CLINICAL/SCIENTIFIC NOTES

# Chronic pain as a neglected core symptom in mitochondrial diseases

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Mitochondrial diseases (MD) affect about 1 in 5,000 and are characterized by dysfunctional structure or function of mitochondria, caused by nuclear or mitochondrial DNA mutations.[1] MD are clinically heterogeneous with core symptoms including muscular fatigue, exercise intolerance, sensorineural deafness, cerebellar ataxia, peripheral neuropathy, dementia, seizures, renal and hepatic impairment, and cardiomyopathy. Pain has not been included in the core symptoms despite occasional reports that pain also affects patients with MD.[2,3] Instigated by patient reports of significant pain, we sought to determine whether chronic pain is a problem in MD. To illustrate the characteristics and the burden of pain, we compared patients with MD with patients with primary chronic back pain (CBP), who are clinically well characterized.

## Methods

We recruited 96 patients with MD with heterogeneous diagnoses, confirmed by the German Network for Mitochondrial Disorders (mitoNET) (see data available from Zenodo table S1, doi.org/10.5281/zenodo.3593837 for subdiagnoses). Owing to the lack of knowledge on pain in MD, an a priori sample size estimation was not possible, but a posteriori power for an observed mean effect size of d = 0.4 (data available from Zenodo table S1, doi.org/10.5281/zenodo.3593837) with $\alpha = 0.05$ was 0.81. The primary outcome was the frequency of pain complaints, secondary outcomes were pain intensity, pain-related interference, affective distress and life control, affective and sensory quality of pain, pain duration and chronicity, quality of life, and depressive symptoms. All participants completed a pain drawing, part 1 of the West Haven-Yale Multidimensional Pain Inventory, the adjective-based Pain Experience Scale, the Short Form Health Survey, and the Center for Epidemiologic Studies—Depression Scale. Patients with MD were compared with 109 patients with primary CBP, using unpaired 2-sided *t* or Wilcoxon tests. Pearson correlations were used to relate pain to indicators of well-being. Statistical analyses were performed with R 3.4.0, and significance was set to $p < 0.05$ with Bonferroni correction for multiple comparisons. The ethics committee of the Medical Faculty Mannheim, Heidelberg University, approved the study. All participants provided written informed consent.

## Results

Patients with MD were severely affected by pain: 87 of 96 patients (91%) reported pain in one or more body areas in the pain drawing (figure 1A). Six of the 9 patients who did not report pain were patients with Leber hereditary optic neuropathy, 2 with CPEOplus, and 1 with mitochondrial myopathy. Most affected body parts included the neck, upper and lower back, and thighs. Fifty-eight patients with MD (60%) had been suffering from pain for more than 5 years and the chronic pain grade was high. Pain-related interference and pain-related distress were comparable with the CBP group as were chronic pain grade, pain duration, impairment in quality of life (physical and mental health), and depression (exact statistics in data available from Zenodo table S1, doi.org/10.5281/zenodo.3593837). Compared with CBP, only LHON patients reported lower pain-related interference ($t_{10.56} = -6.75$, $p < 0.001$) and chronic

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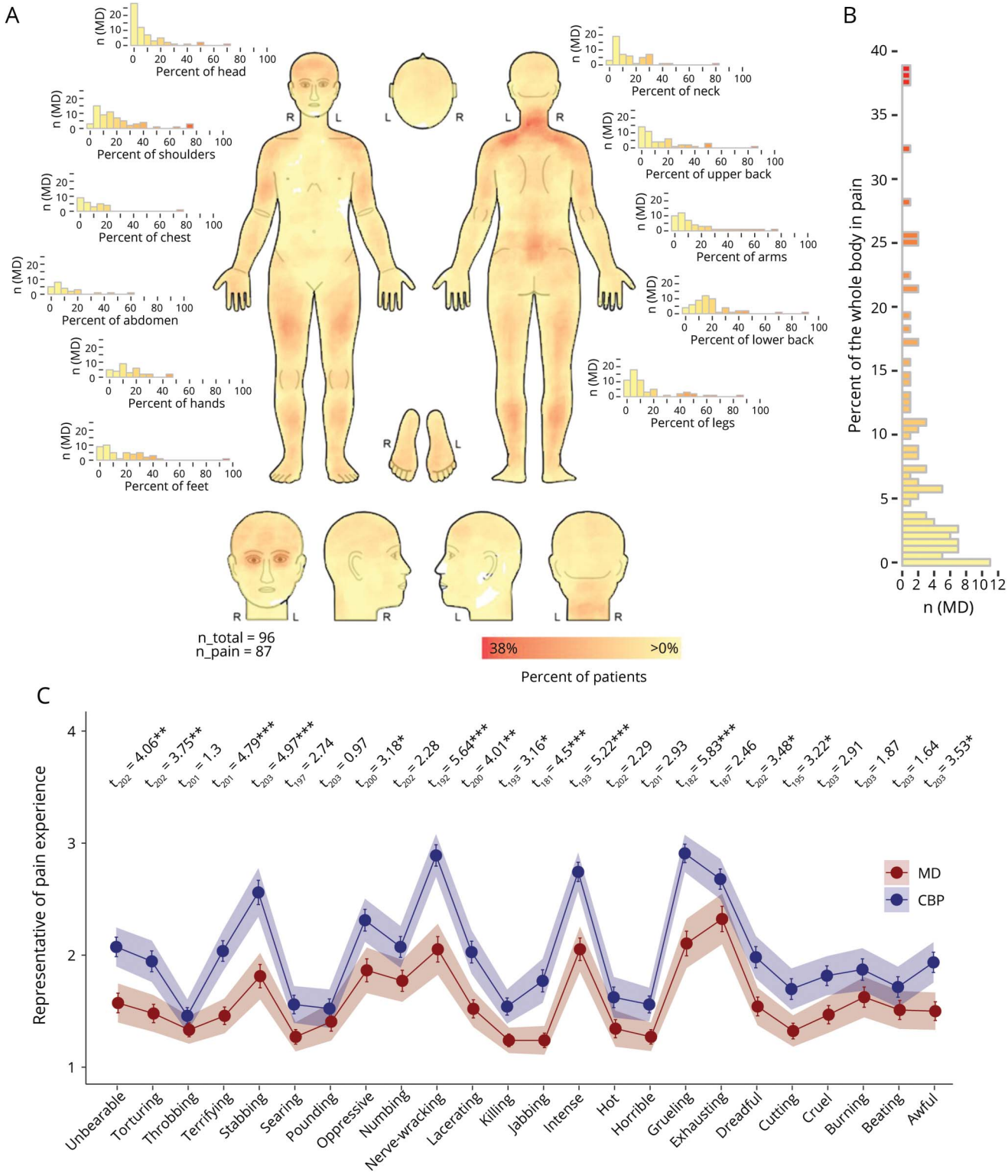
**Figure** Spatial distribution and sensory-affective characteristics of pain in patients with MD




(A) Pain drawings: Red and yellow color codes indicate the percentage of patients with MD reporting pain in an area, with yellow representing fewer patients, red more patients, and white areas no patients who reported pain. Histograms show the number of patients by percentage of the marked pain area relative to the respective body area (only patients who reported pain in the respective body area are depicted). (B) Histogram shows the number of patients by percentage of the marked body area in pain relative to the entire body. (C) Sensory and affective characteristics of the pain experience in patients with MD (red) and patients with CBP (blue). Values are depicted as the mean and standard error of the mean. The shaded areas indicate the 95 percent confidence intervals of the mean. The x-axis depicts how well an adjective represents the pain experience of the patients (1 = "not at all", 2 = "a little", 3 = "mostly", and 4 = "exactly"). The y-axis depicts 24 different pain characteristics derived from the Pain Experience Scale. At the top, *t*-values, degrees of freedom, and significant differences between patients with MD and CBP are depicted after correction for multiple comparisons using the Bonferroni correction with $*p < 0.00208$, $**p < 0.00042$, $***p < 0.00004$. CBP = chronic back pain; MD = Mitochondrial disease.

progressive external ophthalmoplegia patients lower pain-related distress ($t_{42.63} = -3.42$, $p = 0.001$) (data available from Zenodo table S2, doi.org/10.5281/zenodo.3593837). Overall, patients with MD scored significantly lower than the CBP group in perceived pain intensity and affective and sensory quality of pain (figure 1C; data available from Zenodo table S1, doi.org/10.5281/zenodo.3593837). Higher pain severity was associated with less quality of life ($r_{96} = -0.69$, $p < 0.001$) and more depression ($r_{96} = -0.45$, $p < 0.001$; data available from Zenodo table S1, doi.org/10.5281/zenodo.3593837).

## Discussion

This novel study on the prevalence and characteristics of pain in mitochondrial disorders found that pain is present in almost all patients with MD (91%) with different subdiagnoses. Pain-related interference and chronic pain grade were comparable to that of CBP. Pain strongly impairs quality of life in patients with MD and is correlated with depressive symptoms. Our data suggest that pain is a greatly underestimated problem and neglected core symptom in MD. By contrast, a recent study showed that only 12% of a large cohort of patients with MD reported muscle pain;[4] however, this study assessed specifically muscle pain, not considering other types of pain, which may have been included in our study. Furthermore, neuropathic pain in MD was shown to be associated with mitochondrial DNA polymerase gamma mutations.[5] Like the current study, Smits et al.[3] reported high presence of pain (29 of 30 patients) in CPEO patients. Mechanisms related to pain in MD cannot be uncovered by the current study but could involve the mitochondrial energy generating system, reactive oxygen species generation, mitochondrial permeability transition pores, apoptotic pathways, and intracellular calcium mobilization[6,7] in addition to the possible causes not primarily related to mitochondrial dysfunction (e.g., neurologic comorbidities).

### Author contributions

All authors had full access to all of the data obtained in the study. S. Becker and H. Flor contributed equally to this work and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: H. Flor, S. Becker, C. Gamroth, M. Löffler. Acquisition of data: M. Löffler, S. Becker, C. Gamroth. Analysis and interpretation of data: M. Löffler, S. Becker, H. Flor. Drafting of the manuscript: M. Löffler, S. Becker, H. Flor. Critical revision of the manuscript for important intellectual content: H. Flor, S. Becker, M. Löffler, C. Gamroth. Obtained funding: H. Flor, S. Becker. Administrative, technical, or material support: M. Löffler, S. Becker. Study supervision: H. Flor, S. Becker.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### Disclosure

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### Publication history

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