

ACTA MYOLOGICA

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and
Associazione Italiana di Miologia

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PREFACE

In the recent years the field of neuromuscular diseases with onset in childhood has been revolutionized by the discovery of several new genes and the underlying mechanisms responsible for diseases. With this perspective the conference “News and Views. Neuro-muscular disease from child to adulthood: new tools and new opportunities” was held in Pisa at the end of last September.

Starting from the latest scientific advances in the most common neuromuscular diseases, the conference addressed the need to integrate the disciplines and the clinicians daily involved in taking care of patients with these

diseases, focusing in particular on the phase of transition from childhood to adulthood.

The present issue of *Acta Myologica* and the next at the end of the year will collect a series of interventions presented during the conference. The October issue reports two contributions, one on the aspects related to learning disabilities in children with neuromuscular diseases and their potential effects on the young adult skills, the other on the complex vision of the integration of psychosocial aspects and burden in families with patients affected by neuromuscular disorders. The December issue will publish other presentations on the topics of the days of the conference.

ORIGINAL ARTICLES

Eplerenone repolarizes muscle membrane through Na,K-ATPase activation by Tyr10 dephosphorylation

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Eplerenone, an aldosterone antagonist, repolarizes muscle membrane in-vitro and increases strength in-vivo in channelopathies. In Duchenne dystrophy, it is administered for cardiomyopathy. We studied its mechanism of action on skeletal muscle to test its suitability for increasing strength in Duchenne dystrophy.

Using membrane potential measurements, quantitative PCR, ELISA, and Western blots, we examined the effects of eplerenone on skeletal muscle Na,K-ATPase.

The repolarizing effect of eplerenone in muscle fibres was counteracted by ouabain, an ATPase blocker. In our experiment, ATPA1A mRNA and total ATPase protein were not elevated. Instead, Tyr10 of the α 1 subunit was dephosphorylated which would agree with ATPase activation. Dephosphorylation of the coupled Akt kinase corroborated our findings.

We conclude that eplerenone repolarizes muscle membrane by Na,K-ATPase activation by dephosphorylation at Tyr10. Since ATPase protein is known to be compensatorily increased in Duchenne patients without activity change, eplerenone treatment may be beneficial.

Key words: eplerenone, ATPase, Duchenne muscular dystrophy

Introduction

In X-linked Duchenne muscular dystrophy, elevated sodium conductance with intramuscular sodium accumulation and subsequent osmotic oedema has been suggested to be pathogenetically relevant (1). Eplerenone, an aldosterone antagonist which could reduce tissue sodium content, has been shown to reduce fibrosis and improve cardiac function in Duchenne boys (2). Since eplerenone is specific to the mineral corticoid receptor, the risk for glucocorticoid myopathy, a limiting factor of the standard

therapy, would be negligible. A possible positive effect of eplerenone on the strength of skeletal muscle has been suggested (3). To identify a possible mechanism of rapid, non-genomic action and strengthen a putative suitability of the drug for treatment of weakness in Duchenne dystrophy, we examined its effect on the Na,K-ATPase in skeletal muscle.

Materials and methods

Membrane potentials. Rattus norvegicus animals were sacrificed by CO₂-asphyxiation in accordance with German animal protection law (TierSchG) and reported to the Animal Protection Office of Ulm University. Samples of whole rat diaphragm with attached rib fragments and central tendon were kept in carbonate-buffered saline solution of 300 ± 5 mOsmol/L containing 2 mM K⁺ and 1:500 Dimethyl sulfoxide (DMSO) for up to 4 h during the course of the experiment. To mimic depolarization with sodium overload as observed in Duchenne patients (1), 10 μ M of a sodium/potassium ionophore (gramicidin) was added. To prevent a repolarization by ATP depletion during the course of our long-lasting experiments, 4 μ M of a blocker of ATP-sensitive potassium channels (glibenclamide) was also added. This combination of drugs has been successfully used in an in-vitro model of Duchenne muscle in the past and enables comparison of our results to previous work (3). For testing of the drug, 20 mg/L eplerenone with and without 10 μ M ouabain (Na,K-ATPase blocker) were tested. Incubation time was 30 min. Sharp electrodes with resistance of 5-8 M Ω were used to measure resting membrane potentials of 6-31 fibres per sample. Data are mean of means and standard error.

Quantitative polymerase chain reaction (qPCR).

C2C12 cells were cultured in growth medium containing Dulbecco's Modified Eagle Medium (DMEM) with 10% bovine serum at 37°C and 10% CO₂. At 95% confluency, medium was replaced by DMEM with 10% horse serum to initiate myotube fusion. On day 6 after beginning of fusion, medium was replaced with serum-free DMEM and 1:500 DMSO and cells kept at 37°C and 10% CO₂. 24h later, cells were subjected to fresh solutions with or without 20 mg/L eplerenone for 30 min. To enhance eplerenone effect, 10 nM aldosterone was added. Total ribonucleic acid (RNA) was harvested with RNeasy Mini-Kit and cleaned in a QIAshredder. Using commercial primers from QIAGEN for ATP1A1 (Cat.No. PPM04163A) and ACTB (Cat.No. PPM02945B; as control) in the OneStep reverse transcriptase(RT)-PCR and SYBR Green Kit, qPCR was performed. The threshold cycle numbers for significant amplification, C_t-values, were averaged and the average C_t-value of the housekeeping ACTB subtracted (ΔC_t).

Enzyme-linked Immunosorbent Assay (ELISA).

Cultured C2C12 myotubes were lysed with urea buffer and further cleaned with a QIAshredder column. 50 μ g of protein was loaded onto a 96-well high-binding plate and stored over night at 4°C. Wells were incubated with 100 μ g commercial primary (for α 1 subunit of total Na,K-ATPase and of phospho-Na,K-ATPase phosphorylated at Tyr10, ser16, and ser943; all four antibodies from Cell Signalling, Leiden, NL) and HRP-conjugated secondary antibodies for 2h each at 37°C and washed with Tris-buffered saline with 1% Tween 20 (TBST). Bound antibodies were incubated with 150 μ l of 3,3',5,5'-Tetramethylbenzidine, the reaction was stopped after 15 min with 50 μ l of 2M H₂SO₄ and immediately measured. Values for phosphorylation sites were normalized to total protein and their phosphorylated control.

Western Blot. Cultured C2C12 myotubes were lysed with Tris-Triton buffer. The supernatant was run on a 9% sodium dodecyl sulphate polyacrylamide gel, blotted to nitrocellulose membrane, and incubated overnight at 4°C with commercial antibodies for Akt, pAkt S473 and pan-Actin (all three from Cell Signalling, Leiden, NL). After washing in TBST, membranes were incubated for 2h with IRDye800CW (Li-Cor Biosciences, Bad Homburg, GER) and washed. Evaluation was performed with Image Studio Lite 5.2 and with normalization to actin.

Statistics. Data are average with standard deviation unless stated otherwise. Significance was tested using student's t-test.

Results

Resting membrane potentials of diaphragm samples were -85.2 ± 4.9 mV (n = 20 diaphragms with alto-

gether 290 myofibres) for the DMSO control, whereby $3.2 \pm 1.1\%$ of fibres were more depolarized than -70 mV (P2 fraction). Addition of gramicidin and glibenclamide (to mimic the situation in Duchenne) resulted in depolarization to -70.0 ± 4.2 mV (n = 12 with altogether 204 myofibres, $p < 0.0001$) with $42.9 \pm 4.5\%$ ($p < 0.0001$) of fibres in the P2-fraction (Fig. 1A). Incubation with eplerenone repolarized samples by 5.9 mV to -75.9 ± 3.7 mV (n = 9 with altogether 182 myofibres, $p = 0.002$) and concomitantly decreased P2 by more than half to $19.2 \pm 5.1\%$ ($p = 0.002$, Fig. 1B). To test whether the Na,K-ATPase was involved in the repolarization, we added its blocker, ouabain, which depolarized samples by 3.8 mV to -72.1 ± 7.5 mV (n = 25 with altogether 284 myofibres, $p = 0.04$) and increased the P2-fraction to $36.3 \pm 5.5\%$ ($p = 0.11$, Fig. 1C). Therefore, ouabain eliminated the repolarization effect almost completely suggesting that the Na,K-ATPase may be the effector for repolarization by eplerenone.

To test, whether eplerenone, which has a typical steroid structure, increases transcription of ATPase subunits during the 30 min eplerenone incubation, we performed quantitative RT-PCR of ATP1A1 encoding its α 1 subunit. However, even after pre-incubation for 24 h with 10 nM aldosterone expression to maximize effects, eplerenone did not lead to significant changes of ATP1A1 expression compared to DMSO control with ΔC_t values of 12.8 ± 2.8 vs 12.4 ± 1.8 (n = 3; $p = 0.45$).

In the ELISA, incubation with eplerenone did not change total ATPase protein amount which was in agreement with unchanged transcription. Therefore, we postulated a non-genomic effect such as secondary modification of this ATPase subunit. Three phosphorylation sites of different metabolic pathways were considered: i) Ser16 which affects ATPase trafficking (4) and is phosphorylated by the aldosterone-inducible protein kinase C (PKC) (5), ii) Ser943 which affects ATPase activity (6) and is phosphorylated by aldosterone-inducible protein kinase A (PKA) (7), and iii) Tyr10 which affects ATPase activity (8) and is phosphorylated by Lyn kinase which also phosphorylates Akt (9), a kinase that is dephosphorylated by aldosterone (10). Na,K-ATPase α 1 subunit phosphorylation at Ser16 or Ser943 was unchanged (Fig. 1D). In contrast, protein phosphorylated at Tyr10 was significantly reduced (by $56.1 \pm 29.5\%$ compared with DMSO control; n = 4, $p = 0.038$, Fig. 1D). To support this finding, we tested the phosphorylation of a coupled protein, Akt kinase, in Western blot. Total Akt protein was unchanged, but its phosphorylation at Ser473 was decreased significantly to $46 \pm 57\%$ of the DMSO control (n = 14; $p = 0.01$, Fig. 1E).

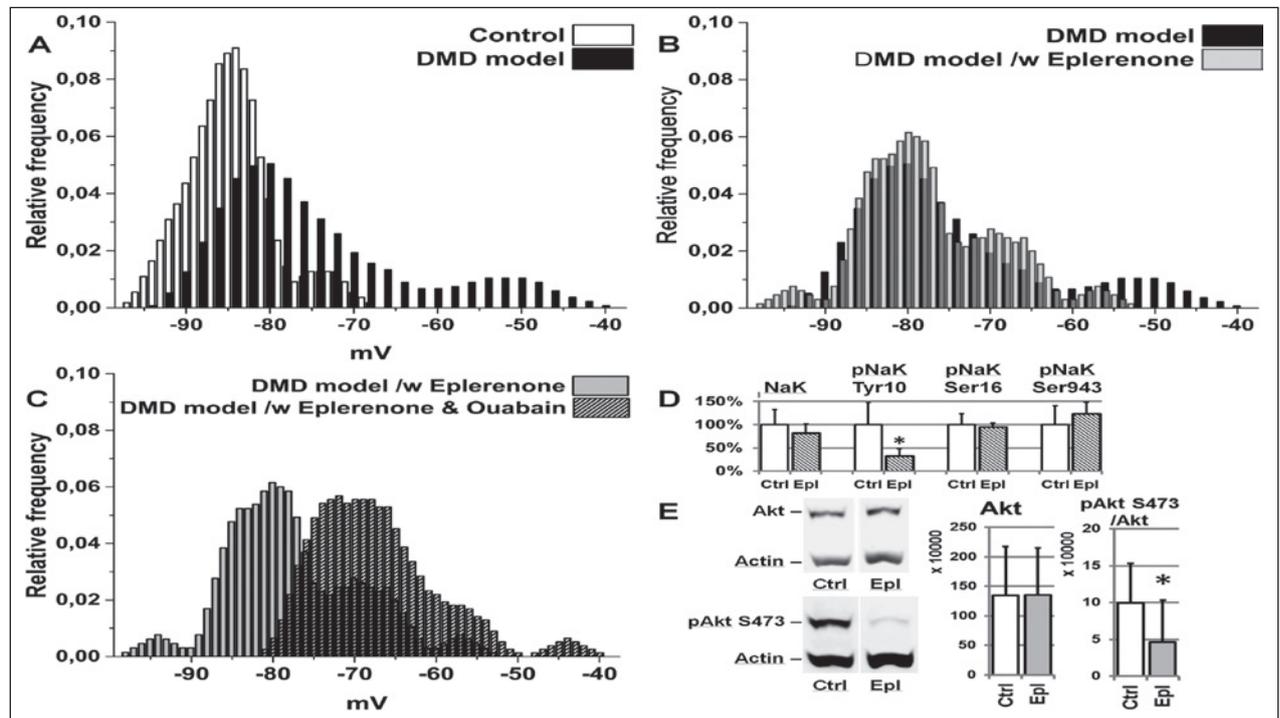


Figure 1. (A-C) Smoothed histograms of relative frequency of resting membrane potentials of all rat diaphragm samples. For smoothing, three data histograms shifted by 1 mV each (class width of 3 mV) were added together ($n = 182-290$). (A) Depolarization in DMD model caused marked depolarization compared to control; (B) Eplerenone repolarised large portion of fibres; (C) Ouabain counteracted the eplerenone effect. (D) ELISA. Original blots for Extinction normalized to total protein and phosphorylated control respectively. Data are mean and standard deviation. Total Na,K-ATPase ($82.2 \pm 20.0\%$, $n = 4$) and phosphorylation of Ser16 ($95.2 \pm 24.9\%$; $n = 4$) and Ser943 ($123.4 \pm 24.9\%$; $n = 4$) remained unchanged, while phosphorylation of Tyr10 was significantly reduced ($56.1 \pm 29.5\%$; $n = 4$; $p = 0.038$) after eplerenone incubation. (E) Western blot. Original blots of Akt (1:1.000) and phosphorylated Akt (1:500) with actin (1:10.000) as standard (left). Intensities normalized to actin and phosphorylated protein relative to total amount (right). Data are mean and standard deviation. Akt remained unchanged ($100 \pm 59\%$; $n = 18$), while phosphorylation at Ser473 was significantly reduced to $46 \pm 57\%$ ($n = 14$; $p = 0.01$) after 30 min eplerenone incubation.

Discussion

The degree of depolarization in our gramicidin/glibenclamide model and the degree of repolarization by eplerenone in this study are consistent with an earlier report (3). Also, the ouabain blockage of the eplerenone-induced repolarization in skeletal muscle strongly suggests Na,K-ATPase activation which is in agreement with a study showing that eplerenone counteracts ouabain-induced decrease of Na,K-ATPase current density in heart muscle (11).

To avoid transcription-mediated effects by eplerenone, we set our maximal eplerenone incubation time to 30 minutes. Our RT-PCR findings confirmed that during this incubation time, no changes of transcription of the Na,K-ATPase genes took place. In agreement with this, the ELISA did not show any change in ATPase protein abundance, i.e. no translation changes either. There-

fore, a modulation of ATPase activity may be the source of the repolarizing effect of eplerenone. We considered a representative phosphorylation site of the three kinases PKA, PKB, and PKC.

Ser16 is phosphorylated by PKC and regulates membrane trafficking of the Na,K-ATPase (4, 5). Previously, aldosterone has been shown to activate PKC-signalling and this pathway was inhibited in cardiomyocytes by eplerenone after 24 h (12). We found no change in ser16 phosphorylation after an incubation time of 30 minutes and deduced that inhibition of this pathway may not be a rapid effect of the drug. However, in long-term therapy, this effect could contribute to fibrosis inhibition and improvement of cardiac function found in the aforementioned clinical trial (2).

Ser943 is phosphorylated by the aldosterone-inducible PKA which regulates Na,K-ATPase (6, 7). However,

we show that eplerenone does not change phosphorylation at this site. This could be due to either short incubation time with drug, or the lack of pre-incubation with aldosterone. Either way since pre-incubation with aldosterone was not required for repolarization in the membrane potential measurements of native rat myofibres, modification of Ser943 phosphorylation does not explain the rapid repolarization we found in the in-vitro Duchenne model.

In contrast, Tyr10 phosphorylation of Na,K-ATPase α 1 subunit was reduced by eplerenone. Since Tyr10 phosphorylation reduces ATPase activity (14), we assume that dephosphorylation will increase its activity. Further, since Duchenne muscle has increased Na,K-ATPase protein quantity without relevant single-protein activity change (15), the rapid effect of eplerenone on Tyr10 which increases ATPase activity could ameliorate muscle weakness in Duchenne dystrophy by repolarizing muscle membrane.

To our knowledge, this is the first report of regulation of Tyr10 phosphorylation by eplerenone. Since Tyr10 is phosphorylated by Lyn kinase (8) and dephosphorylated by protein tyrosine phosphatase 1B (14), our study additionally implicates, for the first time, that the Lyn kinase and/or the protein-tyrosine phosphatase 1B may be regulated by eplerenone.

Acknowledgements

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Learning disabilities in neuromuscular disorders: a springboard for adult life

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Although the presence of cognitive deficits in Duchenne muscular dystrophy or myotonic dystrophy DM1 is well established in view of brain-specific expression of affected muscle proteins, in other neuromuscular disorders, such as congenital myopathies and limb-girdle muscular dystrophies, cognitive profiles are poorly defined. Also, there are limited characterization of the cognitive profile of children with congenital muscular dystrophies, notwithstanding the presence of cerebral abnormality in some forms, and in spinal muscular atrophies, with the exception of distal spinal muscular atrophy (such as the DYN1CH1-associated form).

Starting from the Duchenne muscular dystrophy, which may be considered a kind of paradigm for the co-occurrence of learning disabilities in the context of a progressive muscular involvement, the findings of neuropsychological (or cognitive) dysfunctions in several forms of neuromuscular diseases will be examined and reviewed.

Key words: learning disability, DMD, CMD, CM, SMA-LED

Introduction

Several studies have suggested the presence of central nervous system involvement, manifesting as cognitive deficits or psychiatric problems, in neuromuscular disorders (NMD) (1, 2); however, few data are still known about subtle “not optimal” functions that, especially in a developing perspective, can impact cognitive and learning abilities (3).

It is well recognized indeed that learning disabilities can affect an individual's life beyond academics and can impact relationships with family, friends and in the workplace (4). On the other hand, in adults with NMD, quality of life and well-being are frequently re-

stricted (5). Therefore, early identification of cognitive weakness in children with NMD is imperative to set psychological interventions and consequently improve quality of adult life.

The aim of the present work is to review the studies investigating the occurrence of neuropsychological deficits in children with NMD and their impact on later learning skills and academic achievement.

Duchenne muscular dystrophy

Over the past few decades there has been increasing attention to neurodevelopmental dysfunction in Duchenne muscular dystrophy (DMD), on the other hands research in cognition, learning, and behavior in Becker muscular dystrophy (BMD) is even scarcer, being limited to only few study (6, 7). Boys with DMD display distinct cognitive profiles and also exhibit neurobehavioral comorbidities, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, and obsessive-compulsive disorder (8-12). Several studies have reported a non-progressive lower IQ in DMD boys compared to controls (1, 13), with about 30% having cognitive impairment, repeatedly been associated with mutations affecting brain specific isoforms of dystrophin (2, 14-20). Below-average reading performances have also been reported (21), and difficulty mastering academic material is a frequent concern during the primary years for this boys (22-24). Academic difficulties may be due to specific learning disabilities such as dyslexia or other cognitive deficits, such as impaired working memory (23). In a previous study we confirmed a high incidence of literacy prob-

lems in boys with DMD showing a profile less severe than, but qualitatively similar to, Italian children with developmental dyslexia (DD) (3). Both DMD and DD boys showed specific difficulties in reading and writing words and reduced rapid automatized naming speed, a measure highly related to reading speed. Moreover, the boys with DMD and the subgroup of dyslexic children with a previous language delay showed additional deficits in phonological processing. In a more recent study, analyzing in a larger DMD population high order level cognitive skills, Executive Functions (EF), it has been shown that the neuropsychological profile is characterized by impairments in problem solving, inhibition and working memory, necessary to plan and direct goal oriented behavior in novel and complex tasks (25). It is well known that these processing problems could interfere with learning basic skills, such as reading, writing or math and psychological health in general (26).

Although difficulties in EF may be overlooked by parents and teachers because they are not disruptive, problems with planning, organization, initiation and self-evaluation may become more evident when boys progress through the grades and more and more independence is expected in their work. Moreover, as young men with DMD grow older, and expectations for responsibility increase, problems with short-term memory and EF can interfere with their ability to keep track of, and efficiently complete assignments and projects.

Further studies need to early identify preschool antecedents of cognitive and learning difficulties in DMD in order to better understand their causal relationships and to plan interventions aimed to empower functional strengths and weakness.

Myotonic dystrophy

Since the original descriptions of myotonic dystrophy type 1 (DM1), there have been numerous observations of decreased mental capabilities in these patients (27). From 10% to 24% of DM1 individuals show mental retardation, particularly those affected by the congenital form (28, 29). Studies on children with DM1 demonstrated that lower IQs correlate with longer expansions, mainly related to maternal inheritance and age of onset of symptoms (30, 31) although does not correlate with the neuromuscular impairment and the severity of disease. Nevertheless, patients with the childhood form of DM1 can have an IQ scores similar to those of the normal population, but show learning disabilities correlated to impairment in EF, visual perception, constructional ability and visual memory (32), more specifically in visuospatial recall and in both short and long-term components of verbal memory (33). Moreover,

children and adolescents affected by the childhood type of DM1 presented prominent signs of psychopathology, most frequently an attention deficit with hyperactivity disorder and anxiety disorder (ADHD) (33-36).

Personality and behavioral disturbances, that could have cascade effects on cognitive functioning, are also well documented in the adult form: myotonic dystrophy present an homogeneous personality profile, with statistically significant differences for avoidance, obsessive-compulsive, passive-aggressive, emotional deficits and schizotypic traits. Nevertheless the depressive symptoms may arise from the emotional reaction to a disease, causing physical restrictions and disabilities (37).

These observations, also supported by neurofunctional studies (38, 39), suggest that patients affected by myotonic dystrophy, regardless of the form, may have striking inter-correlated cognitive and psychiatric features. Thus, it may be considered that an intervention on both behavioral and cognitive level may be useful to avoid psychosocial maladjustment.

Congenital muscular dystrophies and Limb-girdle muscular dystrophies

The congenital muscular dystrophies (CMD) encompass as a group, great clinical and genetic heterogeneity (40-42).

The degree of muscular and/or CNS involvement is variable within a spectrum from severe “floppy” infant syndrome with cerebral and cerebellar malformation and white matter abnormalities, to moderate motor delay and mild or moderate limb-girdle involvement during childhood, compatible with survival into adult life and relatively good quality of life. Alike, cognitive abilities can be severely affected, as in some forms of dystroglycanopathies (such as those with mutations in *POMT1*, *POMGnT1*, *LARGE...*) (43-45), or normal, as in the majority of affected individuals with merosin-deficiency (46-48).

Also the new and less characterized forms recently reported, such as *SYNE1*-related CMD (49), and *CHKB*-related muscle disease could be characterized by severe intellectual disability (50). We recently observed a CMD patient with a *TMEM5*-related dystroglycanopathy presenting with a mild muscular phenotype resembling a limb girdle muscle dystrophy (LGMD), in which the neuropsychological assessment revealed a moderate mental delay with low verbal skills and slight deficits in attention, short term working memory, and problem solving (51). The remaining forms of LGMD have usually normal cognitive abilities and low self-esteem and feelings of sadness and culpability as the only defined psy-

chopathological characteristics (52). Probably because of their heterogeneity and severity, there are no studies investigating more in depth possible cognitive impairment or subtle learning deficits.

Congenital myopathies

Congenital myopathies are considered disorders restricted to the skeletal muscle, with few exceptions: anecdotally have been in fact described patient with structure myopathy, developmental delay, and, cerebellar deficits without any radiological sign of cerebral or cerebellar malformation (53, 54), or epileptic seizures and cerebral abnormalities (55). Considering that both cases have not a specific molecular definition and in view of the wide spectrum of genotype that could be related to some histological findings, the diagnosis of congenital myopathy could be questioned.

However, our own, as yet unpublished, observations suggest that patients with congenital myopathy, experience fatigability not only during motor skills but also during cognitive works. To support an involvement of cognitive process in congenital myopathy or in such neuromuscular disorders where fatigability is part of the framework (i.e. metabolic myopathies or congenital myasthenic syndrome), we recall a study on adolescent chronic fatigue syndrome (CFS), defined as persisting or relapsing fatigue of more than 3 months' duration, conduct in Norway, which reported that more than 80% of individuals with CFS complain cognitive problems concerning executive functions. Moreover, this study demonstrates that adolescents with chronic fatigue, perform worse than healthy control on measures of processing speed, working memory, verbal learning and cognitive inhibition response time, but not on cognitive flexibility or delayed recall. Group differences remained largely unaffected when adjusted for symptoms of depression, anxiety traits and sleep problems. According to parents' observations, their children with chronic fatigue have more problems with everyday EF as expected (56).

We suggests to take into consideration the reports of cognitive fatigability, and to systematically annotate this finding, to evaluate subtle cognitive dysfunction in such patients.

Spinal muscular atrophy and distal spinal muscular atrophy

Children with SMA are universally considered as "normal in intellect" or even "brighter than average" and this is a clear distinction if compared to DMD boys (57).

This clinical impression was subsequently confirmed in specific studies showing that SMA children are often more intelligent than healthy controls of the same age and from the same environment, or, than patients with the same degree of motor disabilities (57, 58). Moreover, academic skills required in verbal components of intelligence tests are most developed in patients with SMA, suggesting that these children develop effective and useful strategies to compensate for their physical handicap by the acquisition of cognitive skills and knowledge (59, 60).

However, although this figure still seems to be true for patients with SMA II or III, it has been questioned for patients with SMA I, where not-sufficient long term studies can be achieved due to their reduced life expectancy.

Moreover, while not considering the forms of SMA in which the involvement of the central nervous system is known (i.e. SMA-PME), it has been recently described patients with other form of progressive spinal muscular atrophy with congenital or early-onset, identified as autosomal dominant or sporadic congenital spinal muscular atrophy with lower extremity predominance (SMA-LED) (61) that could be associated with severe intellectual disability or learning difficulties (62-65).

Scoto et al., recently reported a large cohort of children and adults affected by SMA-LED due to *DYNC1H1* mutations, in which one-third presented mild to moderate cognitive impairment and/or behavioral comorbidities consistent with ADHD traits, not appear to be related to the severity of the motor impairment (66).

In continuum of the spectrum, there are the adult onset progressive spinal muscular atrophies (PMA) that has been recently documented to have a cognitive dysfunction similar to those found in patients with motor neuron disease with upper motor neuron (UMN) involvement such as ALS (67). In this study, executive dysfunction and verbal recall deficits were demonstrated in PMA similar but less extensive than in ALS and no differences in depression or anxiety scores have been found between PMA patients with and without cognitive impairment.

Also in Spinal and bulbar muscular atrophy (SBMA), Kennedy's disease, another form of PMA, it was recently found minor cognitive disturbance in the working memory (digit span backward task), verbal fluency category (single letter fluency task) and memory storage capacity (digit span forward task) (68).

These data suggest some continuity between the broad spectrum of SMA (SMA, SMA-LED, SMA-PME) and PMA, also for the brain involvement. Knowledge of this dyadic relationship between muscle and brain is important as, with prolonged life expectancy, these learning and neurobehavioral disorders may have growing impact and may be highly debilitating.

Conclusions

Literature on cognitive and learning skills in NMD diseases is still scarce but the existing studies converge in lighting impairments in the EF domain and three main scenario may be suggested. In several NMD diseases, as supported by neurofunctional studies, abilities in control interference, updating information in memory and cognitive flexibility may represent the “core cognitive difficulties”. In other forms, as in many other neurodevelopmental disorders, the cognitive profile may be characterized by subtle working memory and/or processing speed difficulties. Finally in some NMD it may be the case that motor dysfunctions and psychological co-variables play a major role on higher order cognitive dyfunctions, as executive functions may often due to impaired lower-order functioning, such as perception, information processing and response speed. Although further studies are needed to better understand causal relationships in the different NMD conditions, not optimal cognitive functioning seem a common feature of all (Fig. 1).

Meanwhile the findings so far described suggest to explore cognitive functions to understand the extramotor involvement and the heterogeneity within the NMD spectrum and target the correct interventions for the school, in view of the negative impact that school failure can play on quality of life, school attendance and social and family functioning.



Figure 1. Schematic representation of cognitive dysfunctions in NMD.

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Family context in muscular dystrophies: psychosocial aspects and social integration

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Muscular dystrophies (MDs) are degenerative diseases which may lead to marked functional impairment and reduced life expectancy. Being caregivers of a loved one with MD may be both a rewarding and a demanding experience that may have relevant impact on the quality of life of the whole family. In this short review we summarize the main findings of the first survey on family context in MD in Italy.

The study was carried out on 502 key-relatives of patients suffering from Duchenne, Becker, or Limb-Girdle MD, aged between 4 and 25 years, and attending one of 8 participating Centers, all over 2012. The results revealed that practical difficulties were mainly related to relatives' involvement in helping the patient in moving and in relative's constraints of leisure activities. Furthermore, feelings of loss and perception of patient's condition as having negative effects on the family life were the psychological consequences more frequently complained.

However, despite the difficulties, 88% of the key-relatives acknowledged the caregiving as a positive experience. In fact 94% of the respondents stated they could rely on friends in case of own physical illness, and 88% in case of psychological stress.

Burden was found higher among relatives of patients with lower functional autonomy and longer duration of illness, and among relatives with lower professional and social support. Conversely, the positive aspects of the caregiving were more frequently acknowledged by those who received higher level of professional help and psychological social support.

These results reveal that the caregiving experience has a positive impact on key-relatives quality of life despite the practical demands, and that the support of professionals is essential to help families in identifying the benefits of this experience without denying its difficulties.

Key words: muscular dystrophies, family burden, social network

Introduction

Muscular dystrophies (MDs) are degenerative, rare diseases that lead to muscle strength loss and progressive restriction of functional abilities (1, 2). Although only symptomatic therapies are available for these diseases, improved standards of care have led to a considerable increase in life expectancy (2, 3). Most patients with MD live at home and receive daily assistance from their relatives (4-10).

Difficulties experienced by relatives of patients as a consequence of their caregiving role are commonly referred to as "family burden" and are divided into "practical" and "psychological" burdens (11, 12). Practical burden refers to problems such as disruption of family relationships, constraints in social, leisure, and work activities, and financial difficulties (11-13). Psychological burden describes the reactions that family members experience, e.g. feeling of loss, sadness, tension, and feeling unable to cope with the situation (14-16).

Family involvement may facilitate patients' adaptation to the illness and their clinical response to therapies, but it can lead to high family burden. Practical and psychological consequences of family caregiving have been rarely examined in neuromuscular diseases.

Available data suggest that different pathologies, due to their clinical characteristics and social reactions to them (11), may dictate specific needs for care and require different therapeutic strategies (12, 17-19).

Family involvement in the care of long-term diseases is particularly relevant in Italy, where the national health policy is strongly community oriented (11). In Italy, no study has systematically explored the burden, and social and professional support in key-relatives and healthy sibling of children with MD.

In 2012, a survey on the families of young patients with several forms of MD, including DMD, Becker MD (BMD), and Limb-Girdle MDs (LGMDs) was carried out on a national scale. The project aimed to explore the following aspects: 1) practical and psychological burden in key-relatives; 2) practical and social network support; 3) pattern of care received by the patients and professional support to the caregivers; 4) differences related to type of MD, pattern of care, and geographical areas.

In this invited review, we summarize the main findings from the above mentioned study focusing on psychological benefits, main practical difficulties and social and professional resources (20-22).

Patients and methods

Patients

A total of 502 key relatives of 4-25 year old patients with MDs who were enrolled in 8 specialized Italian centers for MDs participated in the survey (Fig. 1). Patients' selection criteria: age between 4 and 18 years; in charge for at least 6 months; living with at least one relative; not suffering from diseases other than those MD-related. Key-relatives' selection criteria: age between 18 and 80 years; not suffering for illness requiring long-term intensive care; not living with persons suffering from chronic illness but the patient. The study protocol was approved by the Ethics Committee of the Second University of Naples and by the Local Ethics Committee of each participating Center.

Methods

To assess the patient's functional autonomy an *ad hoc* semi-structured interview was developed and used to obtain the Barthel-10 functioning index (23) by the

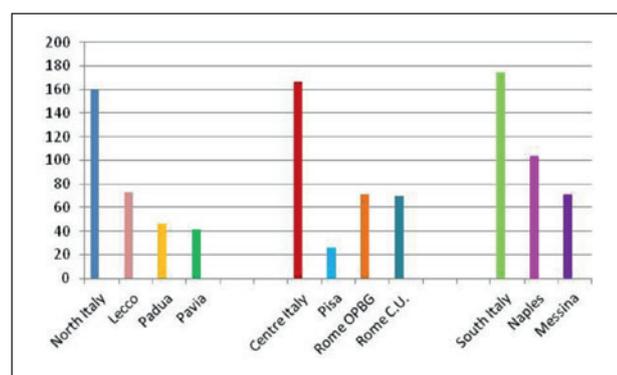


Figure 1. Distribution of the enrolled cases according to the geographical area (North, Center and South Italy). Legend: OPBG: Bambin Gesù Paediatric Hospital; C.U.: Catholic University

key-relative. Family Problems (FPQ) and Social Network (SNQ) Questionnaires were administered to key-relatives in order to focus on the difficulties and resources experienced by the families (11).

Results

Patients

The majority of the patients were male (96%), young (mean age 12.8 (5.6sd), and in school (86%); 66% of them suffered from DMD, 26% from BMD, and 15% from LGMD. Sixty-one percent of patients were ambulant and 39% wheelchair-bound, with a mean level of independence in daily activities, measured by the Barthel Index, of 68.3 (31.3 sd). Most of patients were in drug treatments (73%) and attended rehabilitation programs (67%). Only 72 patients (14%) had received psycho-educational interventions as psychological support (53%) and information on muscular dystrophies' treatments (39%). Moreover, 66% of patients received social/welfare support, mainly economic benefits and 16% school support.

Key-relatives

Most of the key-relatives were mothers (84%) and lived with a partner (88%). Almost half of them (56%) had received higher education and 53% were employed. In the two months preceding the evaluation, key-relatives spent on average 5.7 (4.6sd) daily hours in patient's caregiving. In the previous six months, 31 relatives received psycho-educational interventions including education on clinical and rehabilitative procedures (68%), information on treatments (54%), and psychological support (22%). Of the 55 of relatives (11%) receiving social/welfare support, 46 (84%) were sustained by Family/Patients Associations. As far as the practical consequences of caregiving, the most frequently mentioned difficulties were the neglect of hobbies and free time activities (59%), night awakenings to take care of their patient (45%), and difficulties in work and household activities (45%). Moreover, 35% of relatives stated that they had economic difficulties and 64% reported to have sustained costs for patient's care (doctors/nurses and drugs). Regarding psychological difficulties, 77% of the relatives reported feelings of loss, 74% sadness and/or depression, and 72% worries for the future of other family members.

However, despite the difficulties, 88% of key-relatives acknowledged the caregiving experience as having a positive impact on their lives. In particular, 72% reported changes in life's values, and 18% an increased sense of strength and courage against adversities. Moreover, 94% of the relatives stated they could rely on friends in case

of own physical illness, and 88% in case of psychological stress. Furthermore, 92% felt their friends would help them in case of patient's emergencies, and 97% sure to receive professional help in a crisis situation.

The study revealed that burden was higher among relatives who: a) were unemployed and single; b) had patients not attending school and with DMD; c) had less support by their social network and the professionals. Conversely, the positive aspects of caregiving were more acknowledged by key-relatives who had a higher level of professional help and psychological social support.

Exploring the differences among the geographical areas, the study outlined that the welfare support was more frequently available in Northern Italy, the psycho-educational interventions in Central Italy and the clinical care of cardiological aspects in Southern Italy.

Discussion

These findings confirm that home management of patients with MDs may be demanding for patients' relatives, especially when social and professional resources are poor and patients' functional abilities decrease (24). On the other hand, these findings highlight how to rely on the various types of support (social network, professionals and welfare) make differences in terms of family resilience and coping strategies (25-30). In particular, the results of this study will be useful for clinicians to better understand the complexity of the caregiving process in muscular dystrophies and for the healthy policy managers to plan an appropriate allocation of resources.

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Increased heterogeneity of ventricular repolarization in myotonic dystrophy type 1 population

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Sudden cardiac death in myotonic dystrophy type I (DM1) patients can be attributed to atrioventricular blocks as far as to the development of life-threatening arrhythmias which occur even in hearts with normal left ventricular systolic and diastolic function. Heterogeneity of ventricular repolarization is considered to provide an electrophysiological substrate for malignant arrhythmias. QTc dispersion (QTc-D), JTc dispersion (JTc-D) and transmural dispersion of repolarization (TDR) could reflect the physiological variability of regional and transmural ventricular repolarization. Aim of the present study was to investigate the heterogeneity of ventricular repolarization in patients with DM1 and preserved diastolic and systolic cardiac function. The study enrolled 50 DM1 patients (mean age 44 ± 5 years; M:F: 29:21) with preserved systolic and diastolic function of left ventricle among 247 DM1 patients followed at Cardiomyology and Medical Genetics of Second University of Naples, and 50 sex- and age-matched healthy controls. The electrocardiographic parameters investigated were the following: Heart Rate, QRS duration, maximum and minimum QT and JT intervals, QTc-D, JTc-D and TDR.

Compared to the controls, the DM1 group presented increased values of QTc-D (86.7 ± 40.1 vs 52.3 ± 11.9 ms; $p = 0.03$), JTc-D (78.6 ± 31.3 vs 61.3 ± 10.2 ms; $p = 0.001$) and TDR (101.6 ± 18.06 vs 90.1 ± 14.3 ms; $p = 0.004$) suggesting a significant increase in regional and transmural heterogeneity of the ventricular repolarization in these patients, despite a preserved systolic and diastolic cardiac function.

Key words: QTc dispersion, JTc dispersion, myotonic dystrophy, sudden cardiac death, repolarization, arrhythmias

Introduction

Myotonic dystrophy type 1 (DM1), or Steinert disease, is an autosomal dominant disorder with an estimated incidence of 1:8000 births, caused by an abnormal expansion of an unstable trinucleotide repeat in the 3' untranslated region of DMPK gene on chromosome 19 (1). DM1 is characterized by highly variable clinical manifestations that affect specific tissues, such as distal limb and facial muscles, smooth muscles (gastrointestinal tract, uterus), the eye (primarily the lens), the brain (especially the anterior temporal and frontal lobes), and the endocrine function (testosterone deficiency, abnormal growth hormone regulation, insulin resistance, thyroid dysfunction). Cardiac involvement is noticed in about 80% of cases, often preceding the skeletal muscle one (2), especially in men (3). Heart block is the first and most clinically significant cardiac disease in this group of patients and it is related to fibrosis of the conduction system and fatty infiltration of the His bundle (4). Heart failure occurs late in the course of the disease as the final stage of a progressive dilated cardiomyopathy. In muscular dystrophies with rapid evolution such as Duchenne muscular dystrophy, the treatment with steroids is currently considered "the gold standard" therapy able to delay the progression of the myocardial fibrosis (5); however some studies on animal models demonstrated a harmful effect of long-term deflazacort treatment on the phenotype rescued by gene therapy (6). An early onset of heart failure may occur in relation to the electromechanical delay caused by both intra- and inter-ventricular asynchrony, successfully treated with

cardiac resynchronization therapy (7, 8). Ventricular arrhythmias are common findings in muscular dystrophies (9, 10). In patients with DM1, sudden cardiac death (SCD) is attributed not only to atrio-ventricular blocks, but also to the development of life-threatening arrhythmias which may occur even in the presence of normal left ventricular systolic function (11). SCD in patients with DM1 has not received sufficient recognition in the literature, and its mechanism remains of great interest. QTc dispersion (QTc-D), JTc dispersion (JTc-D) and transmural dispersion of repolarization (TDR) have been proposed as noninvasive methods to measure the regional and transmural heterogeneity of ventricular repolarization (12). Aim of the present study was to investigate the heterogeneity of regional and transmural ventricular repolarization in DM1 patients with preserved cardiac systolic function, by examining the above mentioned electrocardiographic parameters (QTc-D, JTc-D and TDR).

Patients and methods

Patients selection

Among the 247 DM1 patients regularly followed at the Cardiology and Medical Genetics of the Second University of Naples, 50 (29M:21F) – with a mean age of 44 ± 5 years and preserved cardiac systolic function, were consecutively enrolled to participate in the study. Fifty sex- and age-matched healthy subjects were also recruited as controls. Patients with a history of hypertension (systolic/diastolic blood pressure $> 140/90$ mmHg), diabetes or impaired glucose tolerance (IGT), anaemia, electrolyte imbalance, valvular heart disease, heart failure, coronary artery disease, bundle branch block or atrio-ventricular conduction abnormalities, and previous arrhythmic episodes were excluded from the study.

All patients were in sinus rhythm and not taking medications known to affect electrocardiographic intervals such as antiarrhythmic agents, tricyclic antidepressants, antihistaminics or antipsychotics.

The diagnosis of Steinert disease, firstly based on family history and clinical evaluation, was subsequently confirmed by evaluating the CTG triplet expansion. The study was conducted according to the declaration of Helsinki.

Study protocol

Medical history, physical examination, anthropometric evaluation, 12-lead surface ECG, 2D color Doppler echocardiogram and ECG Holter monitoring were performed in all patients, who were rested for at least 15 min

before cardiovascular assessments, including electrocardiography and echocardiography.

Electrocardiographic measurements

All subjects underwent a standard 12-lead body surface ECG, recorded at a paper speed of 50 mm/s and a gain of 10 mm/mV in the supine position, and were invited to breath freely but not to speak during the ECG recording. To avoid diurnal variations, the ECG recordings were generally performed between 9:00 to 10:00 a.m. The analysis of the tracing was performed by the same investigator, who ignored the subjects' clinic status. ECGs were transferred to a personal computer by an optical scanner and then magnified 400 times by Adobe Photoshop software (Adobe Systems Inc., San Jose, CA). QRS duration, QT interval and JT interval were evaluated with the use of a computer software (Configurable Measurement System) using digitizer 34180 (Calcomp, Anaheim, CA, USA). The variability of the measurements was 0.36 ± 4 ms (not statistically significant). In each electrocardiogram lead, the analysis included 3 consecutive heart cycles, whenever possible. Leads were excluded from the analysis when the end of the T-wave was not clearly distinguishable, or in case of poor quality signal. The QRS interval was measured from the start of the Q wave, or, in the absence of the Q wave, from the start of R wave to the end of S wave (return to the isoelectric line). The QT interval was measured from the initial deflection of the QRS complex to the end of the T wave (return to the isoelectric line). In case of T waves not reliably determined, isoelectric or of very low amplitude, the measurements were not done and the leads excluded from the analysis. When the U wave was present, the QT was measured to the nadir of the curve between the T and U waves. QTd was determined as the difference between the maximal and minimal QT value in all leads (13). The JT interval was derived by subtracting the QRS duration from the QT interval. JTd was defined as the difference between the maximal and the minimal JT value in all leads. All measurements were corrected for heart rate using the Bazett's formula ($QTc = QT/\sqrt{RR}$; $JTc = JT/\sqrt{RR}$). TDR was defined as the interval between the peak and the end of the T-wave (14, 15). For the present study, we considered only the values of TDR measured in the precordial leads, because it has been suggested that these leads more accurately reflect transmural dispersion of repolarization (16).

Echocardiographic measurements

All echocardiographic examinations were performed using a standard ultrasound machine with a 3.5-MHz

phased-array probe (M3S). All patients were examined in the left lateral and supine positions by precordial M-mode, 2-Dimensional and Doppler echocardiography. One lead ECG was recorded continuously. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum end-diastolic thickness (IVSEDT) and left ventricular posterior wall end-diastolic thickness (LVPWEDT) were measured from M-mode in the parasternal long-axis views, according to the SOPs of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated by using the Devereux's formula, and indexed for body surface area and height. Left atrium diameter (LAD) was measured during the systole along the parasternal long-axis view from the 2-dimensional guided M-mode tracing. Left Atrial (LA) length was measured from the apical 4-chamber view during systole. The maximum LA volume (LAV) was calculated from the apical 4- and 2-chamber zoomed views using the biplane method of disks. The ejection fraction (EF) was measured using a modified Simpson biplane method. Each representative value was obtained by the average of 3 consecutive measurements. The pulsed-wave Doppler examination was performed to obtain the following indices of Left Ventricle (LV) diastolic function: peak mitral inflow velocities at early (E) and late (A) diastole and E/A ratio. The average values of these indices, obtained by 5 consecutive cardiac cycles, were used for the analysis.

Statistical analysis

The continuous variables are expressed as mean \pm standard deviation. The statistical analysis was performed using the Student's t-test for unpaired data. P-values < 0.05 were considered as statistically significant. The association between two variables was investigated by the Pearson's simple correlation. The analyses were performed using the SPSS 11.0 software for Windows SPSS Inc. (Chicago, IL, USA).

Results

The clinical and echocardiographic characteristics of the study population are summarized in Table 1. The DM1 group did not significantly differ from the healthy control group in body mass index (BMI), heart rate or blood pressure. No significant differences in LVPWEDT, IVSEDT, LVEDD, LVESD, LVM/height, LV shortening fraction (SF), LVEF and E wave, A wave or E/A ratio were also observed between the two groups.

The electrocardiographic characteristics of the study population are shown in Table 2. Compared to the healthy controls, patients with DM1 presented increased values of QTc-D (86.7 ± 40.1 vs 52.3 ± 11.9 ms; $p = 0.03$), JTc-

D (78.6 ± 31.3 vs 61.3 ± 10.2 ms; $p = 0.001$) and TDR (101.6 ± 18.06 vs 90.1 ± 14.3 ms; $p = 0.004$) (Fig. 1). The intra-observer variability of QTc-D, JTc-D and TDR measurements was 7 ± 5 ms, 5 ± 2 ms, and 4 ± 2 ms, respectively. No statistically significant correlation was found between the parameters QTc-D, JTc-D, TDR, BMI ($p = 0.3$), LVM ($p = 0.4$) and EF ($p = 0.2$).

Table 1. Clinical and echocardiographic characteristics of the study population.

	DM1 patients	Control group	P
Patients (n)	50	50	
Age (years)	44 \pm 5	44 \pm 5	n.s.
BMI (Kg/m ²)	21 \pm 4	20 \pm 5	0.2
Sex (male/female)	29/21	29/21	
SBP (mmHg)	120.5 \pm 11	119 \pm 13	0.5
DBP (mmHg)	71.7 \pm 6	68.5 \pm 9	0.3
HR (bpm)	75.8 \pm 4.2	74.9 \pm 5.5	0.3
PR interval (ms)	188 \pm 11	179 \pm 18	0.2
QRS duration (ms)	92 \pm 13	95 \pm 10	0.3
EF (%)	60.4 \pm 7.1	62.6 \pm 4.2	0.2
SF (%)	33.3 \pm 5.2	33.8 \pm 4.3	0.3
LVEDD (mm)	43.5 \pm 8.2	43.3 \pm 6.4	0.2
LVESD (mm)	25.3 \pm 3.1	26.3 \pm 2.7	0.4
IVSEDT (mm)	8.7 \pm 1.5	9 \pm 1.2	0.5
LVPWEDT (mm)	9.7 \pm 1.3	8.9 \pm 1.8	0.3
LVM/H 2.7 (g/m 2.7)	35.5 \pm 9	32.4 \pm 8	0.2
E wave (cm/s)	78.3 \pm 11.3	80.3 \pm 14.5	0.2
A wave (cm/s)	56.4 \pm 7.3	57.5 \pm 8.5	0.4
E/A ratio	1.4 \pm 0.5	1.5 \pm 0.6	0.3

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; EF: ejection fraction; SF: shortening fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; IVSEDT: interventricular septal end diastolic thickness; LVPWEDT: left ventricular posterior wall end diastolic thickness; LVM/H: left ventricular mass/height.

Table 2. Electrocardiographic characteristics of the study population.

Parameters	MD1 group	Control group	P
HR (bpm)	75.8 \pm 4.2	74.9 \pm 5.5	0.3
QRS max (ms)	120 \pm 5.4	108.7 \pm 5.5	0.5
QRS min (ms)	87.6 \pm 21.3	69.5 \pm 8.4	0.2
QTc max (ms)	401.4 \pm 43.5	406.1 \pm 47.1	0.4
QTc min (ms)	377.9 \pm 70.8	382.5 \pm 29.3	0.7
QTc-D (ms)	86.7 \pm 40.1	52.3 \pm 11.9	0.03
JTc max (ms)	345.3 \pm 26.05	338.5 \pm 25.4	0.2
JTc min (ms)	251.5 \pm 20.6	259.5 \pm 15.5	0.7
JTc-D (ms)	78.6 \pm 31.3	61.3 \pm 10.2	0.001
TDR (ms)	101.6 \pm 18.06	90.1 \pm 14.3	0.004

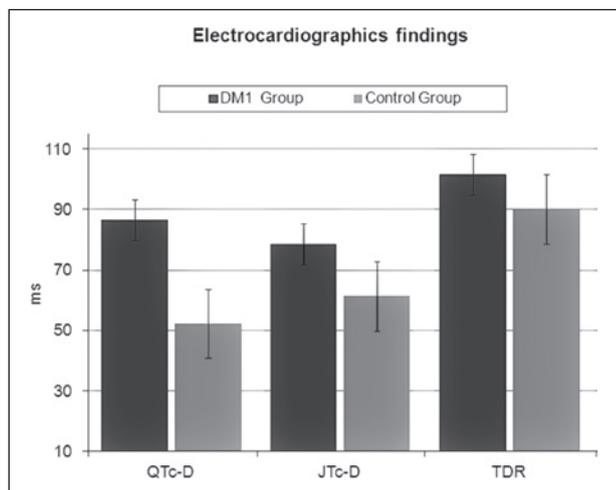


Figure 1. Differences (mean values) in dispersion of ventricular repolarization (QTc-d; JTc-d; TDR) between the DM1 group and the healthy control group.

Discussion

Cardiac arrhythmias

Conduction defects are the most prevalent cardiac abnormalities observed in patients with DM1, and occur in 40% of them. Type 1 atrio-ventricular block has the highest prevalence (28.2%), followed by left bundle branch block (5.7%) and right bundle branch block (4.4%). The prevalence of a QRS > 120 ms and a QTc > 440 ms is 19.9% and 22%, respectively (17). Ventricular premature complex is the most prevalent arrhythmia (14.6%). Ventricular tachycardia (VT) and ventricular fibrillation (VF) may also occur. Paroxysmal supra-ventricular tachyarrhythmias such as atrial fibrillation, atrial flutter, atrial tachycardia are a common finding on 12 lead ECG or 24 hour Holter monitoring, with a prevalence up to 25% in patients, often asymptomatic. Atrial tachycardias are observed in up to 7.3% of patients, both as unsustained and sustained forms. Atrial fibrillation/flutter (AF/AFI) frequently occurs with percentages up to 17% (18, 19).

We have previously shown that AF episodes are more frequently observed in DM1 patients who underwent pacemaker implantation, with a high percentage of right ventricular pacing and a low percentage of atrial stimulation (20). We have also observed that the right atrial septal stimulation in the Bachmann's bundle region is a safe and feasible procedure (21); in fact it allows less atrial pacing and sensing defects (22) as far as less R-wave oversensing on the atrial lead (23), compared to the right atrial appendage stimulation. However it is unable to prevent paroxysmal episodes of AF (24). Moreover, we have shown that the atrial pacing is an efficient algorithm to prevent

AF episodes (25, 26) and to reduce AF burden (27) in patients with atrioventricular conduction disorders implanted with a dual-chamber pacemaker, as it is able to prevent the onset and perpetuation of atrial fibrillation and to reduce the number of atrial premature beats and P-wave dispersion (PD) (28).

Indexes of electrocardiographic arrhythmic risk

Compared to other cardiological conditions or cardiomyopathies, little is known about the mechanisms and electrocardiographic predictors of ventricular and supraventricular tachyarrhythmias in DM1 patients (29-49).

P wave dispersion (PD), a non invasive indicator of intra-atrial conduction heterogeneity producing the substrate for the re-entry known as a pathophysiological mechanism of atrial fibrillation, has been evaluated in conditions such as obesity (30), beta-thalassemia major (31, 32) and Emery-Dreifuss muscular dystrophy (33). We have recently shown (34) that DM1 patients with AF episodes have a statistically significant increase in PD and Pmax compared to those without arrhythmias, confirming that P-wave dispersion may be a simple electrocardiographic parameter to identify patients at high risk of atrial fibrillation.

QTc dispersion (QTcD), JTc dispersion (JTcD) and TDR have been proposed as noninvasive methods to evaluate the transmural and regional heterogeneity of ventricular repolarization.

An increased dispersion of ventricular repolarization is considered to provide the electrophysiological substrate for life-threatening ventricular arrhythmias in several clinical conditions such as dilated cardiomyopathy (35), obesity (36, 37), beta-thalassemia major (38), severe aortic coarctation (39, 40) and Emery-Dreifuss muscular dystrophy (10, 41, 42).

Park et al. (43) suggested that the high incidence of SCD observed in the DM1 population is associated with prolonged QTc intervals in these patients. Magri et al. (44) showed a significant difference in the QT variability index (QTVI) between DM1 patients and healthy controls; according to their results, QTVI and age are independently associated with PR interval and CTG repeats.

Heart Rate Variability (HRV) is a reliable index to assess sympathovagal balance, used to stratify the arrhythmic risk in several clinical conditions (45-53); however previous studies on autonomic modulation of heart rate in DM1 patients have obtained conflicting results (54-57).

The atrial electromechanical delay (AEMD) duration is the sum of impulse propagation from sinus node to the atria and the atrial electromechanical coupling duration (58). Previous studies evaluated the predictive

role of intra-left atrial electromechanical delay in the recurrence of paroxysmal atrial fibrillation in some clinical conditions (59-62). In a recent study evaluating the AEMD in a DM1 population with normal cardiac function and its relationship with the AF onset, intra-left-AEMD and inter-AEMD were found to be independent predictors of AF-onset; in particular a cut-off value of 39.2 ms for intra-left-AEMD had a sensitivity and a specificity of 90% in identifying patients with AF-risk who need a careful cardiac monitoring (63-64). Though it is clear that the arrhythmic risk has a relevant role in the prognosis of DM1 patients, however little is still known about the electrophysiological substrate of these events and what non-invasive parameters are useful to stratify this risk (65-69).

Limitations of the study

As 12-lead surface ECG gives an incomplete picture of cardiac electric activity compared to body surface mapping or vector cardiography, QTd could not be a true manifestation of the local repolarization heterogeneity. Furthermore though QT interval and JT interval were measured on 12-lead ECGs through a computer software and digitized by an experienced cardiologist, however, in the absence of indisputable generally accepted criteria for the definition of the end of T wave, some degree of error in measurements can be occurred.

Conclusions

The present study showed a significant increase of regional and transmural heterogeneity of the ventricular repolarization in patients with DM1, despite a normal systolic and diastolic function. These results suggest that diffuse fibrosis and fat infiltration of initially unaffected myocardial areas may increase ventricular electrical instability and favor the onset of ventricular malignant tachy-arrhythmias and sudden cardiac death, even before the impairment of cardiac function. The results also confirm the needs of a continuous cardiological follow-up in these patients.

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CASE REPORTS

Successful treatment of periodic paralysis with coenzyme Q10: two case reports

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Primary periodic paralyses (PPs) are autosomal dominant ion channel disorders characterized by episodic flaccid weakness associated with variations in serum potassium level. The main prophylactic therapy of choice for PPs is carbonic anhydrase inhibitors that are not always effective. In this report, we described two PP patients who were successfully treated with coenzyme Q10. They remained asymptomatic since initiation of treatment, which may be associated with promotion of energy synthesis, anti-oxidant activity, influence of the fiber type composition and regulation of the expression of gene. To our knowledge, this is the first report of primary periodic paralyses which have been successfully treated with CoQ10. More observations need to substantiate this clinical finding in PPs.

Key words: Periodic paralyses, Therapy, Coenzyme Q10

Introduction

Primary periodic paralyses (PPs) are rare, autosomal-dominant disorders caused by ion channel dysfunction and characterized by recurrent episodes of muscle weakness secondary to abnormal sarcolemmal excitability. Generally, PPs are classified into hyperkalaemic (HyperPP) and hypokalaemic (HypoPP) forms, based on ictal serum potassium level. Current treatment strategies encompass acute treatments to terminate ongoing episodes of paralysis, and prophylactic therapies attempting to reduce ictal frequency or severity. Acute episodes are treated with oral potassium supplement in HypoPP and either inhaled salbutamol or intravenous glucose/insulin therapy in HyperPP. Prophylactic therapy usually involves a combination of avoiding weakness triggers and diuretic medications. The latter include potassium-sparing diuretics in HypoPP, hydrochlorothiazide in HyperPP and carbonic anhydrase in-

hibitors in both disorders. However, there are patients who fail to benefit from these drugs, even worsened particularly for Arg-to-Gly substitutions (1). Here, we report two patients with primary periodic paralyses who were successfully treated with coenzyme Q10 (CoQ10).

Case report

Case 1

A 29-year-old male had a history of several recurrent attacks of limb weakness since the age of 19. The frequency of episodes was at least once a month in the past year and increased to once a week in the last half a year. Severity of weakness varied ranging from mild weakness of lower limbs to tetraplegia. Predisposing factors included poor sleep and exposure to cold conditions. Ictal serum potassium blood level during an attack was normal and potassium supplementation was ineffective. Results of routine hematological and biochemical tests including thyroid function were all normal. Molecular genetic analysis revealed the R675Q mutation in the sodium channel encoded by the SCN4A gene associated with PPs (2). Since prophylactic medicine was unavailable in our hospital, he was only treated *ex adjuvantibus* with CoQ10 – 10 mg three times a day – to improve the energy metabolism of muscle. Surprisingly, the patient did not develop any episodes of paralysis during three months of treatment, even when exposed to the previously known triggers.

Case 2

The second case is a man of 50 years old who complained of paroxysmal generalized muscle weakness accompanied by myalgia and stiffness since he was 37. Epi-

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sodes occurred once or twice a month averagely during the past one year and worsened in the latest weeks, up to nearly twice a week. The blood potassium level during episodes was as low as 2.8 mmol/L and potassium intake could alleviate paralysis. There was a positive family history whereby his father and two of his siblings had similar but less severe attacks. Clinical examination between episodes and thyroid function were normal. The result of a long exercise test was positive. He was diagnosed with HypoPP despite gene tests for CACNA1S and SCN4A were negative, which account for approximately 10% of HypoPP cases (3). In light of the possible therapeutic effectiveness of CoQ10 with little side effect, he was administered tentatively idebenone 30mg three times a day, which is a synthetic quinone similar to CoQ10. Similarly, the patient responded well without any episodes during a one-month treatment.

Discussion

Periodic paralysis is a channelopathy related to abnormal sarcolemmal excitability with limited drugs. We incidentally observed that CoQ10 significantly reduced frequency of episodes in two PP patients without knowing its exact mechanism of action. However a variety of physiological functions of CoQ10 may explain its effect: 1) CoQ10 serves as an electron carrier between respiratory chain enzymes, facilitating cellular energy production and activating the Na⁺-K⁺ exchange pump, which is a central target for regulation of cell membrane excitability (4, 5); 2) acting as an antioxidant, CoQ10 may protect muscle from a Na⁺ overload in muscle fibers, observed in muscle biopsies from PPs patients, and also increase the mitochondrial production of reactive oxygen species (6, 7); 3) CoQ10 can affect the muscle fibers for a long-term by increasing the percentage of type 2 fibers in vastus lateralis muscle (8). Type 2 fibers contain more Na⁺-K⁺ exchange pump and atrophy of type 2 fibers predominated over type 1 in muscles of PPs patients (9, 10). Therefore, CoQ10 may play a protective role from episodes by expanding overall content of Na⁺-K⁺ exchange pump in skeletal muscle. Furthermore, CoQ10 functions as a major skeletal muscle gene regulator, affecting the

expression of a large number of genes (8). This is the first report of primary periodic paralyses which have been successfully treated with CoQ10. More observations need to substantiate this clinical finding in PPs.

Compliance with ethical standards

Ethic standards

Patients gave informed consent prior to making the case report. Details that might disclose the identity of the patients have been omitted.

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Voltage-directed cavo-tricuspid isthmus ablation using a novel ablation catheter mapping technology in a myotonic dystrophy type I patient

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A successful case of maximum voltage-directed cavo-tricuspid isthmus (CTI) ablation using a novel ablation catheter mapping technology in a myotonic dystrophy type I (DM1) patient is reported. The patient complained recurrent episodes of atrial flutter, revealed by the atrio-ventricular electrograms analysis during the routine pacemaker controls.

Key words: myotonic dystrophy, atrial flutter, atrial fibrillation, cavo-tricuspid isthmus ablation, microelectrodes

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder resulting from an amplified CTG trinucleotide repeat (> 50) in the 3-prime untranslated region of the dystrophin myotonia protein kinase gene (DMPK gene) on chromosome 19q13.3. DM1 is the most common muscular dystrophy of the adult life with an incidence of 1 in 8000 births and a worldwide prevalence ranging from 2.1 to 14.3/100.000 inhabitants (1). Cardiac involvement is noticed in about 80% of cases, often preceding the skeletal muscle one (2). Paroxysmal supraventricular tachy-arrhythmias (atrial fibrillation, atrial flutter, atrial tachycardia) represent a common finding on 12 lead electrocardiograms (ECG) or 24 hour ECG-Holter monitoring, with a prevalence up to 25% (3). The patients are often asymptomatic. Atrial tachycardias are observed in up to 7.3% of patients, both as un-sustained and sustained forms (4). Atrial fibrillation/flutter (AF/AFL) frequently

occurs in DM1 patients up to 17% (3, 4), some times representing the first manifestation of the muscular dystrophy in young patients (5). AF/AFL seems to increase mortality in this population (6). We report a successful case of maximum voltage-directed cavo-tricuspid isthmus (CTI) ablation using a novel ablation catheter mapping technology in a DM1 patient with recurrent episodes of typical atrial flutter.

Description

A 71-year-old woman with DM1 and arterial hypertension, with previously dual chambers pacemaker implantation for advanced atrio-ventricular block, was referred to our Division for device check and cardiologic therapy optimization. She never reported palpitations or arrhythmias-related symptoms, she didn't take anti-arrhythmic medications. ECG showed a dual-chamber VDD paced rhythm at 60 bpm. Transthoracic echocardiogram showed normal left ventricular systolic function associated to grade I diastolic dysfunction. The device interrogation showed several episodes of sustained supraventricular tachycardia, with a cycle length of 289 ms (Fig. 1). AFL diagnosis was made by 24 h ECG Holter monitoring that showed the common features of typical CTI dependent atrial flutter. The patient underwent electrophysiological study (EPS) for catheter ablation of the arrhythmogenic substrate. Two decapolar diagnostic catheters were placed in the coronary sinus and in the lateral right atrium wall. An IntellaTip MiFi XP® (IntellaTip

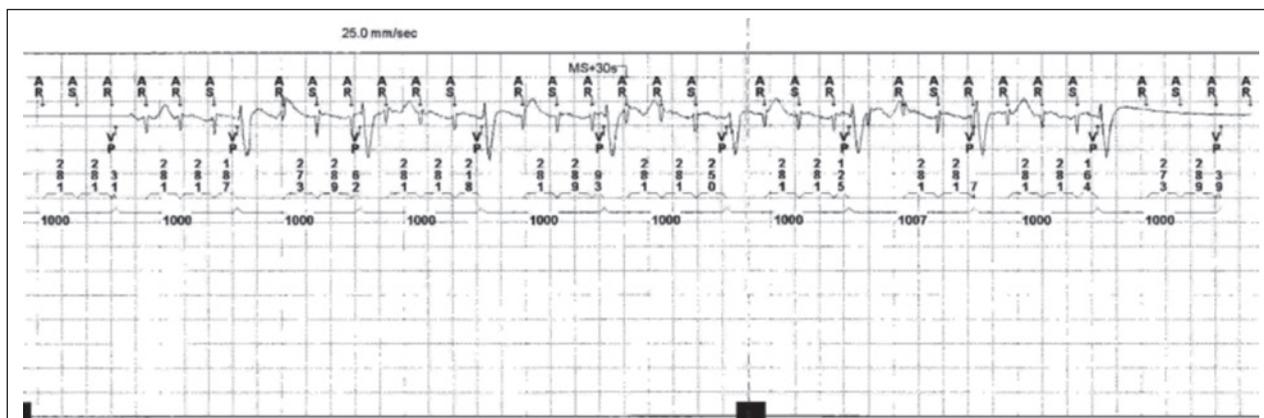


Figure 1. Episode of sustained supraventricular tachycardia with a cycle length of 289 ms revealed by atrio-ventricular electrogram analyses during routine pacemaker control.

MiFi, Boston Scientific, Natick, MA) 8 mm RF catheter was used for CTI mapping and ablation (Fig. 2).

Prior to the onset of the ablation procedure, a baseline electrophysiology study was performed including the measurements of the baseline trans-isthmus interval. This was 112 ms when measured from the pacing stimulus on electrode 9/10 of the coronary sinus catheter to the atrial electrogram detected by electrode 1/2 on the Halo catheter (Fig. 3); and of 118 ms when measured from

the pacing stimulus on electrode 1/2 of the HALO catheter to the atrial electrogram detected by electrode 9/10 on the coronary sinus catheter (Fig. 4). We performed a voltage-directed technique for ablating the only conducting bundles of the CTI, avoiding to ablate the intervening non-conducting fibrous tissue, according to previous experiences (7).

We firstly mapped across the CTI by pulling back from the tricuspid valve annulus to the inferior vena cava at the 6 o'clock position in left anterior oblique (LAO) projection. The signal voltage was noted during this pull-back, and the highest voltage was identified. We returned to this location and have ablated it with an 8 mm dry tip

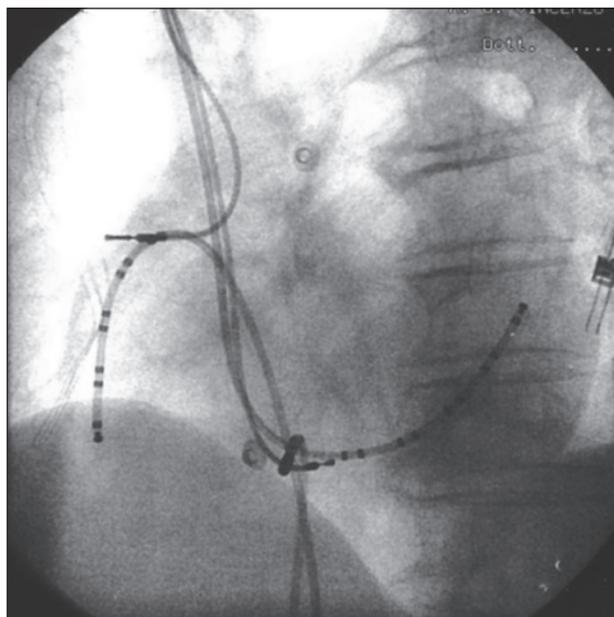


Figure 2. Position of catheters in left anterior oblique (LAO) views during cavo-tricuspid isthmus (CTI) ablation. Two decapolar diagnostic catheters were placed in the coronary sinus and in the lateral right atrium wall. An IntellaTip MiFi XP® 8 mm RF catheter was positioned the 6 o'clock position across the CTI.

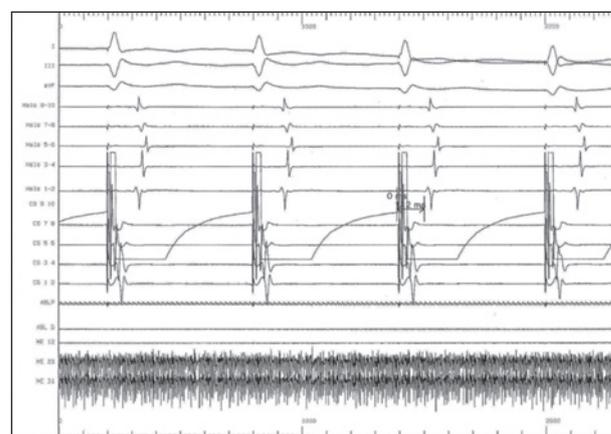


Figure 3. Baseline trans-isthmus interval of 112 ms as measured from the pacing stimuli on electrode 9/10 of the coronary sinus catheter to the atrial electrogram detected by electrode 1/2 on the Halo catheter. In basal conditions the electrical impulse from the coronary sinus ostium spreads with two opposite wave fronts around the tricuspid valve, counterclockwise along the interatrial septum and clockwise along the back edge of the tricuspid.

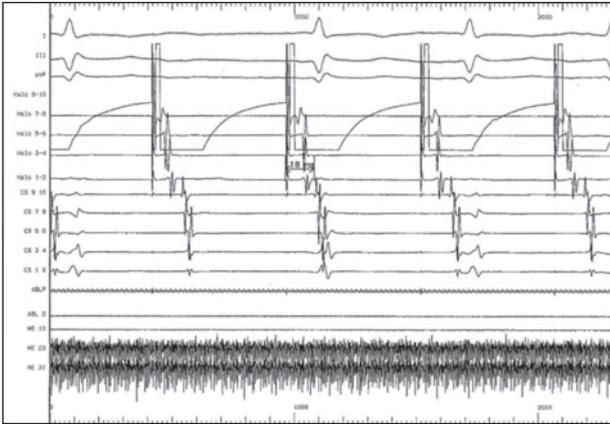


Figure 4. Baseline pacing trans-isthmus interval of 118 ms as measured from the pacing stimuli on electrode 1/2 of the HALO catheter to the atrial electrogram detected by electrode 9/10 on the coronary sinus catheter. In basal conditions the electrical impulse from the posterolateral tricuspid spreads around the tricuspid with two wave fronts, one in a clockwise direction (along the side wall) and another counterclockwise (along the rear wall and medial).

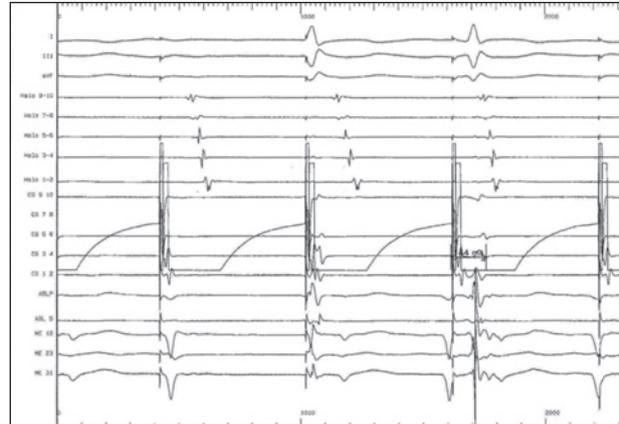


Figure 5. Post-procedure increased trans-isthmus interval as measured from the pacing stimuli on coronary sinus electrode 9/10 (144 ms) to the atrial electrogram detected by electrode 1/2 on the Halo catheter. The electrical impulse is forced to activate the atrial peritricuspid myocardium only counterclockwise.

for 40-60 s (60-70 W, 60-70 uC); this process was then repeated and continued until all sharp atrial electrograms detected on the mini-electrodes along the CTI were eliminated and only low-voltage double potentials were visible. A total of 3 radiofrequency ablation lesions were applied.

We performed a post-procedure evaluation of pacing intervals from both electrode 9/10 of coronary sinus catheter and electrode 1/2 of the HALO catheter. We showed an increased trans-isthmus interval measured by both pacing from coronary sinus electrode 9/10 to the atrial electrogram detected by electrode 1/2 on the Halo catheter and from HALO electrode 1/2 to the atrial electrogram detected by electrode 9/10 on the coronary sinus catheter, of 144 and 140 ms, respectively confirming the bidirectional block (Figs. 5, 6).

The procedure was completed without complications. Six months later, the ambulatory interrogation of the device did not reveal any recurrent atrial arrhythmias; so no long-term anticoagulation therapy was necessary.

Discussion

Cardiac involvement in DM1 patients occurs as a degenerative process with progressive fibrosis and fatty replacement of the myocardium, not limited to the specialized conduction system, but involving also areas – initially unaffected – of the atrial myocardium (8). This anatomopathological substrate, causing the discontinuous and

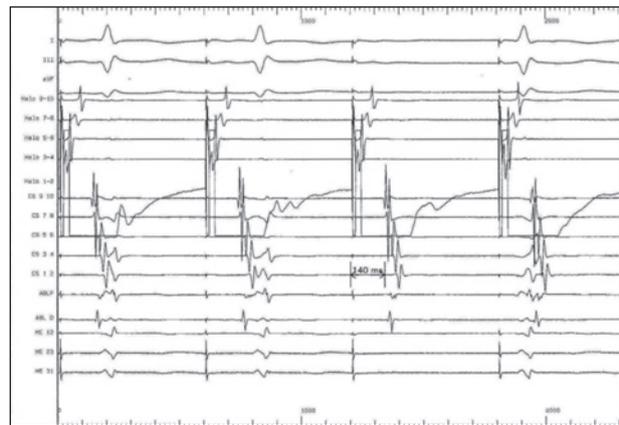


Figure 6. Post-procedure increased trans-isthmus interval as measured from HALO electrode (140 ms). The electrical impulse provided by the posterolateral wall side is forced to activate the peritricuspid myocardium only clockwise.

inhomogeneous propagation of sinus impulses and the prolongation of atrial conduction time, may facilitate the onset and the perpetuation of atrial arrhythmias in DM1 patients (9-12), as usually it happens in other clinical conditions (13-18). The modern pacemakers, including detailed diagnostic functions and therapeutic algorithms, may facilitate the diagnosis and management of frequent paroxysmal atrial tachy-arrhythmias that may remain undetected during conventional clinical follow-up (19-29). Radiofrequency ablation of typical atrial flutter is a very successful procedure with reported acute success rates of 90-95%. The conventional ablation technique requires cre-

ation of a complete line of conduction block across CTI, from the tricuspid valve to the inferior vena cava. Such an approach has a high overall success rate but results in variable, sometimes lengthy procedure times, mainly due to anatomic variation (30-35). The “maximum voltage-guided” (MVG) ablation technique targets high-voltage isthmus electrograms to ablate the functionally important anatomic muscle bundles alone, without drawing a complete anatomic line. Previous reports suggest that this method reduces the mean ablation time and shortens the procedure duration (36, 37). The ablation tip of IntellaTip MiFi catheter may enhance the available data for such a signal dependent technique. In this catheter, bipolar signals can be recorded between the three 0.8 mm-wide electrodes that are arranged radially 1.3 mm from the end of the catheter, alongside the standard distal and proximal bipolar recordings. The use of the Intellatip MiFi radiofrequency ablation catheter has been suggested to improve mapping resolution with a more precise localization of the points with the highest amplitude, potentially allowing less but more effective RF application in less time, in a technique that relies on signal amplitude (38). These features make the maximum voltage guided cavo-tricuspid isthmus ablation using a novel catheter with three mini electrodes within the ablation tip (IntellaTip MiFi, Boston Scientific, Boston, MA) particularly suitable for efficacy and safety during the ablation procedure in DM1 patients with an higher potential risk of complications for the diffuse atrial fibrosis. This novel ablative approach is particularly useful in this category of patients for their inability to maintain for long time the supine position.

Conclusions

We showed a successful case of maximum voltage-guided cavo-tricuspid isthmus ablation using a novel catheter with mini electrodes within the ablation tip in a myotonic dystrophy type 1 patient with typical atrial flutter episodes revealed by atrio-ventricular electrograms analysis during the routine pacemaker controls.

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NEWS FROM AROUND THE WORLD

MSM

The 13th Congress of the Mediterranean Society of Myology will be held in Nice (France), likely in June 2017, organised by Prof. Claude Desnuelle. The symposium will be in the traditional two-days MSM format with selected topics. The 14th Congress of the Mediterranean Society of Myology will be held in Turkey, organised by Prof. Haluk Topaloglu.

GCA

During the Gala dinner of the 13th Congress of the Mediterranean Society of Myology the 2017 Gaetano Conte Prizes will be assigned for basic and clinical research.

AIM

The 16th AIM Congress was held in Lecce from 8 to 11 June 2016. Over 100 scientific contributions were selected by the AIM Board and presented as Oral Communications or Posters.

The Congress was attended by over 200 members and it has been characterized by a high scientific profile and a variety of the topics ranging from the latest knowledge on pathophysiology to molecular pathogenic mechanisms, novel diagnostic methods and advanced therapeutic perspectives.

An interesting joint meeting between AIM and Associations of Italian Dieticians (ADI) also took place. It has allowed to start a cooperation between the two scientific Associations for a more effective and standardized approach to the nutritional problems of patients with neuromuscular diseases.

Great interest was raised by the talks of internationally renowned experts as Frédérique Magdiniér (Marseille), Antoine Muchir (Paris) and Massimo Zeviani (Cambridge) who shared with the participants their experience in their respective fields of research.

The usual meeting with the Associations of patients has been very useful to better define the demands and the needs of care of patients. AIM has always had special attention to the cultural exchange with the associations of patients. AIM members attended the Congresses of Parent Project, Italian Association of Glycogenoses (AIG), Mitocon and UILDM (Italian Musculr Dystrophy Association); collaborative working relationship with Famiglie SMA, ASAMSI, Laminopathy and sarcoglycanopathy Associations, Myotonic Dystrophy Association and the novel Coordination of Associations for Neuromuscular Diseases (CAMN) have been activated.

Collaborations have also been made with various scientific societies such as the Italian Society of Rheumatology (joint event on inflammatory myopathies at the Congress SIR 2016), the Societies of Physical and Rehabilitative Medicine, SIRN and SIMFER, the Italian Association of Neuropsychology (SINP) and the Forum Risk Management-Tuscany Region with the aim of drafting guidelines / recommendations in patients with neuromuscular diseases.

AIM has worked as a scientific hub for maintaining and developing collaborative networks involving different neuromuscular centers in Italy. AIM affiliated collaborative networks include *Registry for Mitochondrial diseases*, *Registry for Myotonic Dystrophy*, *Registry for Muscle Glycogenoses*, *Group of Study for Pompe Disease*, *Laminopathies Network*, *LGMD networks* and others.

AIM had its own space within the Italian Neurology Society Congress which was held in Venice 22 to 25 October 2016. A workshop entitled “Myopathies and Multi-system Disease” and the training course “BRAIN DM1: Neuroimaging and rehabilitation “ were held during the congress. As part of the training course “Emergencies in Neurology”, AIM speakers discussed about neuromuscular diseases.

On 4th March 2017 AIM will organize the first National Day for Neuromuscular Diseases that will take place throughout the national territory and will involve many AIM centers. You will find more info on the AIM website at www.miologia.org.

The 2017 Congress of AIM will take place in the beautiful setting of Syracuse, Sicily from May 31 to June 3, 2017. Topics will include innovations in diagnostic technologies, therapies, disease registries, biobanks, physical activity and muscle diseases and muscle aging; yet will be discussed collaborative scientific projects, relations between myology reference centers, institutions and patient organizations. Details for the registration to the Congress and hotel booking will be available shortly on the website of AIM www.miologia.org as well as the preliminary program and deadline for submission of abstracts.

On the AIM website it is possible to consult the more recent guidelines in neuromuscular disease’s management and a list of the upcoming scientific events sponsored by the Association.

WMS

The 21st International WMS Congress was held in Granada, Spain from 4th to 8th October, 2016.

The Congress was held in the traditional WMS format

with three selected topics. One day of the symposium was dedicated to each of the selected topics addressing emerging discoveries in the field of: 1) Structural myopathies and diseases of the sarcomere; 2) Adult onset myopathies: hereditary and acquired; 3) Advances in the treatment of neuromuscular disorders.

The 22nd International WMS Congress will be held in Saint Malo (France) from 3 to 7 October 2017. The symposium will be held in the traditional format with 3 se-

lected topics:

1. Excitation-contraction coupling: basic aspects and related disorders.
 2. Extra-muscular manifestations in NMD.
 3. Advances in the treatment of neuromuscular disorders
- Contributions will also be welcome on new advances across the neuromuscular field.

FORTHCOMING MEETINGS

2016

October 4-8

21st Congress of World Muscle Society. Granada, Spain. Information: website: www.worldmusclesociety.org

October 5-8

Cardiometabolic Health Congress – 11th Annual CMHC. Boston (MA), USA. Information: website: <http://www.cardiometabolichealth.org/2016/index.html>

October 17-19

Acute Cardiovascular Care 2016. Lisbon, Portugal. Information: website: <http://www.escardio.org/Congresses-&-Events/Acute-Cardiovascular-Care>

October 20-24

ASHG Annual Meeting. Vancouver, Canada. Information: website: www.ashg.org

November 12-16

American Heart Association (AHA) Scientific Sessions 2016. New Orleans (LA), USA. Information: website: <http://www.heart.org/>

November 28-29

10th International Conference on Molecular & Cellular Cardiology. Sao Paulo, Brazil. Information: website: <http://molecularcardiology.conferenceseries.com/>

November 29 - December 2

XVII Edition of Progress in Clinical Pacing (Rome). Information: website: <http://www.pacing2016.com/>

December 1

Annual Congress of the Lithuanian Society of Cardiology 2016. Kaunas, Lithuania. Information: website: <http://www.lcs.lt>

December 2-4

International Society of Cardiomyopathies and Heart Failure 2016 (ISCHF2016). Kyoto, Japan. website: www.npo-apacvd.jp/ischf2016/

December 8-10

68th Annual Conference of the Cardiological Society of India (CSI). Kochi, India. Information: website: www.csikochi2016.org

December 8-10

16th World Cardiology Congress. Dubai, UAE. Information: website: <http://worldcardiology.conferenceseries.com/>

December 16-19

Italian society of cardiology; 77th annual congress. Rome, Italy. Information: website: <http://www.sicardiologia.it/>

2017

February 9-10

36TH Belgian Society of Cardiology Annual Congress. Brussels, Belgium. Information: website: <https://www.eiseverywhere.com/ehome/bsc2017registration/home/?eb=309050>

February 24-26

CardioRhythm 2017. Hong Kong, China. Information: website: www.cardiorhythm.com

March 17-19

American College of Cardiology. ACC.17. Washington, DC. USA. Information: website: <https://accscientificsession.acc.org>

April 2-4

European Cardiac Arrhythmia Society (ECAS). Rome, Italy. Information: website: <http://ecas-heartrhythm.org/>

May 6-8

Mediterranean Cardiology Meeting 2017. Catania, Italy. Information: website: <http://www.mcmweb.it/>

May 10-13

Heart Rhythm 38th Annual Scientific Sessions (HRS). Chicago, IL. Information: website: <https://www.hearhythminternationalgrouphousing.org/>

May 22-24

World Heart Congress 2017. Osaka, Japan. Information: website: <http://heartcongress.conferenceseries.com/>

May 31 - June 3

XVII Meeting of the Italian Association of Myology. Siracusa, Italy. Information: website: www.miologia.it

June 18-21

European Heart Rhythm Association (EHRA). Vienna, Austria. Information: website: [http://www.escardio.org/Sub-specialty-communities/European-Heart-Rhythm-Association-\(EHRA\)](http://www.escardio.org/Sub-specialty-communities/European-Heart-Rhythm-Association-(EHRA))

July 13-15

Asian Pacific Society of Cardiology (APSC). Singapore, Singapore. Information: website: <http://www.apscardio.org/>

July 14-16

20th World Congress on Heart Disease. International Academy of Cardiology. Vancouver BC, Canada. Information: website: <http://www.cardiologyonline.com/>

July 30 - Aug 01

World Congress on Heart Disease-Boston, Mass. Information: website: <http://cardiologyonline.com/wchd2016/index.html>

August 26-30

European Society of Cardiology (ESC). Barcelona, Spain. Information: website: <https://www.escardio.org/>

August 31 - September 1

19th Annual Cardiology Congress. Philadelphia, USA. Information: website: <http://cardiac.conferenceseries.com/>

September 14-17

Asia Pacific Heart Rhythm Society (APHRS). Yokohama, Japan. Information: [website: http://www.aphrs.org/](http://www.aphrs.org/)

September 14-16

International Academy of Cardiology Scientific Sessions, World Congress on Heart Disease. Vancouver, Canada. Information: website: <http://www.cardiologyonline.com/wchd2017/>

October 3-7

22nd Congress of World Muscle Society. St. Malo, France. Information: website: www.worldmusclesociety.org

October 17-21

ASHG Annual Meeting. Orlando, Florida, USA. Information: website: www.ashg.org

October 25-27

15th edition of Venice Arrhythmias. Venice, Italy. Information: website: <http://www.venicearrhythmias.org/>

2018**August 25-29**

European Society of Cardiology (ESC). Munich, Germany. Information: website: <https://www.escardio.org/>

October 16-20

ASHG Annual Meeting. San Diego, CA, USA Information: website: www.ashg.org

October 17-21

Asia Pacific Heart Rhythm Society (APHRS). Taipei, Taiwan. Information: website: <http://www.aphrs.org/>

October 31 - November 02

World Congress on Human Genetics. Valencia, Spain. Information: website: <http://humangenetics.conferenceseries.com/>

To be announced

23rd Congress of World Muscle Society. Mendoza, Argentina. Information: website: www.worldmusclesociety.org

2019**May 2019**

Heart Rhythm 40th Annual Scientific Sessions (HRS). Chicago, IL. Information: website: <http://www.hrssessions.org/>

October 22-26

ASHG Annual Meeting. Toronto, Canada. Information: website: www.ashg.org

To be announced

Asia Pacific Heart Rhythm Society (APHRS). Bangkok, Thailand. Information: website: <http://www.aphrs.org/>
24th Congress of World Muscle Society. Copenhagen, Denmark. Information: website: www.worldmusclesociety.org

2020**October 27-31**

ASHG Annual Meeting. San Diego, CA, USA. Information: website: www.ashg.org

To be announced

24th Congress of World Muscle Society. Toronto, Canada. Information: website: www.worldmusclesociety.org

For application or renewal to MSM

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Acta Myologica publishes articles related to research in and the practice of primary myopathies, cardiomyopathies and neuromyopathies, including observational studies, clinical trials, epidemiology, health services and outcomes studies, and advances in applied (translational) and basic research.

Manuscripts are examined by the editorial staff and usually evaluated by expert reviewers assigned by the editors. Both clinical and basic articles will also be subject to statistical review, when appropriate. Provisional or final acceptance is based on originality, scientific content, and topical balance of the journal. Decisions are communicated by email, generally within eight weeks. All rebuttals must be submitted in writing to the editorial office.

On-line submission

Manuscript submission must be effected on line: **www.actamyologica.it** according to the following categories:

Original articles (maximum 5000 words, 8 figures or tables). A structured abstract of no more than 250 words should be included.

Reviews, Editorials (maximum 4000 words for Reviews and 1600 words for Editorials). These are usually commissioned by the Editors. Before spontaneously writing an Editorial or Review, it is advisable to contact the Editor to make sure that an article on the same or similar topic is not already in preparation.

Case Reports, Scientific Letters (maximum 1500 words, 10 references, 3 figures or tables, maximum 4 authors). A summary of 150 words may be included.

Letters to the Editor (maximum 600 words, 5 references). Letters commenting upon papers published in the journal during the previous year or concerning news in the myologic, cardio-myologic or neuro-myologic field, will be welcome. All Authors must sign the letter.

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Books and other monographs: Dubowitz V. *Muscle disorders in childhood*. London: WB Saunders Company Ltd; 1978.

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