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Myotonic Dystrophy type 2 unmasked by physical activity resumption following COVID-19 lockdown: case discussion and review of the literature

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Objective. Myotonic dystrophy type 2 (DM2; PROMM) is characterized by myotonia and muscle dysfunction, episodic muscle pain, proximal and axial weakness of the neck flexors. We describe the case of a young woman affected with a clinically silent form of DM2 disclosed by her return to physical exercise, a 7 km walk, after Covid-19 lockdown.

Methods. The patient underwent neurological examination, serum CK dosage and electromyography after assessing the Emergency Room complaining of cramps and severe myalgia. Molecular screening for *CNBP* expansions was carried out on the patient and her family.

Results. Clinical signs were generalized muscle weakness, more evident in the lower limb-girdle, myotonia at hands and foot fingers and dramatic elevation in CK levels. DM2 genetic assay revealed a pathological expansion in intron 1 of *CNBP* gene, confirming the clinical suspicion.

Conclusions. The case we describe is the first, to our knowledge, addressing the impact of Covid pandemia on DM2 patients. In particular, we discuss the role of physical training in modulating the onset and the severity of clinical manifestations of DM2, since sustained regular exercise can mask the disease whereas prolonged suspension can cause massive muscle damage. Recent works investigate possible molecular mechanisms altered by forced physical inactivity, preventing skeletal muscle from adapting to the sudden, non-progressive training reactivation. Additional observations on DM2 patients, other myopathic subjects and elders will help clarify this important issue and provide useful behavioural advice.

Key words: DM2, pain, physical exercise, physical training, Covid-19 lockdown

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Introduction

Myotonic dystrophy type 2 (DM2) is a dominantly inherited syndrome, also known as PROMM, PROximal Myotonic Myopathy, since it mainly involves proximal skeletal muscles. Medical description traces back to only thirty years ago [1,2], and the causative gene, *CNBP* (*CCHC-type zinc finger nucleic acid binding protein*, also named *ZNF9*, RefSeqGene NG_011902.1, chromosome 3q21.3), was identified in the early 2000s [3]. CNBP intron 1 contains a complex repeat motif, comprising TG, TCTG, and CCTG tracts, in this order [4]. Normal *CNBP* alleles have up to 30 repeats of the tetranucleotide CCTG. When mutated, the gene displays an abnormal expansion of this unstable tract, CCTG repeats ranging from approximately 75 to more than 11,000 repeats. In DM2 no relationship has been established between size of the expansion and disease severity. This, along with the lower prevalence (5-fold lower) in population compared to Myotonic dystrophy type 1 (DM1) DM1 and DM2. DM2 is generally milder with more phenotypic variability than the classic DM1. Our previous data on co-segregation of heterozygous recessive CLCN1 mu-

tations in DM2 patients indicated a higher than expected DM2 prevalence. The aim of this study was to determine the DM2 and DM1 frequency in the general population, and to explore whether the DM2 mutation functions as a modifier in other neuromuscular diseases (NMD) [5,6], the lack of a congenital form, and a partial clinical overlap with DM1, has made DM2 less investigated and, consequently, underdiagnosed. However, important differences between the two forms have emerged from experimental data, partially explaining the different pathophysiology. Among them, temporal expression of the relative genes during foetal life; reduction of the relative proteins, CNBP in DM2 and DMPK in DM1 [7]; expression of the contiguous genes, and overall splicing features [8,9].

Indeed, prominent features of DM2 are proximal weakness, slowly progressive in most cases, clinical myotonia in about half of patients, and prevalence of pain often described as "invalidating" [10]. Compared to DM1, an overall better prognosis can be predicted, with less frequent respiratory insufficiency and cognitive impairment [11]. Early onset cataracts, as well as endocrinal and cardiological disfunctions may be present [1,2]. The disease severity may widely vary from asymptomatic to wheelchair-bound subjects, female gender and ageing being associated with a more severe disease burden [12]. Due to this large heterogeneity, it may be difficult to identify clinically relevant aspects of the disease, wherefrom the significant percentage of undiagnosed individuals.

Muscle function preservation by regular active physical exercise is essential for disease management in a number of neuromuscular diseases. As far as myotonic dystrophies, only a limited number of observations are available, all restricted to DM1 cases. Herein we describe the case of a young woman affected with a clinically silent form of DM2 which was disclosed by her return to physical exercise after Covid-19 lockdown.

Materials and methods

Case report

The patient is a 25 years old woman, second born from unrelated parents native to two different Italian regions. Regarding her family history, the father (born in 1960) suffers from acromegaly and diabetes, her mother (born in 1959) underwent bilateral cataract surgery at the age of 55 years, and her 35-years-old brother (born in1986) is healthy and performs regular sport activity. Of note proband's past medical history is unremarkable except for left cataract surgery at the age of 20 years and a diagnosis of secondary amenorrhea, treated with hormones, at the age of 24 years. She sought medical attention in May 2020, at the age of 25 years, due to the onset of severe and diffuse skeletal muscle cramps and weakness following a 7 km long walk she had taken after a period of forced physical inactivity. Symptoms were so severe that she was compelled to use a wheelchair. Before COVID-induced lockdown she used to take long daily walks without any problems, though she had noticed difficulties in opening her hands after prolonged contraction a few weeks before the episode, during the lockdown. At neurological examination, she presented generalized muscle weakness, especially in the lower limb-girdle and proximal lower limbs, which were only partially pain-related. She suffered from severe quadriceps cramps even at rest, and muscle pain, which was heavily worsened by movement. Ileo-psoas and quadriceps weakness and myalgia were still prominent three months after the acute episode, consistently conditioning her work activity. Myotonia was evident in both hands and in foot fingers and was confirmed at electromyography. Serum creatine kinase (CK) levels at the Emergency Room were over 47,000 U/L, and went back to normal in few months alongside with muscle strength. Skeletal

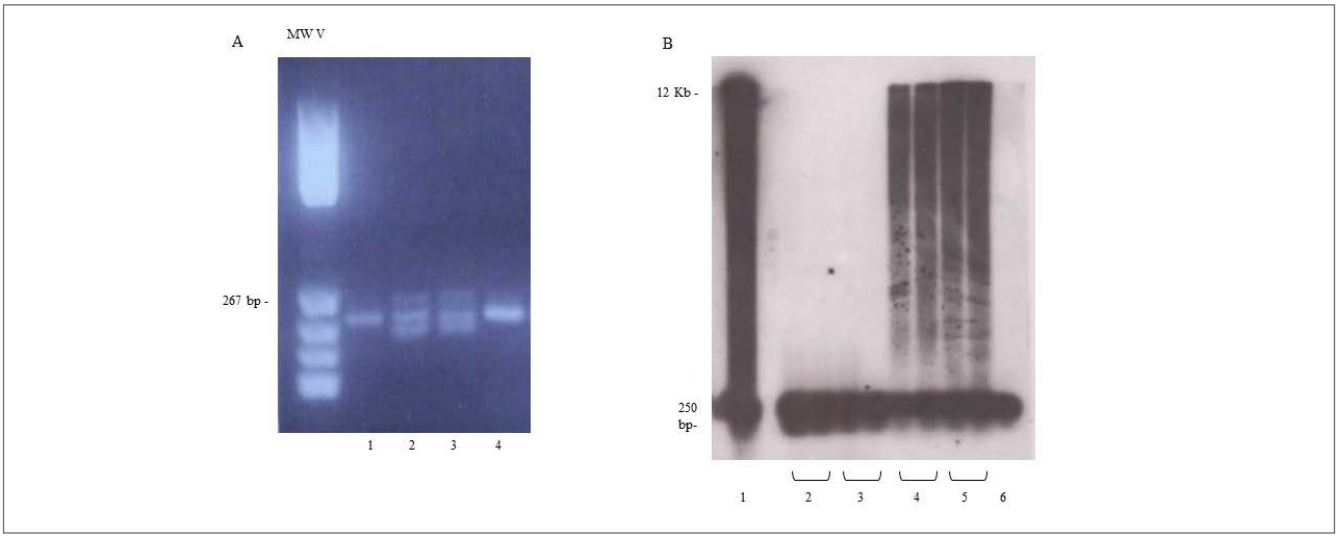

Figure 1. (A) Cropped gel showing the amplification of normal alleles by short PCR. One normal allele was detected in the patient (lane 1) and her mother (lane 4), two normal alleles were detected in patient's brother (lane 2) and father (lane 3). For each subject 100 ng DNA were amplified. (B) Pathological expanded alleles are shown by Southern blot of XL-PCR amplification. For each target subjects two DNA amounts were amplified (50 ng and 100 ng), whereas 100 ng DNA were amplified for positive and negative controls. CCTG pathologic expansions are visible as continuous intense smears.1: patient; 2: brother; 3: father; 4: mother; 5: two positive controls; 6: negative control. (C) Electropherogram showing the heterozygote mutation p.Phe168Leu on patient's DNA. (D) Genetic tree of the family in study.

muscle MRI was not performed because she is claustrophobic and, given her physical and emotional debilitation, we decided not to force her. In November 2020 she contracted SARS-Cov2 which temporarily worsened her residual myalgia. At the follow-up visit in our Outpatient Department for Neuromuscular Disorders, in January 2021, the patient had a normal neurological examination except for persistent hand myotonia with warmup. Cardiological screening evaluation (with Echocardiogram and Holter-EKG) revealed a slight mitral valve prolapse and rare ventricular extrasystoles.

Taken together, patient's history and clinical data suggested a diagnosis of DM2. Indeed, a genetic assay for DM2 revealed a pathological expansion in intron 1 of *CNBP* gene. Parents' DNA testing confirmed the maternal origin of the expansion which was absent in the brother. Amplification of *CL3N58* marker detected only a single allele in the normal size range on the gDNA of the proband and her mother, while her father and brother showed healthy patterns (Fig. 1A). Southern blot revealed the presence of a broad smear in the patient and her mother, indicating the presence of pathological expansions (Fig. 1B), number of CCTG repeats ranging from 75 (normally inherited allele) to more than 1600. Furthermore, *CLCN1* and *SCN4A* genes, coding respectively for muscle ion channel CLC-1 and sodium voltage-gated channel alpha subunit 4, were directly sequenced. On *CLCN1* gene the previously reported [13] pathogenic mutation p.Phe167Leu (c.501C > G) on exon 4, was detected on patient's DNA (Fig. 1 C). The missense was maternally transmitted (Fig. 1 D), and inherited also by patient's brother. Sequencing results were negative for SCN4A. The clinical situation has remained stable since then except for a transient worsening in February 2022, when she referred increasing fatigue, myalgia and muscle stiffness and discrete proximal weakness – though mainly antalgic – in both upper and lower limbs, confirmed at neurological examination. In the same period, she underwent a control EMG examination which was unchanged and confirmed myotonia.

Discussion and review of the literature

We describe the case of a young woman affected with a form of DM2 which remained clinically silent until the age of 25 years and which was brought about by a moderate, but prolonged physical exercise performed after the long period of inactivity caused by the Covid-19 lockdown.

As well documented by Gonzalez-Perez and colleagues [14], a maternal inheritance of the disease is generally associated with an age of symptom onset within the third decade of life. This is also the case of the patient under study, who inherited the *CNBP* expansion from her mother and showed the first signs at 25 years of age. In particular, she presented with muscle pain and stiffness in the lower extremities, which are the most common early onset symptoms in DM2 [15,16]. A further relevant clinical event was cataract surgery at the age of 20 years, which is reported in more than half of the female patients. Patient's mother had undergone bilateral cataract surgical correction as well, at the age of 55 years. The peculiarity of our case is not related to the neuromuscular manifestations per se, i.e. myotonia, but to the fact that they began during a long period of inactivity and, more overtly, when resuming physical activity.

Though the patient did not show severe myotonia, *CLCN1* and *SCN4A* genes, coding respectively for muscle ion channel CLC-1 and sodium voltage-gated channel alpha subunit 4, were screened to rule out possible mutations capable of sustaining the early onset of myotonia [17,18].

The relatively early onset of myotonic discharges shown by the patient and the peculiar triggering condition could be at least partially explained by the presence of the heterozygote missense p.Phe167Leu on *CLCN1* gene. Indeed, this mutation has been described in association with the autosomal recessive form of myotonia congenita; however, functional studies in heterologous expression systems have proven that the effect of this mutation is a slight shift in the Cl potential [19,20]. However, the same genotype did not have any effects on the mother, who remains paucisymptomatic, which strengthens the fact that sudden and consistent resumption of physical activity, causing rhabdomyolysis, precipitated a potentially not so severe condition and unmasked the underlying disease.

As in other muscle disorders – i.e. dystrophinopathies, glycogen storage and mitochondrial diseases – exercise-related pain is frequent in DM2 patients [10,11]. Nevertheless, our patient had always and systematically performed moderate, but prolonged (up to 10 Km) physical exercise without ever complaining of muscle pain, cramps or weakness in her leg muscles before being forced to inactivity. A retrospective study on the association between long-term habitual exercise and improved muscle strength in 150 DM1 patients [21,22]pointed out that regular physical activity, both aerobic and anaerobic, positively impacted on the maintenance of muscle health in DM1 affected individuals. Clinicians underline that a number of patients have a sceptical, if not fearful, approach to regular physical activity because they are worried about possible negative effects on their muscle pathology. It is known, however, that moderate-intensity training programs, suitable for individuals with neuromuscular disorders, are not only safe, but, also, carry long-term benefits most probably because they are able to slow or reverse muscle fibre atrophy. Quite interesting observations were made by Roussel and colleagues [23] who examined pre- and post-training skeletal muscle biopsies in two DM1 patients who underwent a 12-week strength/endurance training program. In patient 1, who completed 72% of the program, post-training muscle biopsies showed an increase in both type I and type II myofiber diameter along with a substantial increase in the proportion in type II myofibers. Conversely, no significant skeletal muscle adaptations were noticed in patient 2 who had only completed 39% of the program. Post-exercise increase in myofiber diameter was statistically demonstrated also by Mikhail and colleagues [24] in a thorough pre- and post- aerobic training study on 11 DM1 subjects.

Other studies aiming at verifying the effects of physical exercise did confirm a trend toward the increase in cross-sectional area of muscle fibers (though not statistically significant due to the small number of subjects) [25] and recorded an improvement in lower limb muscle strength. Moreover, the participants felt as if they had stronger lower limbs, followed by having a better physical shape and having more energy and less fatigue [25,26]. In addition, the positive value of physical exercise in patients affected by DM1 has been further assessed by other studies aimed at determining the effects of strength training

at molecular and/or metabolic level. Davey and colleagues [27] found post-training transcriptomic improvements in both alternative splicing and gene expression in nine male DM1 patients, whereas Mikhail et colleagues provided evidence for the implication of snoRNAs and other noncoding RNAs in DM1 pathophysiology [28]. The latter authors also demonstrated clinical, respiratory, physical, and metabolic exercise-induced improvements in the same group of DM1 patients and they concluded that these results are largely due to improved mitochondrial quality and content. Post-exercise partial rescue of mitochondrial dysfunction in DM1 patients has even more recently been confirmed by Leo et al [29]. Altogether, these studies indicate physical exercise as a valuable, inexpensive and accessible therapy option. This is especially true for younger patients in the early stages of the disease, because the amount of "trainable muscle", whose tonicity needs being preserved as long as possible, is still considerable. It is true that most available studies on physically trained myotonic subjects have been conducted on DM1 patients, however, given the data emerged at molecular level and considering that the two diseases share the same pathogenetic mechanism, we can infer that the results obtained pertain to DM2 subjects as well. Indeed, Kontou and colleagues [30] described the effect of exercise training on functional capacity and body composition in DM2 patients enrolled in a supervised aerobic and resistance protocol training for 16 weeks. The final evaluation evidenced an increase in walking distance, handgrip strength, lean body mass and bone mineral density, in maximum aerobic power, and a reduced blood pressure.

Noteworthy observations have been made in these years on the relationship between muscle loss of strength in physiological aging/sarcopenia and in myotonic disorders, and on the possible role of physical exercise in modulating these two conditions. Aged skeletal muscles share quite few morphological features with myotonic dystrophy, including fibre size variability and centrally-located nuclei. This parallelism becomes even more intriguing in view of the several studies that, in the last years, have pointed out the crucial role of skeletal muscle microRNA (miRNA) in modulating skeletal muscle health, growth, regeneration and aging, the latter being associated with reduction in muscle repair capacities and, consequently, with sarcopenia and related disability. A downregulation of skeletal muscle miRNA occurs also in chronic myopathies and it has been specifically demonstrated in both DM1 [31] and DM2 skeletal muscles [32]. More specifically, a strict relationship has been demonstrated between miRNA expression and physical exercise, available data suggesting that miRNA regulate skeletal muscle growth and capacity of adaptation in response to physical training in both healthy and myopathic individuals [33,34]. Thus, it has been inferred that thoroughly understanding miRNA modulation following physical activity could turn these molecules into useful biomarkers of skeletal muscle health status and lead to therapeutic approaches in aging and/or myopathic muscles [33].

We can hypothesize that in the DM2 patient described the forced physical inactivity has worsened dysregulation of myo-miRNAs thus preventing skeletal muscle from adapting to the sudden, non-progressive training reactivation. Additional observations and studies on DM2 patients, other myopathic subjects and elders will help clarify this important issue and provide useful behavioural advice. In the meantime, we think neurologists and geriatricians should have these considerations in mind when treating skeletal muscle strength and performance issues in their patients.

Conclusions

The case we reported – the first, to our knowledge, addressing the impact of Covid pandemia on DM2 patients - adds a little piece of information about the role that physical training can play in modulating the onset and the severity of clinical manifestations of DM2, indicating that sustained regular exercise can mask the disease and that, conversely, sudden and prolonged suspension can be detrimental to the point of causing massive rhabdomyolysis. Even more, it underlines that the balance is very precarious and that the tolerance threshold beyond which physical conditions can degenerate is quite low.

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Conflict of interest statement

The authors declare that they have no competing interests, and that the research was conducted in the absence of any commercial or financial relationship potentially being a conflict of interest.

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Authors contributions

SL and MS designed the study and edited the manuscript. SL and SP performed molecular studies. MS and FM contributed to the clinical examination of the patient. MR, SC and GPC revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethical consideration

The case under submission has been approved by the "Comitato Etico Milano Area 2 Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico" (Milan, Italy) and the study was conducted in accordance with Helsinki Declaration as revised in 2013.

Informed consent was obtained from all subjects involved in the study and it is available to the Editors of this journal on request.

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