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ORIGINAL COMMUNICATION

Muscle pain in mitochondrial diseases: a picture from the Italian network

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Abstract

Muscle pain may be part of many neuromuscular disorders including myopathies, peripheral neuropathies and lower motor neuron diseases. Although it has been reported also in mitochondrial diseases (MD), no extensive studies in this group of diseases have been performed so far. We reviewed clinical data from 1398 patients affected with mitochondrial diseases listed in the database of the "Nation-wide Italian Collaborative Network of Mitochondrial Diseases", to assess muscle pain and its features. Muscle pain was present in 164 patients (11.7%). It was commonly observed in subjects with chronic progressive external ophthalmoplegia (cPEO) and with primary myopathy without cPEO, but also—although less frequently—in multisystem phenotypes such as MELAS, MERFF, Kearns Sayre syndrome, NARP, MNGIE and Leigh syndrome. Patients mainly complain of diffuse exercise-related muscle pain, but focal/multifocal and at rest myalgia were often also reported. Muscle pain was more commonly detected in patients with mitochondrial DNA mutations (67.8%) than with nuclear DNA changes (32.2%). Only 34% of the patients showed a good response to drug therapy. Interestingly, patients with nuclear DNA mutations tend to have a better therapeutic response than patients with mtDNA mutations. Muscle pain is present in a significant number of patients with MD, being one of the most common symptoms. Although patients with a myopathic phenotype are more prone to develop muscle pain, this is also observed in patients with a multi system involvement, representing an important and disabling symptom having poor response to current therapy.

Keywords Mitochondrial diseases · Muscle pain · Myalgia · cPEO · Mitochondrial myopathy

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Introduction

Mitochondria are a double membrane-bound organelles largely present in every tissue of human body, especially in those who require more energy as skeletal muscles and nervous tissue [1, 2]. Their functions are very vast, mainly supporting aerobic respiration and producing energy substrates such as ATP by oxidative phosphorylation (OXPHOS). They also contribute to various cellular metabolisms as β-oxidation, Krebs circle and lipid synthesis [1, 2].

Mitochondrial diseases (MD) are caused by a deficiency of OXPHOS function, which is under control of both mitochondrial (mtDNA) and nuclear (nDNA) genomes [1–3].

Prevalence of nDNA and mtDNA mutations related to adult MD has been estimated around 1 of 4300 [4].

OXPHOS-affecting diseases have a wide spectrum of clinical manifestations ranging from complex multisystem disorders to more easily identifiable mitochondrial syndromes or mild non-specific conditions characterized by fatigue and exercise intolerance [1–3].

Muscle pain can be part of many neuromuscular disorders including myopathies, peripheral neuropathies and lower motor neuron diseases [5]. Although it has been reported also in mitochondrial patients, no extensive studies to quantify and clinically characterize muscle pain in MD have been performed so far [6–12].

Aim of the present study is to better investigate the symptom "muscle pain" in a large cohort of patients affected with MD collected through the "Nation-wide Italian Collaborative Network of Mitochondrial Diseases" [13–15].

Patients and methods

We retrospectively reviewed the clinical data of all the 1398 patients present in the "Nation-wide Italian Collaborative Network of Mitochondrial Diseases" database updated at December 31st, 2016.

The inclusion of patients in the database was approved by the Ethics Committee of each single center belonging to the network. We obtained the informed consent of all patients or their tutors in accordance with ethical standards of the 1964 Declaration of Helsinki.

All involved centers have specific expertise in mitochondrial disorders and neuromuscular diseases. The clinical section of our web-based database includes "yes or no" dichotomic items agreed by all centers in a preliminary consensus phase, which was specifically designed to define the clinical features known to be relevant in mitochondrial medicine, including muscle pain [13–15].

Patients were selected on the basis of the complaint, at least for the past 4 months, of muscle pain. After identifying patients complaining of muscle pain, we designed a specific form to obtain more detailed informations. For every patient the following clinical data were collected: age, final diagnosis, distribution of pain (generalized or limited to one or more muscles) and its association with cramps/contractures, mode of presentation (at rest, exercise-related or both), at rest serum creatine kinase (CK) and lactic acid levels, electromyography/electroneurography (EMG/ENG) findings, histologic and histochemical studies and genetic results. The form was sent to the individual centers that had recruited at least one patient with muscle pain.

Assessment of active rheumatologic, infectious, metabolic or endocrine disorders, myoglobinuria, fibromyalgia, restless leg syndrome, radiculo- or plexopathy, regular use of drugs known to trigger muscle pain (i.e., zidovudine, emetine, hydroxychloroquine, simvastatin, and pravastatin), alcohol abuse, electrolyte imbalance, and hypereosinophilia was conducted. Patients affected with these conditions and those having neuropathic pain (published in Ref. [14]) were excluded from the study.

Prevalence, distribution, and mode of presentation of muscle pain and related phenotypes and genotypes were analyzed; the correlation with EMG/ENG findings, serum CK and lactate values, muscle biopsy and clinical response to therapy was also investigated.

Comparisons of proportions have been performed by Chi-squared test, two-tailed Fischer's exact test and *t* student test. A P value < 0.05 was considered as significant. Data analysis was carried out using SPSS Version 20.

Results

Among the 1398 patients included on database, 164 (11.7%) complained of muscle pain.

Figure 1 analyses the frequency of muscle pain within each main phenotype and reveals that muscle pain is more commonly reported by patients with primary mitochondrial myopathy without chronic progressive external ophthalmoplegia (PMM) (44.6% of the total PMM subjects) and by chronic progressive external ophthalmoplegia (cPEO) patients (11% of the total cPEO subjects). However, it is also a common symptom in multi system phenotypes such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (6.1% of the total MELAS subjects), myoclonic epilepsy with ragged red fibers (MERRF) (11.3% of the total MELAS subjects) and mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE) (17.7% of the total MNGIE subjects).

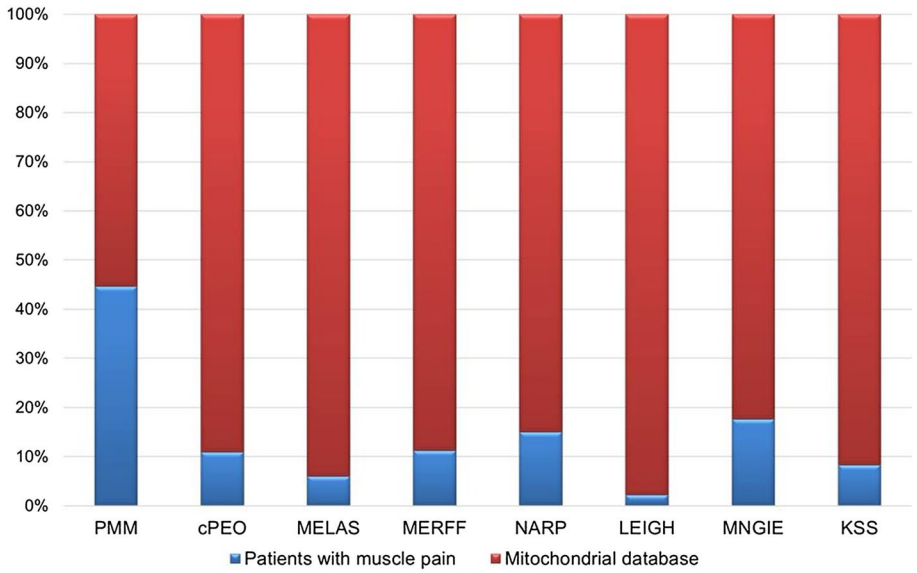

Fig. 1 Muscle pain along different mitochondrial phenotypes in the cohort from Italian National Database. Frequency expressed in percentage of patients. *PMM* primary mitochondrial myopathy without cPEO, *cPEO* chronic progressive external ophthalmoplegia, *MELAS* mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke, *MERRF* myoclonic epilepsy with ragged red fibers, *NARP* neuropathy, ataxia, and retinitis pigmentosa, *Leigh* Leigh syndrome, *MNGIE* mitochondrial neurogastrointestinal encephalopathy, *KSS* Kearns–Sayre syndrome. In vertical axis percentage of patients

Clinical findings

We could collect full information in 132 of the 164 subjects.

Median age at the diagnosis of MD was 58.2 ± 14.4 years, range 4–85. Seventy-four subjects are males (56%) and 58 (44%) females. A childhood disease was reported in 3.7% of cases.

Muscle pain was reported by all the patients, in 59 (44.7%) in association with muscle cramps/contractures. Symptoms were present from a minimum of 4 months to a maximum of 18 years; they were widespread in 74 patients (56%) while were focal or multifocal in 58 patients (44%), mainly at lower limbs (40.2%) than upper limbs or trunk (12.9% and 2.2%, respectively) (Fig. 2a).

In 53 patients (40.2%; 32.4% of widespread and 50% of focal/multifocal patients) muscle pain was exercise-related, in 25 (18.9%; 25.7% of widespread and 10.3% of focal/multifocal patients) only at rest, and in the remaining 54 (40.9%; 41.9% of widespread and 39.7% of focal/multifocal patients) either at rest or after exertion (Fig. 2b).

Few patients had some conditions that might have influenced muscle pain in their past medical history as diabetes mellitus (22%), hypothyroidism (9.1%), Hashimoto thyroiditis, hemochromatosis and sarcoidosis (0.7% each), although

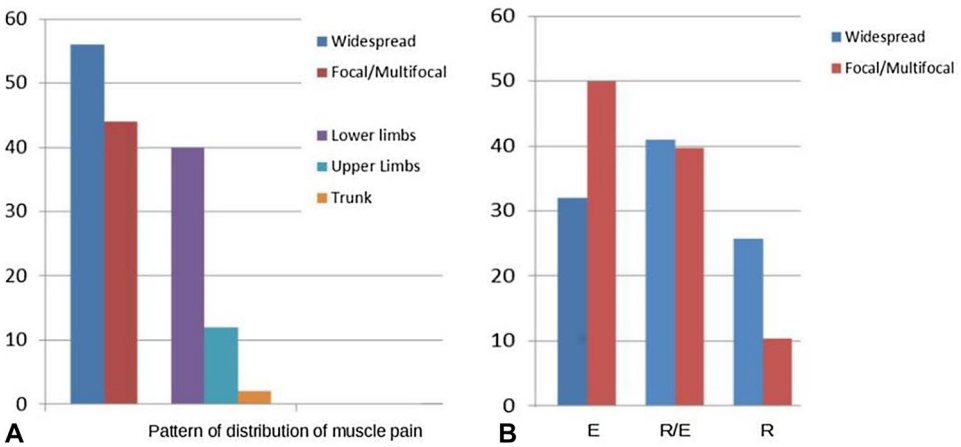

Fig. 2 **a** Pattern of distribution of muscle pain in our cohort. In blue are represented patients having widespread muscle pain while in red patients complaining of focal/multifocal muscle pain. Purple, light blue, and orange bars represent main segments involved (lower limbs, upper limbs and trunk, respectively) in the subgroup of patients having focal/multifocal muscle pain. In vertical axis percentage of patients. **b** Mode of presentation (*E* exercise-related, *R/E* at rest and exercise-related, *R* at rest) of muscle pain in our cohort. In vertical axis percentage of patients

all these conditions were well treated and under control when the patients have been evaluated.

Among the 132 patients selected for this study, PMM (34.8%), cPEO (32.6%), MELAS (6.7%), and MERFF (6.7%) were the more represented phenotypes while other non-specific phenotypes account for 11.1% of the patients (Fig. 3).

Although diagnosis is defined in all the patients by clinical, biochemical and/or morphological findings, a conclusive molecular diagnosis was available in 87 subjects out of 132 (65.9%); 59 (67.8%) patients harbored a mtDNA mutation (22% a single deletion and 78% a point mutation). Only one out of these patients had a mutation in the *MT-CYB* gene [m.15800C-T (p.Glu352*)]. Mutations in nDNA genes were detected in 28 patients (32.2%). More frequent mutated genes were *POLG* (39.3%), *TWNK* (17.8%), *TYMP* (10.7%) and *OPA1* (7.1%).

The median age at the diagnosis was 43.79 ± 14.06 in the genetically defined patients and 53.72 ± 16.42 in patients with still not defined genetic diagnosis ($p < 0.001$). No significant statistical differences in all the considered characteristics of pain were found between the two groups.

Nerve conduction studies were normal except a mild sensory-motor neuropathy observed in five patients (3.8%). Electromyography revealed myopathic changes in 42.6%, neurogenic changes in 20.8%, a mixed pattern in 24.8%, while it was normal in 11.8% of patients.

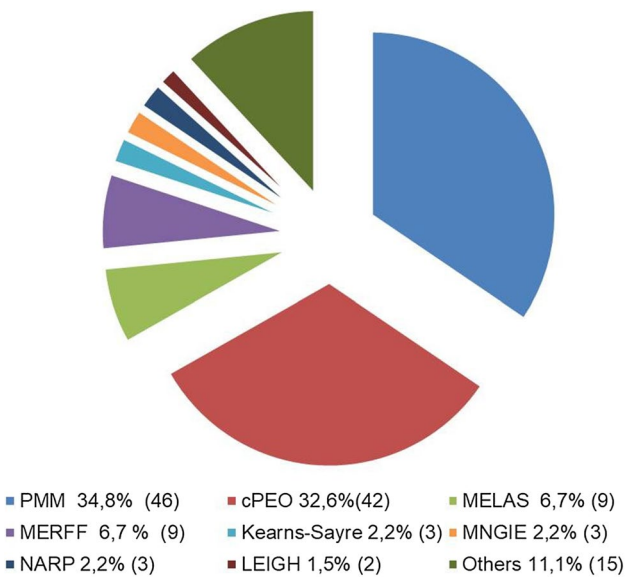

Fig. 3 Distribution of muscle pain within the main mitochondrial phenotypes in our cohort. *PMM* primary mitochondrial myopathy without cPEO, *cPEO* chronic progressive external ophthalmoplegia, *MELAS* mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke, *MERRF* myoclonic epilepsy with ragged red fibers, *MNGIE* mitochondrial neurogastrointestinal encephalopathy, *NARP* neuropathy, ataxia, and retinitis pigmentosa, *Leigh* Leigh syndrome

Serum CK level, measured in all the patients, was normal in 47% of them, while it was elevated up to two times beyond the normal limit in 53%.

Blood lactate level was available in 92 (69.7%) patients: 58 (63%) had normal level (below 2.2 mmol/L), 18 (19.6%) a level between 2.2 and 3.0 mmol/L, 11 (12%) between 3.0 and 4.0 mmol/L and 5 (5.4%) over 4.0 mmol/L.

Muscle biopsy was performed on 127 patients (96.2%) and showed pathological signs in 115 (90.5%). Some of them were non-specific signs of muscle damage, such as poly-dimensionalism of the fibers (47.7%) or centralization of nuclei (40.9%). More specific signs of mitochondrial dysfunction were accumulation of lipids (26.5%), ragged red fibers (61.4%), COX negative fibers (78.2%) and subsarcolemmal rims (48.5%).

Statistical analysis did not reveal any significant correlation between muscle pain appearance/characteristics and genotype, EMG/ENG findings, serum CK and lactate values and histological data. There was no statistically significant difference in EMG–ENG findings between patients with or without muscle cramps/contractures.

Management of muscle pain and response to therapy

The most used drugs in the treatment of muscle pain were nonsteroidal anti-inflammatory drugs (NSAIDs) and modulators of neuropathic pain such as pregabalin, gabapentin, SSRI, SNRI (i.e., venlafaxine) and tricyclic antidepressant (i.e., amitriptyline). All the patients received at least one medication for treating pain and they were considered non-responders if response to multiple drugs (at least three) was unsatisfactory. Only 45 subjects (34%) showed a satisfactory improvement in painful symptoms after drug administration; 27 were male and 18 were female (no statistically difference was detected).

In this subgroup, main used drugs were NSAIDs such as ASA or paracetamol, pregabalin and gabapentin.

We analyzed the characteristics of the subgroup who showed a clinical response to treatment.

These patients presented a similar muscle pain distribution to those who did not respond to therapy: 24 (53.3%) complained about diffuse muscle pain and 21 (46.7%) of focal/multifocal myalgia.

Responders/non-responders comparison of EMG data, available in 38 cases, showed a similar prevalence of myopathic pattern (44.7% vs. 42.6%) with a higher prevalence of neurogenic signs in responders (34.2% vs. 20.8%) and a high prevalence of mixed pattern in non-responders (7.9% vs. 24.8%) but with no statistical significance. Normal EMG pattern was found in 13.2% of responders and in 11.8% of non-responders.

Among the 87 patients with molecular diagnosis, 35 were responders and 52 were non-responders. In responder subjects the frequency of mtDNA mutations was 62.9% (22 subjects) and of nDNA mutations 37.1% (13 subjects). In non-responders the frequency of mtDNA mutations was 84.6% (44 subjects) and of nDNA mutations 15.4% (8 subjects). The analysis of the difference in frequency of mtDNA vs. nDNA mutations between responders and non-responders showed an increased frequency of nDNA mutations in responder patients with statistical significance with $p < 0.01$ (Fig. 4).

Discussion

The relation between muscle pain and mitochondrial abnormalities is already known, although the exact underlying mechanisms are poorly understood.

Twenty per cent out of 240 patients submitted to muscle biopsy for muscle pain have been reported to have mitochondrial abnormalities at the muscle biopsy, including COX negative and ragged red fibers or subsarcolemmal mitochondrial accumulation [16].

Several studies showed mitochondrial damage as one of the mechanisms by which statins (a well-known class of drugs causing muscle pain) can cause myotoxicity thus indirectly confirming the role of mitochondrial dysfunction in causing muscle pain [17–19].

The best characterized muscle pain MD syndrome is due to cytochrome-*b* mutations, the only mtDNA-encoded subunit of complex III, that commonly cause a myopathy characterized by exercise intolerance, muscle pain and myoglobinuria [6].

At rest or exercise-related muscle pain was also described, usually as isolated case reports, in some patients harboring mitochondrial tRNA gene mutations, including *MT-TL1, MT-TS1* and *MT-TK* [7–12].

However, systematic studies in this field are missing in the literature and muscle pain clinical characterization remains poorly investigated.

As a first significant finding, our study shows that muscle pain appears to be an important clinical feature of MD, being present in almost 12% of cases, thus representing a daily clinical and therapeutic problem.

Muscle pain characteristics are heterogeneous. It (1) is more generalized than focal/multifocal, (2) involves lower limbs more than upper limbs, and (3) manifests more frequently after exercise than only at rest. However, the global number of subjects complaining of rest pain, either associated or not to exercise-induced muscle pain, is about 60% and this is an interesting evidence to keep in mind in a clinical setting.

A second important finding coming from our analysis is that muscle pain is a frequent complain not only in patients with myopathic pictures but also in subjects having more complex phenotypes such as MELAS, MERRF, neuropathy, ataxia, and retinitis pigmentosa (NARP), MNGIE, Kearns Sayre syndrome (KSS) and Leigh syndrome.

Although these complex phenotypes account for a minority of the cases in our database, the evidence that a part of the affected subjects complains of muscle pain as an important and disabling symptom should be stigmatized.

Interestingly, only 11% out of cPEO patients collected in our database complained of muscle pain, even though progressive ophthalmoplegia is typically a myopathic phenotype.

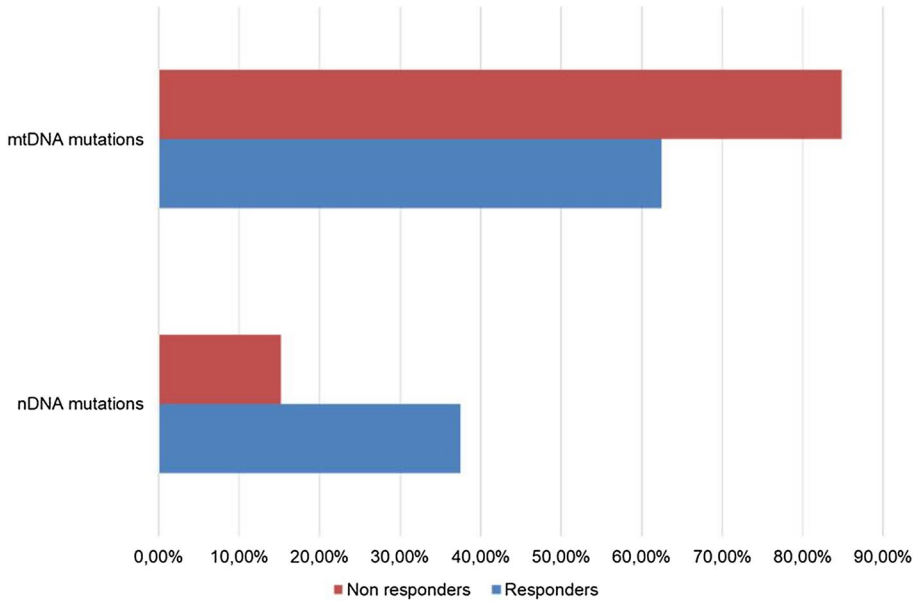

Fig. 4 Relation between genotype and response to treatment. The analysis of the difference in frequency of mtDNA vs. nDNA mutations between responders and non-responders showed an increased frequency of nDNA mutations in responder patients with statistical significance with $p < 0.01$. In horizontal axis percentage of patients

EMG, serum CK, and lactate remain of scarce usefulness in characterizing MD patients with muscle pain because of variable EMG patterns and serum CK/lactate values. We can stress that most of the patients presents with a myopathic or mixed neurogenic/myopathic EMG pattern and serum CK values variably above normal values. Only in 37% of the patients, increased values of serum lactate were detected.

No significant correlation between muscle biopsy findings and muscle pain which can help in better characterize and diagnose it was found. At the same way, no significant correlation between genotype (mtDNA mutations vs. nDNA mutations) and muscle pain was found, although patients with mtDNA mutations more frequently complained of muscle pain than nDNA-mutated patients (67.8% vs. 32.2%).

A third interesting observation deriving from this study is that pharmacological control of muscle pain in these patients is largely unsatisfactory, being reached in only 34% of them by using a variety of analgesic and modulating drugs.

Although an assessment of quality of life was out of the scope of this study, it is self-evident that, as in other settings, quality of life of our non-responder patients is largely compromised by the presence of chronic pain and better and more specific therapies appear necessary.

An additional interesting observation, although of elusive significance, is the higher prevalence of responder patients among the nDNA-mutated subjects respect to mtDNA-mutated ones, which is a statistically significant difference suggesting a possible role of genotype in influencing the response to therapy.

Certainly, our study has some limitations. First of all its retrospective design, which did not allowed to obtain assessment scales such as the visual analog scale (VAS score) or depression scale findings. Therefore, for example, we cannot entirely exclude that, in a number of patients, the origin of pain could be not strictly metabolic related, since, in the course of chronic diseases as MD, overlapping conditions including fibromyalgia, depression and psychosomatic illness can appear making it difficult to distinguish between pain due primarily to mitochondrial deficiency and that due to associated comorbidities.

However, independently from the cause of muscle pain, our study represents the first picture of the "real world" as physicians usually observe in clinical practice.

Our findings indicate that muscle pain is frequent in patients with MD and it is a management and therapeutic problem. Further research should be guaranteed to better understand pathogenesis and improve the current unsatisfactory treatment.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards All human studies have been approved by the appropriate ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Specifically, the inclusion of patients in the database was approved by the Ethics Committee of each single center belonging to the network. All persons gave their informed consent to be included in the database of Nation-wide Italian Collaborative Network of Mitochondrial Diseases.

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