complete questionnaires due to limited decision-making capacity, language barriers, or organizational difficulties were excluded from this study. All patients were enrolled during their ambulatory or stationary stay at the neuromuscular expert center Friedrich-Baur-Institute at the LMU Munich, Germany, or were invited online through the German patient organizations (Deutsche Gesellschaft für Muskelkranke e.V.). The study was approved by the ethics committee of the LMU Klinikum, Project No. 20-0980, and the protocol was registered on a public clinical trials registry (ClinicalTrials.gov Identifier NCT04907162). Written informed consent to participate in the study was obtained before any study-related procedure.

Detailed methods are described in our previous paper [6]. Summarized, patients´ disease-related history and perceived pain, including quality-of-life-related information, was collected. Therefore, we used a battery of questionnaires consisting of the Brief Pain Inventory (BPI), the Fatigue severity scale (FSS) and the German Pain Questionnaire (GPQ), which included the Marburg Questionnaire (MFHW) and the Depression, Anxiety and Stress Scale (DASS). The short form of the BPI thematizes the distribution and intensity of pain as well as the functional limitation due to the pain in the past 24 hours [12]. To assess a possible contributing fatigue, we included the FSS, which measures the severity of fatigue and its effect on persons' activities. A detailed description of pain was evaluated with the German Pain Questionnaire (GPQ), including pain sites, duration, intensity, pain-relieving and aggravating conditions, and subjective pain perception [13]. The GPQ includes the MFHW and the DASS. The MFHW was used to assess habitual well-being about perceived pain [14]. The DASS is a brief and reliable questionnaire to describe the likelihood of the pres-

ence of a depressive disorder, an anxiety disorder, or an increased stress load [15].

Musculoskeletal strength was assessed by the MRC scale (Medical Research Council scale) and dynamometry. A 6-minute walk test (6MWT) and a Quick Motor Function Test (QMFT) were performed to examine the patient's physical function and muscular endurance. To quantify local nociceptive pain, we used a pressure algometer to measure the pressure pain threshold (PPT) in different muscles. For the non-invasive measurement of muscle fibers' characteristics, myotonometry was performed using the commercially available MyotonPro® [16]. The tip of the MyotonPro® is placed perpendicular to the underlying muscle. Applying a slight preloaded pressure of 0.18 N initiates compression of the superficial subcutaneous tissue, causing oscillation. This oscillation leads to a brief deformation of the muscle underneath. An acceleration sensor now analyzes the vibration behavior of the muscle (see below). The device calculates the tone of the muscle (in Hz), the stiffness of the muscle (in N/m), the relaxation time after deformation (in ms), and the creep, which puts in relation the relaxation time to the total time of deformation [17].

We selected three body regions for which we created sum scores for nociceptive pain and muscle strength to better compare them between subgroups: the neck and shoulder region, the arm region and the leg region. For the assessment of nociceptive pain in each body region, a pressure pain threshold score was calculated by summarizing the PPT values [kg] of the included muscles (deltoid and biceps for the arm region, neck extensor, supraspinatus and trapezius for the neck and shoulder region and knee extensor, foot flexor and extensor for the leg region). To compare muscle strength in each region, MRC or dynamometer values were used. For the arm and leg region, we summarized dynamometer values [kg] for the legs (including hip flexor, knee flexor and extensor and foot flexor and extensor) and arm muscles (including biceps, triceps and deltoid muscle). For the neck region, MRC (Medical Research Council) scale was specified for the neck extensor muscles by assigning a value from 0 (complete paralysis) to 5 (normal strength).

We performed multiple linear regression analyses to show whether gender, muscle strength and psychological components have a significant influence on muscle pain. We chose PPT sum scores as the dependent variables to quantify muscle pain via the pressure pain threshold of the muscles in the three body regions. We chose QMFT, FSS points, and gender as the independent variables. One model was performed for the leg, one for the arm, and one for the shoulder/neck region. For the multiple regression analysis, we chose the inclusion method, in which all variables are inserted in the model simultaneously. This method examines which of the potential variables should ultimately be included in an explanatory model. Correlations were graphically checked for linearity. Because all variables were recorded only one time, the independence of the residuals is present. Because all observations belong to different patients, all observations are independent. To exclude any multicollinearity, absolute Pearson correlations between independent variables exceeding 0.7 were excluded (Table 2). For each independent variable we used at least 15 independent observations. So, at least 45 (3 * 15) observations were needed. Our sample size of 81 independent observations is sufficient for this analysis. Because of list-wise case exclusion because of some missing values, we sometimes worked with fewer cases (but at least 75 cases, which is still sufficient). The significance level (alpha) was set at ≤ 0.05. A Bonferroni correction was carried out to protect against type I errors. Cohen's D was calculated for significant test results to estimate the effect size.

SPSS Statistics® Version 27 and Microsoft Excel® 2016 were used for statistical analysis. For the illustrations of the human body, BioRender® was used.

RESULTS

Of 111 patients screened for eligibility, 81 patients were enrolled in the study. 5 patients declined to participate after the study information. 25 patients were not eligible due to BDI score of > 3 at screening.

Patients with the following neuromuscular disorders were included: 20 patients with genetically confirmed spinal muscular atrophy type 3 (walkers), 13 patients with genetically confirmed late-onset Pompe disease (LOPD), 12 patients with genetically confirmed myotonic dystrophy type 1 (DM1), 12 patients with genetically confirmed myotonic dystrophy type 2 (DM2), 12 patients with genetically confirmed facio-scapulo-humeral muscle dystrophy (FSHD), and 12 healthy participants.

Baseline demographics and characteristics

Baseline characteristics of the enrolled patients are presented in Table 1. We created neuromuscular subgroups that are similar concerning baseline

Table 1
Demographic characteristics of the enrolled patients

	SMA3	LOPD	FSHD	DM1	DM2	Control	*p*
Number (*n*)	20	13	12	12	12	12	
Gender (male: female)	65 : 35	46 : 54	67 : 33	42 : 58	42 : 58	50 : 50	0.611
Age at baseline (years) Mean (±SD; min; max)	38.25 (±13.19; 20; 57)	49.0 (±18.4; 22; 81)	38.6 (±13.8; 20; 58)	40.5 (±15.6; 18; 63)	46.7 (±13.5; 20; 62)	41.6 (±16.3; 20; 63)	0.369
Age at first symptom (years) Mean (*pm*SD; min; max)	10.70 (±8.65; 2; 40)	28.1 (±15.1; 4; 47)	27.7 (±16.7; 4 53)	21.9 (±14.6; 7; 50)	28.7 (±14.3; 6; 46)	–	<0.01**
Age at diagnosis (years) Mean (±SD; min; max)	18.30 (±13.64; 4; 51)	33.5 (±21.0; 4; 61)	26.7 (±17.6; 3; 52)	28.5 (±14.3; 13; 56)	38.45 (±12.9; 13; 54)	–	
Disease duration (years) Mean (±SD; min; max)	27.6 (±12.80; 9; 53)	23.2 (±10.3; 12; 51)	10.9 (±7.7; 3; 28)	16.1 (±6.5; 5; 24)	17.4 (±13.0; 3; 49)	–	<0.01**
BMI Mean (±SD; min; max)	24.60 (±4.68; 17.5; 35.5)	23.94 (±6.07; 15.6; 35.7)	23.63 (±7.5; 12.2; 37.4)	26.94 (±8.8; 18.8; 51.9)	24.63 (±5.4; 17.4; 34.2)	22.74 (±3.7; 14.2; 27.8)	0.879
Report of pain (historical)	*N* = 11 (55%)	*N* = 8 (62%)	*N* = 11 (92%)	*N* = 9 (75%)	*N* = 12 (100%)	*N* = 2 (16.7%)	<0.01**
-nociceptive	*N* = 6 (54.5%)	*N* = 2 (25%)	*N* = 7 (63.6%)	*N* = 3 (33.3%)	*N* = 3 (25%)	*N* = 0	
-mixed	*N* = 5 (45.5%)	*N* = 6 (75%)	*N* = 4 (36.4%)	*N* = 6 (66.7%)	*N* = 9 (75%)	*N* = 2 (100%)	
Report of pain in women (% of examined women)	*N* = 7 (100%)	*N* = 3 (42.9%)	*N* = 4 (100%)	*N* = 5 (71.4%)	*N* = 7 (100%)	*N* = 1(16.7%)	

BMI=weight[kg]/(height [m]); *significance at a level ≤ 0.05 **significance at a level ≤ 0.01.

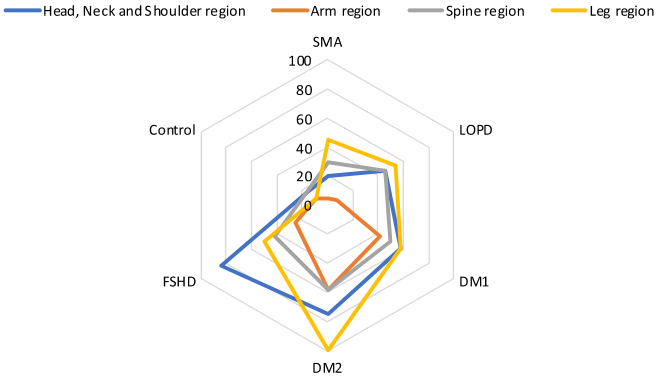

Fig. 1. Pain frequency for all six subgroups in four different locations of the body Four body regions: the head, neck and shoulder region; the arm region (including upper arm, forearm and hands); the spine region (including thoracal and lumbar spine); the leg region (including gluteal region, thigh, knee, calf, shin and feet region); the unit of the scale is percentage of patients experiencing pain;

demographics. The subgroups did not differ significantly in the categories of gender, age at baseline, and BMI. Disease duration was significantly shorter in FSHD patients than in LOPD and SMA patients ($p = <0.01^{**}$). The report of pain was significantly ($p = <0.01^{**}$) higher in DM1, DM2, and FSHD patients compared to the control group (Fig. 3).

Prevalence of pain and fatigue

Pain was distributed with a high variability of frequency and location among the subgroups. Results of perceived pain in the patients are shown in Figs. 1 and 2.

Pain was especially reported by patients with FSHD and DM2 (Figs. 1 and 3). In FSHD patients, it was mainly the head, neck, and shoulder region (83,3%; $N = 10$) that was indicated as painful. We found an especially high prevalence of reported pain in the shoulders (75%) and in the neck (58,3%) (Fig. 2, picture 5). In DM2 patients, the leg region (100%; $n = 12$) was most affected by the pain: 83,3% of the patients reported pain in the thigh region, 50% in the calf region, and 33,3% in the gluteal region. Furthermore, DM2 patients also indicated pain in the shoulder region (58,3%), the lumbar spine (58,3%) and upper arm region (50%) (Fig. 2, picture 2). Back pain was present in 30 to 60 % of all participants.

Objective pain measurement

The distribution of PPT scores in different body regions (arm region, leg region (proximal and distal), shoulder and neck region) is identical across the category "type of neuromuscular disease" and showed no significant group differences (supplementary table 1).

Fatigue and psychological factors

Data about presence of fatigue, depression, anxiety, stress and general well-being are presented in supplementary table 2. The distribution of scores for anxiety ($p = 0.125$), depression ($p = 0.280$), and stress ($p = 0.173$) is identical across the category "type of neuromuscular disease" and showed no significant group differences. The distribution of scores for the "Marburg questionnaire on habitual well-being" (MFHW) and the FSS score across the category "type of neuromuscular disease" showed significant group differences. Patients with DM2 had significantly lower scores in the MFHW ($p = 0.031^{*}$) and significantly higher scores in the FSS ($p = 0.021^{*}$) compared to the control group and the other subgroups. Further analysis using Cohen's d suggests a high effect size ($d = 2.057$), reflecting clinical meaningfulness.

MULTIPLE REGRESSION ANALYSIS

Variables

We have selected our independent variables (QMFT/MRC, FSS points and gender) on the basis of theoretical considerations and the results of previous research. As dependent variables we chose the PTT

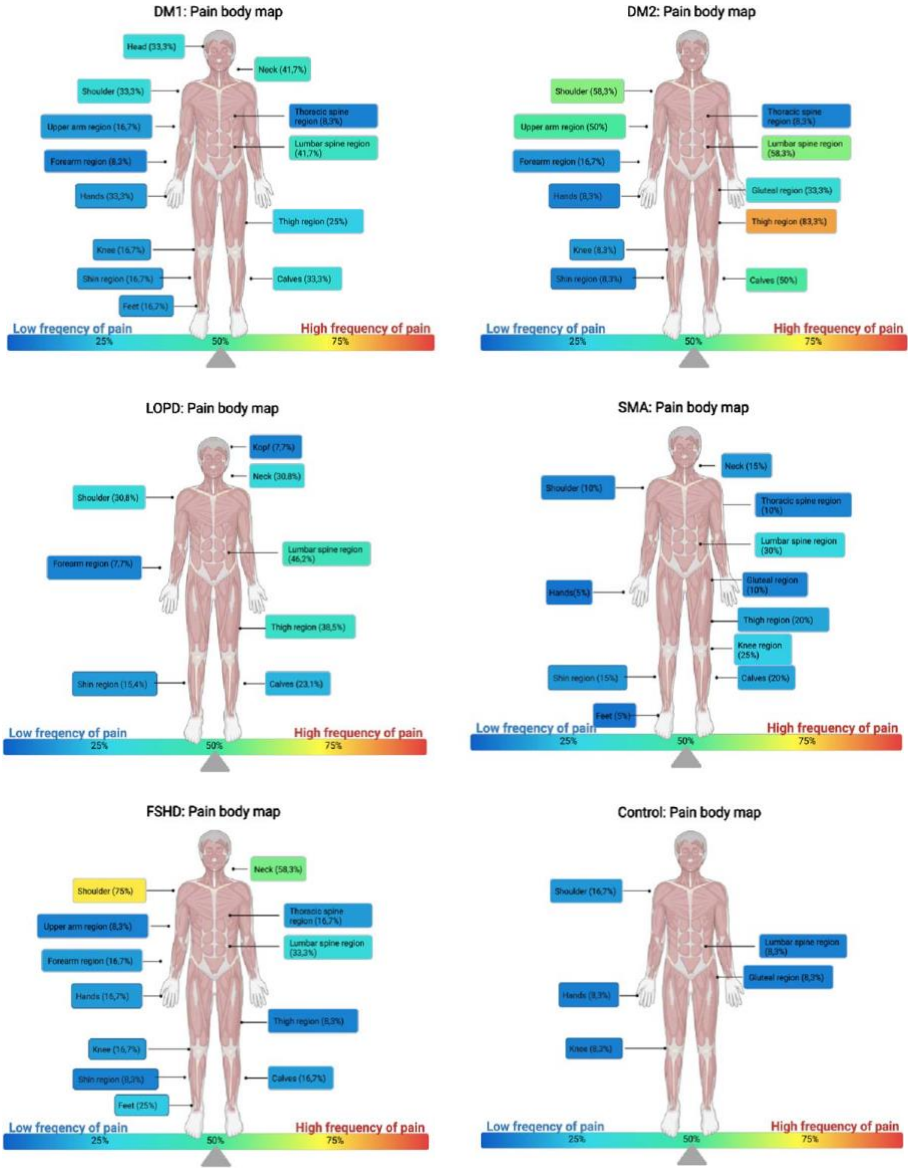

Fig. 2. Pain body maps for the different subgroups DM1 (picture 1), DM2 (picture 2), LOPD (picture 3), SMA (picture 4), FSHD (picture 5) and the control group (picture 6) indicating the frequency of pain in different colors from a low frequency (blue) to a high frequency (red) in different locations.

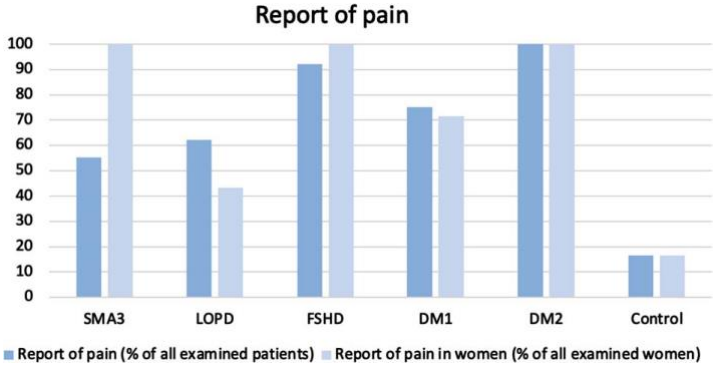

Fig. 3. Report of pain. Percentage of subjective pain prevalence in all examined patients and in all examined women. The report of pain was significantly ($p = <0.01^{**}$) higher in DM1, DM2, and FSHD patients compared to the control group.

Table 2
Univariate analysis, Pearson (P) and Kendalls Tau (KT) correlation coefficients of the dependent and independent variables

	Mean	SD	1.	2.	3.	4.	5.	6.
1. PPT leg [kg]	30.0	12.0	–	–	–	0.210**(KT)–0.303** (P)	0.229**(KT)**0.366****(P)**	0.106 (KT)0.058 (P)
2. PPT arm [kg]	14.3	6.6	–	–	–	0.255**(KT)–0.331**(P)	0.179**(KT)0.310**(P)	0.311**(KT)0.324**(P)
3. PPT neck [kg]	20.8	9.5	–	–	–	0.210**(KT)–0.299**(P)	0.134(KT)0.226*(P)	0.003 (KT)–0.153 (P)
4. FSS [points]	3.82	1.5	–	–	–	–	–0.160(KT)–0.214(P)	–0.151(KT)–0.154 (P)
5. QMFT [points]	46.8	16.7	–	–	–	–	–	–
6. MRC neck			–	–	–	–	–	–

*significance at a level ≤ 0.05 **significance at a level ≤ 0.01.

sum scores of the three body regions to reflect nociceptive pain. We performed an univariate analysis and computed Pearson correlations (Table 2) between dependent and independent variables. Absolute or too high Pearson correlations between variables exceeding 0.7 can cause complications (known as multicollinearity) for the actual regression analysis. None of the Pearson correlations for this data exceeds **0.366** (marked bold in Table 3). So, the assumption of multicollinearity could be excluded.

We chose QMFT/MRC, FSS points and gender as three independent variables:

The QMFT represents muscle strength and muscular endurance. Based on findings in our previous paper about nociceptive pain in SMA patients [6], muscle strength is likely to have an impact on muscle pain and was therefore included in our regression model. The QMFT showed strong and almost absolute correlations with the values for the 6MWT (Pearson: 0.854**), the dynamometer of the leg region (Pearson: 0.761**), the dynamometer of the arm region (Pearson: 0.639**) and the MRC sum score (Pearson: 0.862**). To avoid multicollinearity, we chose only the QMFT to represent patients' muscle strength and muscular endurance (the 6MWT, Dynamometer, and MRC scores). Because the QMFT did not show a high Pearson correlation with the MRC scores of the neck and shoulder region (Pearson: 0.226*), we could not include the QMFT as an influencing factor for the 'Neck and Shoulder' model. Instead, we chose the MRC of the neck region as the influencing variable for the 'Neck and Shoulder' regression model.

The values of the Fatigue severity score (FSS) represent the emotional component, which is likely to have an impact on the perception of pressure pain [10, 11]. The FSS showed strong correlations with the scores for anxiety (Pearson: 0.529**), depression (Pearson: 0.561**), and stress (Pearson: 0.538**), and the MFHR (Pearson: –0.568**, Kendall-Tau: –0.442**, supplements, figure 1). To avoid multicollinearity, we chose the FSS to represent the emotional component.

Because gender is likely to greatly influence PPT values as described in literature [7, 18–20], it was included in the regression model.

Table 3
Regression coefficients for predicting PPT values [kg] in of the leg region

Variable	B	95%CI	ß	t	p
QMFT(x_1)	0.23	[0.08, 0.39]	0.32	2.98	**0.004****
Sex/Gender (x_2)	5.45	[0.52, 10.39]	0.23	2.20	**0.031***
FSS points (x_3)	–1.64	[–3.42, 0.14]	–0.20	–1.84	0.070

CI=confidence interval for B; *B* = regression coefficient; $R = 0.481$; $R^2 = 0.232$; R^2adj.=0.200; Regression model: $22.4 + 0.23^{*}x_1 + 5.45^{*}x_2 - 1.64^{*}x_3$; significance of the regression model:<0.001**; f^2 Cohen: 0.232/0.768 = 0.302 à medium effect; *significance at a level ≤ 0.05 **significance at a level ≤ 0.01.

Table 4
Regression coefficients for predicting PPT values [kg] in of the arm region

Variable	B	95% CI	ß	*t*	*p*
QMFT(x_1)	0.11	[0.03, 0.18]	0.29	2.91	**0.005****
Sex/Gender (x_2)	4.82	[2.30, 7.33]	0.37	3.82	**<0.001****
FSS points (x_3)	–1.02	[–1.92, –0.12]	–0.23	–2.27	**0.03***

CI = confidence interval for B; *B* = regression coefficient; $R = 0.552$; $R^2 = 0.305$; $R^2_{adj.} = 0.277$; Regression model: $10.68 + 0.11 * x_1 + 4.82 * x_2 - 1.02 * x_3$; significance of the regression model: **<0.001****, f^2 Cohen: 0.305/0.695 = 0.4388 ⟶ high effect, *significance at a level ≤ 0.05 **significance at a level ≤ 0.01.

Table 5
Regression coefficients for predicting PPT values [kg] in of the neck and shoulder region

Variable	B	95% CI	ß	*t*	*p*
MRC neck (x_1)	–1.44	[–2.72, –0.16]	–0.24	–2.25	**0.028***
Sex/Gender (x_2)	5.75	[1.81, 9.69]	0.30	2.92	**0.005****
FSS points (x_3)	–1.96	[–3.34, –0.58]	–0.30	–2.85	**0.006****

CI = confidence interval for B; *B* = regression coefficient; $R = 0.473$; $R^2 = 0.224$; $R^2_{adj.} = 0.191$; Regression model: $37.91 - 1.44 * x_1 + 5.75 * x_2 - 1.96 * x_3$; significance of the regression model: **<0.001****, f^2 Cohen: 0.224/0.776 = 0.289 ⟶ medium effect, *significance at a level ≤ 0.05 **significance at a level ≤ 0.01.

Model fit

R^2 and $R^2_{adj.}$ were calculated for the three regression models (Tables 3–5). For $R^2_{adj.}$, also the number of influencing factors and the number of cases is considered, so we used $R^2_{adj.}$ to assess goodness of fit. For the leg region ($R^2_{adj.}$=0.200), 20% of the dispersion of the dependent variable can be explained by the regression model. For the arm region ($R^2_{adj.} = 0.277$), it is 28%, and for the neck and shoulder region ($R^2_{adj.} = 0.191$) it is 19,1%. Effect strength according to Cohen showed a medium effect for the leg region (0.302) and the neck and shoulder region (0.289) and a high effect for the arm region (0.439).

Significance and coefficients

Leg region

There is a significant influence on PPT values of the leg region by the values of the QMFT and gender of the participants (Table 3). QMFT points range from 0 to 64 points. With the increase of one point in the QMFT, PPT values increase by about 0.23 kg. For male participants, PPT values increased by about 5.45 kg. The influence of the FSS was not significant for the leg region.

Arm region

There is a significant influence on PPT values of the arm region by the values of the QMFT, the FSS, and the gender of the participants (Table 4). With the increase of point increase in the QMFT, PPT values increase by about 0.11 kg. For male participants, PPT values increased by about 4.82 kg. The FSS total score is the average of the 9 item scores and ranges from 1 (“no signs of fatigue”) to 7 (“most disabling fatigue”). With one point increase in the FSS, PPT values decreased by 1.02 kg.

Neck and shoulder region

There is a significant influence on PPT values of the neck and shoulder region by the values of the FSS and gender of the participants (Table 5). For male participants, PPT values increased by about 5.75 kg. With the increase of one point in the FSS, PPT values decreased by 1.96 kg. For this region, we took the MRC of the neck instead of the QMFT as an independent variable (4.10.1). With the increase of one point

Table 6
Significance of correlations (Kendall Tau) between PPT values with their corresponding Myoton parameters (frequency, stiffness, relaxation, creep) in the same muscle

Corresponding PPT and Myoton Pro parameters	frequency	stiffness	relaxation	creep
Neck extensor rightNeck extensor left	0.017*(0.197)	0.013*(0.204)	0.009**(–0.215)	**0.002****(–0.253)**
	0.003**(0.238)**	**0.004****(0.230)**	**0.005****(–0.225)**	0.006**(–0.223)

In case of significant results, the correlation coefficient is indicated in parentheses. All correlations, that show significance at level 0.05 ($\alpha_{original} = 0.05$) are marked with *. All correlations, that show significance at level 0.01 are marked with **. All statistically significant values after Bonferroni correction ($\alpha_{altered} = 0.006$) are printed **bold**. We performed eight correlations between PPT values of the neck muscles and 8 corresponding MyotonPro values. A Bonferroni correction was carried out to protect against type I errors. The new p-value results from the alpha value ($\alpha_{original} = 0.05$) divided by the number of comparisons (8): ($\alpha_{altered} = 0.05/8 = 0.006$). To determine whether one of the 8 correlations for each PPT value is statistically significant, the p-value must be $p < 0.01$.

in the MRC of the neck, the PPT value decreases by about 1.44 kg.

Parameters of the MyotonPro

The findings revealed that neck pain exhibited distinct characteristics compared to pain in the extremities. In contrast to limb pain, we observed stronger neck muscles correlated with heightened pressure sensitivity. To gain deeper insights into the differences in the findings of the origin of neck pain, we integrated MyotonPro values of the neck extensor muscles in our study (Table 6). We conducted eight correlations between PPT values of the neck muscles and their corresponding MyotonPro values (frequency, stiffness, relaxation, creep). A Bonferroni correction was carried out to protect against type I errors. We found positive correlations of the PPT values with frequency and stiffness and negative correlations with relaxation and creep. Even after Bonferroni correction, results were highly significant (Table 6).

DISCUSSION

We examined differences in pain perception among different neuromuscular subgroups and investigated the impact on possible influencing factors on muscle pain by evaluating clinical assessments and patient-reported outcomes (PROMs). We also examined the association of muscle pain and parameters of a relatively new method by myotonometry.

For the leg and arm region (but not for the neck region), higher values in the QMFT (reflecting higher muscle strength) are associated with decreased muscular sensitivity to pressure. Other significant factors that lead to decreased muscular sensitivity to pressure are male gender and a low score in the FSS (low levels of fatigue). Findings of the myotonometry analysis collectively suggest that the intrinsic muscular tone and stiffness of the neck muscles may play an important role in their pain pressure sensitivity.

It is important to mention, that 22,5% of all screened patients were excluded from the study in advance due to high scores in the Beck Depression Inventory Fast Screen (BDI-FS), suggesting potential interference between manifest depression and pain perception. The prevalence of possible depression in this sample is higher than the prevalence of depression in the general German population (10,1%) [21]. However, the BDI-FS is not equivalent to a psychiatric diagnosis of depression, which is likely a contributing factor to this observed bias.

Regarding the first objective of the study, our results (Figs. 1 and 2) indicate differences in the subjective pain experience among patients with different neuromuscular diseases. Pain was especially reported by patients with FSHD and DM2 (Fig. 3). The impairment of pain in daily life (assessed by the MFHW) and fatigue levels were also significantly higher in DM2 patients than in the other subgroups and in the control group (supplements table 2).

To examine the impact of influencing factors on muscle pain, we extended the analysis by performing a multiple regression analysis (table 4–6). We chose the three variables muscle strength (represented by QMFT), gender and psychological component (represented by FSS). Results show, that patients who are overall stronger (higher QMFT score) are less likely to experience pain in the muscles of the extremities (Tables 3 and 4). In contrast, the multiple regression analysis suggests that, in the neck region, higher muscle strength is associated with higher sensitivity to pressure (Table 5).

A further finding of this analysis is that gender influences PPT scores. Female gender is associated with lower PPT values and increased muscular pressure sensitivity. This result is consistent with the literature [7, 18, 19]: male participants were less

sensitive to pain pressure threshold measures than women. In a 2009 study [22], Fillingim et al. showed that overall, women are more sensitive to mechanically induced pressure than to other noxious agents and are more likely to develop and maintain musculoskeletal pain conditions. In another study, women showed higher sensitivities to musculoskeletal pain [19]. Differences in the gender-specific perception of pain are frequently reported, but their cause is not yet fully understood. The influence of sex hormones and endogenous opioid structures, as well as psychosocial differences in coping strategies, early childhood stress or the influence of stereotypical gender roles and the associated social gender bias in dealing with pain are widely discussed [5, 19]. The influence of these factors needs to be further investigated in future studies to better understand and treat pain perception, especially in female patients.

Psychological components greatly influence the perception of pain [10]. The influence of the FSS was significant for the arms, neck, and shoulder regions, but not for the leg region. An increase of FSS points, reflecting higher levels of fatigue, resulted in lower PPT scores (and so in higher muscular sensitivity to pressure).

The analysis of the MyotonPro is shown in Table 6. Frequency is measured in Hz and characterizes the intrinsic tension of the neck muscles in a resting and not contracted state [17]. The positive correlation with frequency suggests that higher PPT values (decreased sensitivity to pressure) are associated with increased muscle tone of the neck muscles. Consequently, neck muscles with low intrinsic tension seem to be more likely to cause neck pain. Dynamic stiffness is measured in N/m and characterizes the resistance of the muscle to an external deformation [17]. The positive correlation we found in the analysis suggests that high resistance to the external force of deformation leads to less sensitivity to pressure-induced pain. Mechanical stress relaxation time is measured in ms and shows how fast a muscle can recover after deformation. The parameter of creep is the relaxation time to the total deformation time. The higher the frequency (tension) and the stiffness of a muscle, the shorter the recovery time (the relaxation), and the lower the creep [17]. The correlation was negative for relaxation time and the creep of the neck muscles indicating that PPT values are higher (pain sensitivity is decreased) when muscle recovery time is shorter. In conclusion, less pain seems to be experienced in neck muscles with a high muscle tone, high stiffness (resistance), high structural integrity and a short relaxation time. These factors significantly interacted with our cohort group's perception of neck pain.

With regard to DM1 and DM2, the symptom of myotonia must also be addressed. This is characterized as involuntary muscle contraction with delayed relaxation and can therefore also influence the MyotonPro measurements. Due to the parallel presence of myotonia and pain, alternative treatment options are also available for myotonic dystrophies. Mexiletine, for example, is used both to treat myotonia and for pain therapy [23].

However, as shown in the multiple regression analysis, the interaction of factors is more complex, and the origin of neck pain must be investigated in further studies.

Study limitations

Because the examined neuromuscular diseases are quite rare, selecting completely homogenous groups was impossible. Despite this, we examined neuromuscular subgroups and a control group for comparison, which did not differ significantly in the categories of gender, age at baseline, and BMI. We used validated questionnaires to minimize bias. Nociceptive pain was distinguished from neuropathic pain by precisely describing the reported pain. We are aware that the recruitment of patients through a patient organization or recruitment in neuromuscular expert centers may have a potential source of selection bias, as the participating group may be particularly motivated and perhaps more severely affected. Since patients with severe depression were excluded from study participation and severe mental illnesses are likely to interact with the perception of pain, this adapted patient group can cause bias. In addition to physiological differences in pain perception, the gender of the investigator may have also biased the results. In a 2007 study by Aslaksen et al. [24] male participants showed lower sensitivity to pain when the examiner was female. In contrast, in a study from Gijsbers et al. [25], men showed a higher average pain sensitivity when tested by a female examiner.

Pain perception in general is very heterogenous and influenced by many known and unknown factors, such as further psychological aspects, medication, social aspects and individual factors. This pilot study is only an attempt to gain a deeper sight in the origin of muscle pain in patients with NMDs and their influences.

CONCLUSION

Patients with Myotonic Dystrophy type 2 had significantly higher levels of pain prevalence, fatigue, and impairment of quality of life compared to other examined NMD subgroups and the control group. In contrast, the PPT values of the different body regions were not significantly lower for DM2 patients than those of the other NMD.

We performed a multiple regression analysis to subsume most possible influences on the PPT values. Female gender, high fatigue levels (representing factors such as depression, anxiety, stress, and impairment of quality of life), and low QMFT scores (representing reduced muscle strength) showed an association with increased sensitivity to pressure pain in both the arm and leg regions. These factors should not be underestimated, especially when managing pain in female patients with neuromuscular conditions. Individualized therapeutic concepts including psychological and physical approaches in the pain management of patients with NMDs should be considered. Further research in this field is necessary to gain a more detailed insight into the perception of muscle pain.

The findings revealed that neck pain exhibited distinct characteristics compared to pain in the extremities. In contrast to limb pain, we observed stronger neck muscles correlated with heightened pressure sensitivity. The correlation between PPT values of the neck extensor muscles and corresponding MyotonPro values suggest that the intrinsic muscular tone and stiffness of the neck muscles play an important role in the pain pressure sensitivity of the neck.

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CONFLICT OF INTEREST

All authors report no disclosures regarding this study. Outside of this context, SW has received research grant by the DGM – Deutsche Gesellschaft für Muskelkranke e.V. He has served on advisory boards for Alexion Pharma, CSL Behring and Sanofi Genzyme GmbH. He received funding for travel or speaker Honoraria from Sanofi-Aventis Germany GmbH; SH Glykogenose Gesellschaft; AbbVie Germany GmbH; Recordati Pharma GmbH; CSLBehring GmbH; Alexion Pharma GmbH; Desitin Germany; Akcea GmbH. Outside of this context, BS has served on advisory boards for Alexion, Argenex, Amicus, Astellas, Spark, and Sanofi; he has undertaken contracted unrestricted research for Sanofi and Amicus; and has received honoraria from Kedrion. The other authors have no conflicts of interest to declare.

AVAILABILITY OF DATA AND MATERIAL

The anonymized participant data presented here are available upon request from the correspondent author (stephan.wenninger@med.uni-muenchen.de).

AUTHORS' CONTRIBUTIONS

Elena Sagerer: Statistical analysis and interpretation of data, discussion of results, critical revision of the manuscript for intellectual content, first and final manuscript draft. A guarantor who accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Stephan Wenninger: Interpretation of data, discussion of results, critical revision of the manuscript for intellectual content.

Corinna Wirner: Data acquisition, critical revision of the manuscript for intellectual content.

Marko Mijic: critical revision of the manuscript for intellectual content.

Marcela Arndt: critical revision of the manuscript for intellectual content.

Natalia Garcia-Angarita: critical revision of the manuscript for intellectual content.

Benedikt Schoser: Discussion of results, critical revision of the manuscript for intellectual content.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JND-240068

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Appendix: Case Report Form Version 4

Case Report Form zur Studie: „Nociceptive musculoskeletal pain in NMD“

Name: _____ Geburtsdatum: _____ ID: ____
Untersuchungsdatum:_____ Kontakt:_____

☐ **Screening:**
Einverständnis O ja O nein BDI-FS (Cut Off Wert 4): _____

o FSS (___P)	o BPI	o Deutscher Schmerzfragebogen

☐ **Demographische Daten:**
Alter: _____ Alter bei Diagnose:_____ Alter bei Beginn der Symptomatik:_____
Größe:_____ Gewicht:_____ Geschlecht:_____ BMI:_____
Karpaltunnelsyndrom: O JA O Nein Dominante Seite: O Links O Rechts

☐ **Erkrankung:**

o DM1	o DM2	o LOPD	o FSHD
o SMA3	o sIBM	o Kontrollgruppe	

Behandlung (&evtl. Mutation) _____

☐ **Medikamente:** Welche Medikamentengruppe wird oder wurde ausprobiert?

O NSAR	O Antikonvulsiva	O Analgetika	O Cannabinoide
O Antidepressiva	O Antiarrythmika	O Muskelrelaxantien	O Sonstige
O Manuelle Therapie	O Methocarbamol	O	O

Was hat geholfen (und in welcher Dosierung und Frequenz)? _____
_____
Was hat nicht geholfen?_____
_____
NW?_____

☐ **Stationärer Patient: MRC am zweiten Tag wiederholen!**

Muskel	**MRC(0-5)**	**Dynamometer**	**Algometer 3x**	**MW(D|A)**
Deltoideus R				
Deltoideus L				
Supraspinatus R				
Supraspinatus L				
Trapezius R				
Trapezius L				
Biceps R				
Biceps L				
Triceps R				
Triceps L				
Fingerbeuger R				
Fingerbeuger L				
Handgelenkstr. R				
Handgelenkstr. L				
Hüftstrecker R				
Hüftstrecker L				
Hüftbeuger R				
Hüftbeuger L				

Case Report Form zur Studie: „Nociceptive musculoskeletal pain in NMD“

Knieextension R															
Knieextension L															
Kniebeuger R															
Kniebeuger L															
Fußsenker R															
Fußsenker L															
Fußheber R															
Fußheber L															
Nackenbeuger															
Nackenstrecker															
Rumpfmuskulatur															
Erector. Spinae R															
Erector. Spinae L															

Warum nicht möglich? (Schmerz, Transfer, Kontraktur)_____

_____

Auftreten von Schmerz beim MRC Grading? _____

☐ **Handdynamometer** (inkl MW):

Links				
Rechts				

☐ **Messung mitttels MyotonPro:** O JA O Nein

☐ **QMFT** (Score jeweils von 0-4):

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
S:	S:	S:	S:	S:	S:	S:	S:
9	**10**	**11**	**12**	**13**	**14**	**15**	**16**
S:	S:	S:	S:	S:	S:	S:	S:

Score gesamt (0 bis 64): _____

☐ **6MWT:**

Zeitpunkt	SpO2	Herzfrequenz	Blutdruck	Borg Skala
5 min vor 6MWT				
5 min nach 6MWT				
	Anzahl Runden	=Distanz	+letzte Distanz	**=Gesamtdistanz**
30 Meter Strecke		m	m	m

6-MWT vollständig abgeschlossen : O JA O Nein (wie viele m geschafft:_____)

Pausen:_____

Gehhilfe: _____

Nach wie vielen Metern zum ersten Mal Muskelschmerzen/Krämpfe: _____

Qualität/Intensität/Lokalisation:_____

Adverse Events:_____

☐ **Algometer nach Belastung**

Algometer	Rect. femoris R				Rect. femoris L				Gastrocnem. R				Gastrocnem. L			
Vor 6MWT																
Nach 6MWT																

☐ Beschreibung Schmerz:_____

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Curriculum Vitae