

Neuropathic pain in adult Myotonic Dystrophy type 1. Presence of small and large fibre neuropathy?

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Neuropathic pain in adult Myotonic Dystrophy type 1

Presence of small and large fibre neuropathy?

G. Solbakken, S. Løseth, T. Nærland, J. Frich, E. Dietrichs, K. Ørstavik

Background: Myotonic Dystrophy type 1 (DM1) is an inherited neuromuscular disorder affecting multiple organs. There is an increasing awareness of chronic pain in DM1. In this cross-sectional study, we investigated symptoms of neuropathic pain and small and large fiber neuropathy in the adult form of DM1. We also studied if neuropathy was related to the number of CTG repeats, disease duration and other clinical DM1 symptoms, and investigated if skin biopsy tests for small fiber neuropathy differed in the DM1 group compared to reference values from healthy controls.

Methods: 20 genetically verified DM1 adult patients were included in the study. Pain descriptions, neurologic examination and objective investigations of the peripheral nerve system by quantitative sensory testing, skin biopsies and neurography were conducted. Statistical analyses of group differences and frequencies were performed.

Results: Six patients (30%) out of 20 patients with DM1 described neuropathic pain, and three of these had objective findings on both small and large fiber neuropathy, as well as clinically sensory findings. Together, large and/or small fibre neuropathy is present in 50% of the patients with DM1. The intra epidermal nerve fiber density was significantly lower ($p < 0.001$, Cohen's $d = 1.2$) in the 20 patients with DM1 (mean 8.16, SD: 2.28) compared to a reference group (N = 106, mean 12.43, SD: 4.59). Patients with large fiber neuropathy had significantly lower muscle strength ($p = 0.01$, Cohen's $d = 1.6$, mean difference 0.4, CI: 0.7 - 0.1) than patients without large fiber neuropathy.

Conclusion: Symptoms of neuropathic pain was more frequent in patients with DM1 compared to the general population. Intra epidermal nerve fiber density was significantly lower in the DM1 group than in a sample of healthy controls. Neuropathy may be a mechanism of pain in DM1.

Abbreviations

- DM1: Myotonic dystrophy type 1
- CTG: Cyanine, Thymine, Guanine nucleotide
- NRS: Numeric rating scale 0-10
- MMT: Manual muscle strength test
- IQ: Intelligence Quotient
- NCV: Nerve conduction velocity
- QST: Quantitative sensory testing
- IENFD: Intraepidermal nerve fiber density
- TSH: Thyroid stimulating hormone

Introduction

Myotonic Dystrophy type 1 (DM1) is an inherited myopathy with involvement of multiple organs. DM1 is caused by an unstable CTG nucleotide repeat on the long arm of chromosome 19q¹. The disorder may affect the central nervous system, leading to severe developmental delays in the early onset subtypes and often cognitive impairment and personality changes in the adult onset type^{2, 3, 4}. Some studies have also shown that DM1 may affect the peripheral nervous system⁵⁻⁷. Lately Boland-Freitas and Ng found indications of a subclinical small-fiber neuropathy measured by quantitative sensory testing in patients with DM1 without large fiber neuropathy⁸. Chronic pain has been reported in about 60% of DM1 patients^{3, 9, 10}. Pain location is widespread and pain in hands and feet are frequent¹¹. This pain distribution, together with previous studies on large and small fiber neuropathy could indicate that there might be a neuropathic component to pain in DM1. Neuropathic pain is reported in 8% in general populations¹². Pathology of small nerve fibers (unmyelinated C fibers and thinly myelinated A δ -fibers) are important for peripheral neuropathic pain¹³. These fibers may be tested indirectly by quantitative sensory testing (QST) while the golden standard include skin biopsy for examining intraepidermal small nerve fiber density (IENFD)¹³. To our knowledge, there is a lack of research on IENFD in DM1 patients, and studies of symptoms of neuropathic pain in combination with objective findings of neuropathy have not been reported previously.

In this cross-sectional study, we investigated the presence of neuropathic pain and small and large fiber neuropathy in the adult form of Myotonic dystrophy type 1 (DM1), and explored if neuropathy was related to the number of CTG repeats, disease duration and other clinical DM1 symptoms. We further investigated if small fiber findings on skin biopsy were different in the DM1 group compared to reference values from healthy controls.

Participants and methods

Recruitment and inclusion

DM1 outpatients from the North and South-Eastern regions of Norway, were invited to participate in a large clinical study on DM1^{14, 15}. This study also included investigation of pain. The congenital and childhood forms of DM1 were not included. The inclusion period was between 2012 and 2017. Patients were contacted through the National Registry of Neuromuscular Diseases, via the patient organisation's journal, and through hospitals. From a total sample of 50 patients with DM1, 32 were invited to participate in study of neuropathy and neuropathic pain. Invitations were sent to patients living in proximity to the hospitals performing this investigation. The most severely impaired and fatigued were excluded (e.g. patients who needed support from another person to be able to travel to the investigation site). Of the 32 invited, 20 (62%) patients accepted the invitation to participate. Patients were examined between 2016 and 2017.

Disease measures: disease duration and CTG size

Disease duration was calculated based on time between onset of DM1 symptoms and inclusion in the present study⁴. Southern blot analysis for number of CTG repeats¹ was obtained from all patients within four years from the time of inclusion.

Pain measures

Pain was investigated by pain drawings to register the presence of pain¹⁶. A Numeric Rating scale (NRS) from 1-10; 0: no pain, mild scores: 1-3, moderate scores: 4-6, severe scores: 7-10, was used for registration of pain intensity¹⁷. Patients were instructed to mark mean pain intensity of chronic pain (pain lasting more than 3 months). Further, they were asked to

describe the quality of pain sensations like burning, lancinating or deep pain. In addition, all patients went through a general neurological examination including sensory testing for light touch and pinprick in the lower extremities, and deep tendon reflexes.

Other clinical measures

Muscle strength in the extremities and trunk muscles were assessed by manual muscle strength test (MMT) and was initially graded from 0-5¹⁸, subsequently recoded into a 0-3 scale¹⁴. Mean muscle strength was calculated based on the following muscle groups tested: distal extremities: (wrist extensors, and dorsal flexors of the ankle), proximal extremities: (shoulder abductors, elbow flexors, elbow extensors, and hip flexors, knee flexors, knee extensors), and trunk muscles: (the anterior trunk flexors/abdominals and the back extensors). Due to previously reported symmetry, only one side was tested¹⁹.

General cognitive function was assessed with the WAIS IV Intelligent quotient (IQ).²⁰ Endocrinological results (HbA1c and thyroid function), and additional diagnoses were collected from the patients' medical files.

Neuropathy measurements

The 20 patients included were asked about the presence of pain and its quality. In addition, large and small fibers were investigated with neurography, QST of thermal thresholds, and skin biopsy for quantification of IENFD. Neurography was performed on Keypoint Classic® and Keypoint G4® machines. Nerve conduction velocities (NCV), amplitudes and distal latencies of the median and ulnar (motor and sensory) nerves in one upper extremity were examined. In the lower extremities the motor NCV, amplitudes and distal latencies of the peroneal and tibial nerves as well as the sensory sural, medial plantar and peroneal superficial

nerves were examined in both legs. The neurography results were compared with normal values available by the manufacturer. In this study, we regarded three pathological nerves in the lower extremities including at least one sensory nerve as compatible with large fiber neuropathy. Heat detection thresholds (HDT), cold detection thresholds (CDT), heat pain detection thresholds (HPDT) and cold pain detection thresholds (CPDT) were determined using a computerized Thermotest® (Somedic AB, Sweden) as described elsewhere ²¹. HDT and CDT were calculated as the average of five consecutive temperature recordings. These thresholds were determined at the thenar eminence of left hand, at the lateral aspect of the left thigh approximately 20 cm above knee level, at the lateral aspect of the left leg approximately 15 cm below knee level, and at the dorsum of the left foot. HPDT was determined at the dorsum of the foot and calculated as the average of three recordings at 10-seconds intervals. Thresholds were compared to normal material obtained in our lab ²². Findings of increased thresholds for either CDT, HDT or both at the dorsum of the foot indicated small fiber neuropathy.

Two skin biopsies were obtained from the distal part of the leg, 5-10 cm above the lateral malleolus with a 3-mm disposable circular needle under local anesthesia. Fifty-micron freezing sections were immunostained with the panaxonal marker PGP 9.5. The number of separate intraepidermal nerve fibers (IENFs) in three sections from each biopsy was counted, and the total length of epidermis was measured.

IENF density (IENFD) in patients was compared with data from 106 healthy adult individuals analysed in the same laboratory ²³.

Statistics

The SPSS 25 (IBM Corporation Armonk, NY, USA) was used for calculations. Normal distributed variables are presented with mean, standard deviation (SD) and range. Differences between DM1 patients with and without neuropathic pain, and with and without neuropathy were explored with students t-tests. IENFD in DM1 patients were compared to normative values ²³ with students t-test, Z-scores taking gender and age into account were also calculated.

Effect sizes (Cohens d) were calculated using the online social science statistics service: <http://www.socscistatistics.com/effectsize/Default3.aspx>. Cohens d at 0.2 were interpreted as small, 0.5 as medium and >0.8 as large. P-values were set at two tailed < 0.05. Power analysis was done using Jamovi 1.1.9. Effect sizes (d) between 0.7-0.9 could be detected with a power of 80-95%, with groups of 20 (DM1) and 106 (controls).

Results

Twenty patients with the adult form of DM1 participated in the study, including 7 men and 13 women (Table 1). Participants were mildly to severely affected, according to the number of CTG repeats, strength measures and disease duration. There was no difference between genders regarding these measures. IQ was within the normal range (+/- 2SD). None of these patients had abnormal blood sugar findings or were diagnosed with diabetes. Only two patients had elevated TSH indicating possible hypothyroidism.

Table 1. Characteristics of the 20 study participants with the adult form of DM1.

Measures	Mean, SD, (Range)
Age, years	38.7, SD: 12.8, (19-62)
CTG kb	1.7, SD: 1.3, (0.270-4.5)
Disease duration, years	18.6, SD: 9.7, (5-39)

IQ n16	96, SD: 12, (74-115)
Mean strength	2.3, SD: 0.4, (1.7-2.9)
Pain intensity (NRS)	5.6, SD: 2.4, (0-8)

Mean, standard deviation (SD) and range is reported. The IQ measure was obtained for 16 patients.

Symptoms of pain

Symptoms of neuropathic pain like burning or lancinating pain in their feet was reported by six patients. Seventeen patients (85%) reported chronic pain, of which 14 patients reported other types of pain and three reported both types of pain.

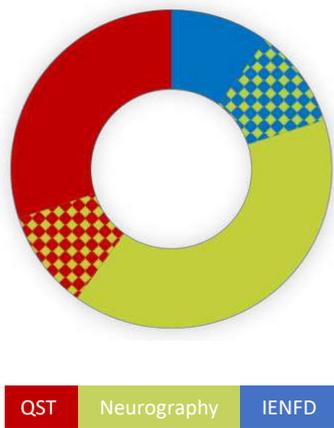
Clinical findings indicating neuropathy

We found decreased or absent deep tendon reflexes in at least two sites in the lower extremities in 14 patients indicating a possible large fiber neuropathy. Six patients had decreased distal sensibility for pinprick or light touch or both.

Objective findings indicating a large or small fiber neuropathy

In 10 of the 20 patients, neurography and/or QST revealed findings of neuropathy (Figure 1). Six patients had findings on neurography compatible with large fiber neuropathy, while four patients had abnormal values on QST for thermal thresholds at the dorsum of the foot.

Figure 1. Distribution of objective findings of neuropathy in 10 patients, in which six had findings compatible with large fiber neuropathy four had abnormal findings on QST, and two had abnormal skin biopsy (IENFD). There was an overlap between large fiber findings and the two small fiber tests, as shown by the chess pattern.



Results from skin biopsies

Only two patients had a significant depletion of small fibers on skin biopsy, and thereby objective findings typical for small-fiber neuropathy. These two had no clinical symptoms of neuropathic pain. However, when comparing absolute values of IENFD in the DM1 group (N = 20, mean 8.16, SD: 2.28) to the reference group (N = 106, mean 12.43, SD: 4.59), there was a highly, significant difference ($p = <0.001$, Cohen's $d = 1.2$) with a lower number of nerve endings in the patient group compared to controls. This difference was also significant when using IENFD Z-scores (DM1 group mean -1.16, SD: 0.8. Reference group: mean 0.05, SD: 1.0, $p = <0.001$, Cohen's $d = 1.8$).

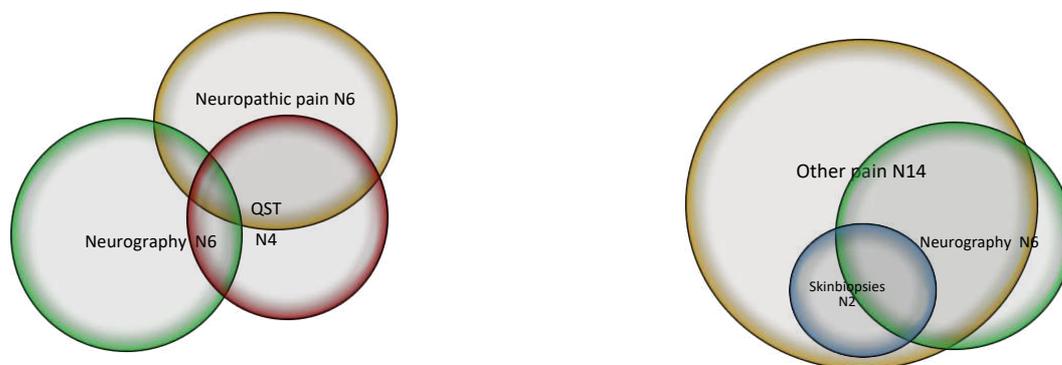
Overlap between small and large fiber neuropathy findings and pain

Of the six participants with large fiber neuropathy based on neurography findings, one had findings on QST and one on skin biopsy. This indicate two patients having both small and large fiber neuropathy (Figure 1).

Of the six patients with symptoms typical for neuropathic pain, two patients had QST findings indicating small fiber neuropathy, and one patient had neurography findings indicating large fiber neuropathy (Figure 2). Of the 14 patients reporting other types of pain, five patients had

findings on neurography indicating large fiber neuropathy and two patients had findings on skin biopsies indicating small fiber neuropathy (Figure 2).

Figure 2. Combination between objective findings and pain reports. The figure represents the group reporting symptoms typical for neuropathic pain, and the group reporting other types of pain. The circles show how patients' subjective reports of pain overlap with different objective findings from investigations on large and small fiber neuropathy.



Relations between neuropathy findings and DM1 symptoms

Patients with large fiber neuropathy as measured by neurography (n=6) had significantly lower mean muscle strength: (mean difference 0.4, CI: 0.7 - 0.1, $p=0.01$, $p=0.01$, Cohen's $d = 1.6$) than patients without large fiber neuropathy. In addition, the number of CTG repeats showed a tendency to be higher in the group with large fiber neuropathy. However, this did not reach significant difference in this small group of patients ($p=0.056$: mean difference - 1.1, CI: -2.2 - 0.03, Cohen's $d = 0.95$).

All the patients with abnormal neurography findings had absent reflexes. Patients with clinical large fibre neuropathy as measured by absent reflexes (n=14) had significantly lower muscle strength (mean difference -0.5, $p=0.002$, CI: -0.7 - -0.2, Cohen's $d = 2.0$).

Discussion

In this study, 30 % of patients with DM1 reported symptoms typical for chronic neuropathic pain. In addition, we found small or large fibre neuropathy, as well as clinical sensory deficits, in 50 % of these, thus in 15 % of the participants.

Our finding that presence and frequency of large fiber neuropathy is related to muscle strength is in line with previous studies of peripheral neuropathy in DM1 patients ⁵. We found that the number of CTG repeats seemed to be higher in the group with large fiber neuropathy, which indicate that the development of neuropathy may be associated with a more severe version of DM1. This finding is supported by a study that found neuropathy in transgenic DM1 mice with high numbers of CTG repeats ²⁴.

We investigated small fiber neuropathy by both QST and skin biopsies. The most frequent positive findings were large fibre neuropathy, but the two methods investigating small fibre involvement together expose the same frequency of small fibre involvement as large fibre. However, QST is a semi-objective method and there is risk that findings are false positive for small fiber neuropathy ²⁵.

We found that 30% of the patients in our study reported symptoms typical for neuropathic pain, which is a substantially higher frequency compared to a prevalence of 8 % in the general population ¹². However only 50% of the patients reporting such symptoms had findings on objective tests for small or large fiber neuropathy. Further, two of the three patients with neuropathic pain and objective findings, had findings on QST, which indicate small fibre neuropathy ²⁵. The two patients who had findings on skin biopsies did not report neuropathic pain. Important though is the highly significant difference of IENFD between the whole DM1 group of 20 subjects and normative values for IENFD. This may indicate a tendency to small

fibre neuropathy in a larger number of DM1 patients not detected by QST^{23, 26}, and could be an explanation for why as many as 30% reporting neuropathic pain.

Patients with DM1 have a higher risk of developing diabetes. However, none of the patients included had a diagnosis of diabetes and their HbA1c was within the normal range. Therefore, a subclinical diabetes is not a plausible cause of the presence of small and large fibre neuropathy in this study. Patients with DM1 may also have central nervous system involvement. This could also play a role in the development of neuropathic pain¹². However, clinical neurological testing and anamnestic details did not indicate central nervous system involvement in the included patients.

We found that 70% of patients in our study reported other pain qualities than typical neuropathic pain. A similar high frequency of pain is also previously documented in DM1 patients²⁷. In our patients with chronic pain, without typical qualities for neuropathic pain, large fiber neuropathy was more frequent than small fiber deficits. Large fiber neuropathy may impair muscle function²⁸. In addition, MRI studies of DM1 muscles show myopathy in both trunk and extremity muscles, which are correlated to decreased strength and function¹⁵²⁹. A possible explanation for chronic non-neuropathic pain in DM1 patients could be a consequence of increased and unbalanced weight on joints and ligaments because of myopathy. Myotonia in itself could be painful,^{9, 30} and myopathy that threaten function may cause nociceptive pain³¹.

Strengths and limitations

The main strength of our study is the combination of subjective and objective measurements of neuropathy. Further, the use of the golden standard for the diagnoses of small fiber neuropathy, involves skin-biopsies^{13, 32}. Another strength is the well-defined patient group

with genetic verification of the diagnosis for all participants. Subjective reports of pain and thermal thresholds may be biased by cognitive deficits, therefore general cognitive function was investigated and show the patients to be within normal functioning. We lack IQ information for 4 of the patients but none of these were diagnosed with cognitive impairments.

A limitation is the cross-sectional design which does not allow for conclusions according to change over time. Except from the analysis between the reference group and the DM1 group for IENFD, the sample size is small and can only capture large effects sizes, smaller effects are likely to be missed. The sample may also be biased because patients who experience pain may be more likely to participate. On the other hand, patients who were severely affected by DM1 were excluded which may be a bias in the other direction.

Conclusion

We found that patients with the adult form of DM1 reported a higher frequency of symptoms typical for neuropathic pain compared with the general population. Objective findings of large or small fiber neuropathy was found in half of patients with DM1. This study suggests that small fiber neuropathy may be more frequent than large fiber neuropathy in the group with neuropathic pain and that neuropathy may be a mechanism of pain in DM1. The findings are of importance for clinical follow up and future research, including longitudinal studies.

Declarations

Ethical approval and consent to participate

This study was approved by the Regional Committees for Medical and health Research Ethics, South East (2015/2364). All patients gave their written informed consent to participate.

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Authors contributions

Wrote the first draft of the paper: GS.

Conceived and designed the study: GS, SL, ED, KØ.

Performed the study: GS, SL, KØ.

Analysed the data: GS, SL, TN, KØ.

Interpreted the data: GS, SL, TN, JF, ED, KØ.

Revised the manuscript: GS, SL, TN, JF, ED, KØ.

All authors read and proved the final manuscript.

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Availability of data and materials

The dataset generated and /or analysed during the current study are nor publicly available due to the consent form used, some limitation of data sharing may apply, but are available from

the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures



Figure 1

Distribution of objective findings of neuropathy in 10 patients, in which six had findings compatible with large fiber neuropathy four had abnormal findings on QST, and two had abnormal skin biopsy (IENFD). There was an overlap between large fiber findings and the two small fiber tests, as shown by the chess pattern.

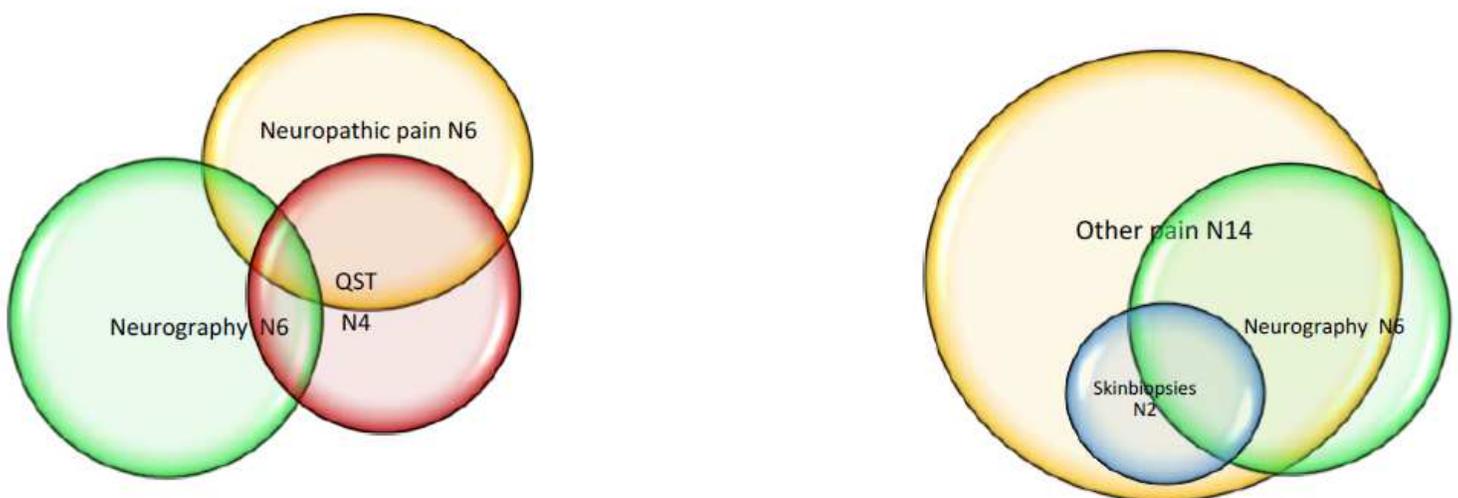


Figure 2

Combination between objective findings and pain reports. The figure represents the group reporting symptoms typical for neuropathic pain, and the group reporting other types of pain. The circles show how patients' subjective reports of pain overlap with different objective findings from investigations on large and small fiber neuropathy.