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Letter to the Editor

Selection of Sample, Reliable Diagnosis, and Specification of Pain Items Are Crucial To Assess Muscle Pain in Mitochondrial Disorders

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In a recent article, Filosto *et al.*, (2019) reported about a retrospective evaluation of a national database of patients with a mitochondrial disorder (MID) for the item "muscle pain" (Filosto, M. *et al.*, 2013). Twelve percent of the MID patients in the database reported muscle pain (Filosto, M. *et al.*, 2013). Clinical details were available from 132 patients (Filosto, M. *et al.*, 2013). The study has a number of shortcomings.

The first shortcoming is the missing definition and specification of "muscle pain". Muscle pain has various etiologies, various qualities, different intensities, different distribution, different triggers, different courses, and different reactions to treatment. The study did not consider most of these different issues concerning the etiology, there are several reasons why MID patients may develop muscle pain. Muscle pain in MID patients may not only originate from myopathy, rhabdomyolysis, or myotonia, but also from epilepsy, dystonia, Parkinson's disease, endocrine disorder, kidney disease, neuropathy, or secondary orthopaedic disease. Since all these conditions may be associated with muscle pain (Henriksson, K. G. 1989), we should know in how many of the 132 patients muscle pain was attributable to any of these conditions. Furthermore, during the withdrawal of certain drugs patients may react with myalgia, why we should know, in how many of the included patients "muscle pain" was attributable to drug withdrawal (e.g. from opiates). Since MIDs are multisystem diseases in the majority of the cases (Finsterer, J. 2018), it is conceivable that muscle pain derived not only from a single abnormality but from several. Concerning the quality of pain, it may be itching, drawing, pressing, bruising, pulsating, cramping, myalgic, neuropathic, or electrical,. Differentiating between these qualities is crucial to know which quality of pain was regarded as muscle pain, to relate the symptom to a particular etiology, and to apply an appropriate treatment. The study does not inform about intensities of muscle pain, as obviously no intensity scale was applied in their survey, e.g. the visual analogue scale.

A second shortcoming of the study is the list of exclusion criteria. Excluded were patients with active rheumatologic, metabolic, endocrine, disorders, myoglobinurea, fibromyalgia, restless-leg syndrome, radiculopathy, plexopathy, alcoholism, electrolyte disturbances, eosinophilia, and those taking drugs known to cause muscle pain. In contradiction to this, 22% of the patients had diabetes, 9% hypothyroidism, 0.7% Hashimoto thyroiditis, 0.7% hemochromatosis, and 0.7% sarcoidosis (Filosto, M. *et al.*, 2013). Thus we should know how many of the 1398 patients of the database were excluded because they met one or several of the exclusion criteria. Generally, it is not comprehensible why patients with typical manifestations of a MID, such as diabetes, neuropathy, rhabdomyolysis, renal insufficiency, or endocrine disorders were excluded. According to our own experience the rate of MID patients experiencing muscle pain is much higher than the reported 12%. We should be particularly informed why patients with multisystem MID, such as those with KSS, LS, MERRF, and MNGIE, were included in the study, as given in figure 1. Did all these latter patients truly present with only myopathy? This would contradict with the definition of the disease.

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A third shortcoming of the study is that the diagnosis MID was genetically confirmed in only two thirds of the cases (Filosto, M. *et al.*, 2013). In 45 of the patients the diagnosis based on clinical, histological, and biochemical investigations, which makes uncertain if these patient truly suffered from a MID.

Overall, this interesting study has some shortcomings with regard to the specification of muscle pain, the in- and exclusion criteria, and the reliability of the diagnosis MID. To assess the frequency of muscle pain in MID patients only patients with primary mitochondrial myopathy, without affection of any other organ should be included. Based on the considerations outlined above, the figure of 12% of the patients reporting muscle pain is not reliable.

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