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Founders: Giovanni Nigro and Lucia Ines Comi

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G. CONTE ACADEMY - NAPOLI

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ORIGINAL ARTICLES

Predictors of prognosis in type 1 myotonic dystrophy (DM1): longitudinal 18-years experience from a single center

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The aim of the study was to identify possible predictors of neurological worsening and need of non-invasive ventilation (NIV) in individuals affected by myotonic dystrophy type 1 (DM1), the most common form of adult-onset muscular dystrophy.

Methods. A retrospective observational cohort study was undertaken. Thirty-three patients with genetic diagnosis of DM1 were followed at our Neuromuscular unit in Modena. Abnormal trinucleotide repeat (CTG) expansion of dystrophy protein kinase gene (MDPK) on chromosome 19q 13.3 was the prerequisite for inclusion. The number of CTG repeats was determined. All the participants were older than 14 at the time of enrolment, therefore they could be included into the juvenile or adult form of the disease. Participants were neurologically evaluated every 6-8 months up to 18 years. Neurological impairment was assessed by Muscular Impairment Rating (MIRS), Medical Research Council (MRC), and modified Rankin (mRS) scales. The independent variables considered for prognosis were age at first evaluation, duration of the disease, CTG repeat number, gender, and presence of cardiac and vascular morbidities.

Male patients were 51.5% and female patients 48.5%. Sixteen patients were younger than the mean age of 30.1 years, while the remaining 17 were up to 65. Twelve subjects (36.4%) underwent NIV before the end of follow-up. Muscle force and disability scores showed statistically significant deterioration ($p < 0.001$) during follow-up. The worsening was significantly higher among patients carrying higher number of CTG repeats and of younger age. The presence of cardio-vascular involvement has significant impact on neurological and respiratory progression.

Neurological worsening is predicted by CTG expansion size, young age and presence of cardio-vascular morbidities.

Key words: myotonic dystrophy type I, muscular impairment rating scale, CTG trinucleotide repeat

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Conflict of interest
The Authors declare no conflict of interest

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Introduction

Myotonic dystrophy type 1 (DM1) is the most common form of adult-onset muscular dystrophy with a prevalence in Europe of 3-15/100.000 inhabitants [1-12]. DM1 is caused by an unstable expansion of the cytosine thymine-guanine (CTG) trinucleotide repeat located in the 3′UTR of *DMPK* gene, chromosome 19q13.3, encoding a serine/threonine protein kinase (DMPK) trinucleotide [8-19]. The disease is transmitted across generations in an autosomal dominant fashion with incomplete penetrance, variable phenotypic expression and somatic mosaicism [1,3,6,8-12,19-21]. Anticipation, i.e. increased number of CTG repeats in subsequent generations, is associated with increased severity of disease, more marked with maternal transmission [1,3,5,8,11,12,21-24]. The disorder is multisystemic and affects muscles and central nervous, ocular, respiratory, heart, digestive, endocrine systems in relation to the variable number of triple repeats in each organ [2-5,7-12,24-30]. Regular cardiological and ventilatory assessment is important in DM1, as respiratory failure accounts for almost 40% of mortality at an average age of 53 years [4,24,29-37]. The introduction of non-invasive ventilation (NIV) combined with treatments for cardiac manifestations have improved survival in DM1 [4,30-32]. Due to the broad clinical spectrum, DM1 subjects can be classified into five clinical forms according to age of onset of first symptoms: congenital, infantile, juvenile, adult, and late onset [24-26]. The progression rate of muscle strength loss in different phenotypes (juvenile, adult and late onset) needs to be documented and has an impact on patient prognosis. Our study was aimed at identifying predictors of neurologic and respiratory impairment in an Italian cohort of patients affected by DM1, followed longitudinally up to 18 years.

Patients and methods

Setting and study population

We conducted a retrospective observational study in a single neuromuscular disease center (*Center for Neuromuscular Diseases, University Hospital of Modena, Italy*). Inclusion criteria were as follows: diagnosis of DM1 attested by clinical evaluation and molecular genetic testing. No patients at the time of enrolment had end-stage lung diseases (chronic obstructive pulmonary disease, interstitial lung disease, severe kyphoscoliosis and disorders of the chest walls). Between January 1st, 2000 and December 2018, 33 patients with clinical diagnosis of DM1 were included according to genetic diagnosis. All patients enrolled showed an abnormal expansion of CTG in the 3′ untranslated region of the Myotonic Dystrophy Protein Kinase (MDPK) assessed by long-PCR and Southern blot analysis gene (MIM #160900) The study design was approved by the local Ethical Committee (N°325/2019). A multidisciplinary team including neurologists, pulmonologists and cardiologists, evaluated the subjects during a follow-up which lasted from the first to the last visit or to death. Patients were followed for at least 24 months.

Predictive variables and assessments

Our genetic reference laboratory defined subjects as E1 with number of repeats less than 200, E2 from 201 to 699 repeats, and E3 from 700 and larger. All participants were older than 14 at the time of enrollment, therefore with juvenile or adult form of the disease [24-27]. Patients were further classified according to onset of symptoms at an age above or below 30.1 years, which was the mean in our cohort. Clinical onset in patients with very mild/asymptomatic disease was set at the date of their first clinical/genetic diagnosis or it was retrieved from previous medical history. For the specific purpose of the study, the following data were included: muscle impairment and disability scores, gender, serum creatine kinase (CK) titer assessed at least once per year, and electromyographical changes. In addition, the presence or absence of multisystemic involvement such as cardiac, vascular, endocrine, ophthalmological and hematological disorders was assessed at the time of enrollment and in subsequent follow-up. Each neurologist collected the informations at the time of enrollment on presence/absence of the above mentioned conditions.

Muscle strength was determined with manual muscle testing (MMT) by three neurologists (GG, AA, MM) using Medical Research Council Scale (MRC) in six muscles for each limb in upper (UE) and lower (LE) extremities: deltoid, biceps brachii, extensor digitorum communis, ileopsoas, quadriceps and anterior tibial. The maximal score for each muscle ranged between 0 and 5, and the total score obtained was 60. Disability was measured with the Rankin Scale (mRS) (range 0-5). Muscular Impairment Rating Scale (MIRS), a validated DM1-specific rating scale, was also used [9,25-27].

Respiratory assessments included arterial blood gas analysis and pulmonary function tests (PFTs) with evaluation of forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1) and FEV1/FVC (Tiffeneau index) performed at the time of enrollment and at every follow-up visit. Arterial blood gases were measured in samples drawn at rest from the radial artery. Arterial oxygen partial pressure (PaO2) and arterial carbon dioxide partial pressure (PaCO2) were determined within 10 minutes of sampling. Hypercapnia was defined as PaCO2 > 45 mmHg and hypoxemia as PaO2 < 80 mmHg 3,29-31. NIV (meaning the use for more than 4 hours/daily) included initiation of Nocturnal Positive Airway Pressure (NPAP), either continuous (CPAP) or bilevel (BPAP) 31.

NIV was planned by a pulmonologist in the presence of symptoms suggestive of chronic respiratory failure (dyspnea at rest, daytime hypersomnolence, orthopnea), plus at least one of the following criteria: FVC less than 50% predicted in seated position, apnea/hypopnea index greater than 15 events/hour, nocturnal arterial saturation less than 88% for more than 2 cumulative minutes, arterial pH < 7.35 and PaCO2 > 45 mmHg [2,4,31-33,35].

Cardiological evaluations included clinical assessment, basal blood pressure, ECG, 24h ECG Holter monitoring, and trans-thoracic echocardiography. Impulse conduction abnormalities and arrhythmias on a standard ECG, including sinus rate < 50 BPM, PR interval > 200 ms, QRS duration > 100 ms, left anterior or posterior fascicular block, abnormal Q waves, atrial tachycardia and fibrillation (AF) or flutter were considered indicative of cardiac involvement. We measured systolic left ventricular dysfunction as reduction of ejection fraction (EF) below 50% [4,22,29,30,38,39].

Only 4 cases could be studied with 1.5T Magnetic Resonance Imaging (MRI) scan of limb girdle, thigh and lower leg to assess muscular hypotrophy or atrophy, muscle edema and fat replacement on T1, T2 and on short time inversion recovery (STIR) sequences with fat suppression. After clinical indication, a brain neuroradiological study either with CT or MRI was obtained or reviewed in 17 subjects at the median age of 44.5 years (range 20-70, IQR 23.7). The retrospective quantitative evaluation of available images was carried out by two neuroradiologists looking for structural abnormalities, such as whole brain atrophy, and white matter subcortical and periventricular changes especially in the temporal pole [40]. White matter temporal changes were detected in 31.2% of the subjects. During follow-up, no patients exhibited detectable ischemic lesions.

End points

Primary end points of the study were analysis of clinical and genetic parameters associated with significant neurological impairment, defined as worsening in 2 out of the 3 neurological assessment scales applied. A change of ≥ 1 point in MIRS was considered significant, as well as a worsening of ≥ 7 points in total MRC score, of ≥ 4 points in UE MRC score, of ≥ 3 points in LE MRC score and a change of ≥ 1 point in mRS. Secondary outcome was the identification of clinical and genetic parameters associated with functional impairment and need for NIV.

Statistical analysis

Statistical analysis was performed using Stata 14.2 (Stata Corporation, College Station, TX, USA). Patient characteristics were analysed using descriptive statistics. Data were presented as median with minimum–maximum range or as mean with standard deviation (SD). For comparison of change between independent groups, Mann-Whitney U test was used for continuous variables and Mantel-Haenszel Chi Square Exact test for ordered categorical variables. The differences in MRC, mRS, and MIRS between baseline and times of follow-up were computed using t-test. Kaplan-Meier method was used to estimate progression with respect to outcomes; curves were compared with Log-rank test to determine any difference in terms of age at the time of onset of end points. Hazard ratio and 95% confidence interval (CI) from Cox proportional hazard regression model were used to estimate the risk of each end point, based on clinical attributes at baseline (i.e. gender, age, CTG expansion, presence of cardiovascular morbidities). The impact of clinical variables on MIRS and NIV requirement was evaluated using a logistic regression model. To improve statistical strength, genotypes based on number of CTG repeats were pooled into two groups that were E1 *vs* E2 plus E3. Clinical factors associated with *P* values below 0.05 in the univariable model were analyzed in a multivariable model with a stepwise forward selection. Missing data on MRC, MIRS, and mRS during follow-up were estimated by multiple imputation method (MI) using either linear or ordinal regression, if appropriate [41]. Variance analysis (ANOVA) and Tukey-Kramer test were used to compare clinical scores at baseline and at 24, 48, 72 and 96 months in patients having different genetic profiles.

Results

Patients baseline clinical data

Demographic characteristics of patients are listed in Table I. Mean duration of follow up was 121.6 months ± 69.4 (median 100 months, range 24-220, IQR 125). Median duration of illness was 237 months (range 24-553, IQR 202). Demographic analysis of DM1 population showed a 1:1 male to female ratio with 17 males (51.5%) and 16 females (48.5%). The age of onset had similar gender distribution. Median age of diagnosis was 31 years (range 14-65). Ten patients (30.3%) had lower number of expansions (E1) whereas those classified as E2 were 39.4%, and E3 were 30.3%.

At baseline, the median total MRC muscle strength assessed with MMT was 48 (range 30-60, IQR 12; mean 48.8, ± 7.74), and 24 (range 18-30 IQR 8; mean 24.4 ± 3.5) in UE and 24 in LE (range 10-30, IQR 6, mean 24.3 ± 4.4). Regarding disability scores, mean MIRS was 3.66 ± 0.88 and mRS was 2.1 ± 1.30. At baseline, muscle strength, either computed as total or separately in UE and LE, and mRS were not significantly different among genders ($p = 0.66$); conversely, MIRS scores in females were

Table I. Summary of demographic and clinical characteristics of our patients.

		Overall [33 (100%)]
Gender [n (%)]	Male	17 (51.5%)
	Female	16 (48.5%)
Age of onset/diagnosis (y) [median (range)]		31 (14-65)
	Male	32 (15-65)
	Female	29.5 (14-53)
Duration of follow-up (mo) [median (range)]		100 (24-220, IQR 125)
Duration of disease (mo) [median (range)]		237 (24-553, IQR 202)
CTG repeat [n (%)]	E 1	10 (30.3%)
	E 2	13 (39.4%)
	E 3	10 (30.3%)
Death [n (%)]		4 (12.1%)
	Male [n (%)]	2/4 (50.0%)
	Age (y) [median (range)]	64 (54-67)
Pace maker or ICD [n (%)]		5 (15.2%)
	Male [n (%)]	4/5 (80.0%)
	Age (y) [median (range)]	51 (42-68)
Systemic involvement [n (%)]		30 (90.9%)

significantly worse than in males (p = 0.03). Abnormal EMG findings were detected in 63.6% of cases, and CK level above 170 IU/L was found in 48.

Multisystemic involvement

Multisystemic involvement was detected in 90% of cases. Cataract occurred in 78.8%, while thyroid and endocrine dysfunction requiring treatments in 51.5%. The cardiac abnormalities were detected in 63,6% of cases and included conduction disturbances (66%) namely, prolonged PR interval (A-V block of I°), bradyarrhythmias, II° and III° atrioventricular blocks, AF, ventricular arrhythmias, left ventricular systolic dysfunction with depressed EF and clinical heart failure, and mitral valve prolapse. No ventricular tachycardia was detected. Vascu-

Table II. Outcome measures at baseline and at last follow-up in patients according to genotypes.

		Overall		***P overall***	**Genotype E1**		***P***	***P basal***	**Genotypes E2, E3**		***P***	***P final***
		Base-line	**Last f-up**		**Base-line**	**Last f-up**			**Base-line**	**Last f-up**		
EGAa	pCO2 (mmHg)	41.8 (±6.4)	43.0 (± 6.8)	0.15	40.4 (± 4.04)	40.3 (± 3.9)	0.95	0.07	42.6 (± 7.1)	44.2 (± 7.5)	0.46	**0.04**
	pO2 (mmHg)	80.8 (±14.0)	83.5 (± 13.1)	0.33	86.9 (± 10.3)	86 (± 8.1)	0.83	0.07	78.2 (± 14.7)	82.4 (± 14.8)	0.33	0.24
Spirometry	FVC (% predicted)	75.4 (±18.5)	67.2 (± 21.4)	**0.002**	82.9 (± 7.4)	78.9 (± 9.8)	0.31	**0.03**	72.1 (± 21.04)	62.1 (± .1)	0.13	**0.006**
MRC	Total	48.8 (±7.74)	37.8 (± 12.3)	**< 0.001**	55.4 (± 6.1)	50.4 (± 10.3)	0.20	**0.002**	46 (± 6.6)	32.3 (± 8.6)	**< 0.001**	**< 0.001**
	Upper limbs	24.4 (±3.5)	19.7 (± 5.81)	**< 0.001**	27.4 (± 3.2)	25.4 (± 5.0)	0.30	**0.003**	23.2 (± 2.9)	17.3 (± 4.2)	**< 0.001**	**< 0.001**
	Lower limbs	24.3 (±4.4)	18 (± 6.81)	**< 0.001**	28 (± 2.9)	25 (± 5.3)	0.13	**< 0.001**	22.7 (± 3.9)	15.1 (± 5.0)	**< 0.001**	**< 0.001**
MIRS		3.66 (± 0.88)	4.24 (± 1.0)	**0.001**	2.9 (± 0.99)	3.2 (± 1.3)	0.56	**< 0.001**	4 (± 0.6)	4.6 (± 0.5)	**< 0.001**	**< 0.001**
mRS		2.1 (± 1.30)	3.0 (± 1.4)	**0.001**	1. 1 (± 1.2)	1.6 (± 1.7)	0.45	**0.003**	2.6 (± 1.0)	3.6 (± 0.8)	**< 0.001**	**< 0.001**

EGA: arterial blood gas analysis. pCO2/O2: partial blood pressure of CO2/O2. FVC: forced vital capacity. MRC: Medical Research Council. MIRS: muscular impairment rating scale. mRS: modified Rankin Scale. The values are expressed as mean with standard deviation (SD) in brackets. P overall expresses the significance between baseline and last follow-up for each variable.
P *basal and p final* express respectively the significance of the comparisons between subjects carrying the different genotype at baseline and at the last follow-up for each studied variable. Significance: p < 0.05 two tailed. Significant results are in bold. See text for details.

lar comorbidities included severe hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 120 mmHg) and large vessel atherosclerosis; the latter, for statistical purposes, were pooled in the analysis with cardiac abnormalities. Regarding cardiac therapies, patients were treated according to published guidelines with angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, beta-blockers, diuretics, oral anticoagulants, and flecainide, if appropriate [38,39]. Five patients had prophylactic pace-maker (PM) implantation; in 2 cases, an implantable cardioverter defibrillator (ICD) was subsequently applied.

Predictors of neurological worsening

A statistically significant decline between baseline and last visit was seen in the whole sample for all the clinical outcome measures; 54.5% of subjects showed deterioration in all the scales. A significant decline in global muscle force (total MRC scores) was found in 27 cases (81.8%): loss of strength in LE was found in 78.6% of cases, and 66.6% worsened in UE with no significant difference between UE and LE (p = 0.87 and 0.10, respectively). The worsening occurred at mean age of 43.2 y (± SD 13.2) in LE and of 43.9 y (± SD 13.3) in UE. A worsening in mRS and in MIRS was found in 60.6 and in 63.6% of patients respectively.

Expansion size

Table II shows the measures of muscle strength, MIRS and disability scores obtained at baseline and at last follow-up in the whole cohort and in patient groups subdivided according to lower or higher than 200 CTG triplet repeats (i.e. E1 and E2/E3). The significance of clinical and functional scores in the whole cohort *(p overall)* and in those carrying genotype E1 were compared to pooled E2/E3 genotypes and estimated at the beginning and at the end of follow-up. The estimation of MRC, mRS and MIRS gave the following results: at baseline and at last assessment in group E1, neither MRC nor MIRS and disability scores worsened significantly (p > 0.05), whereas in E2/E3 groups the worsening in total MRC and MRC subdivided in UE and LE, in MIRS and mRS was statistically significant (p = 0.002, 0.003 and below 0.001, respectively). We further calculated clinical and functional scores at baseline and at end of follow-up between groups, and we found that groups E1 and E2/E3 were statistically different: basal p and final p expresses the significance of the comparison for each variable between the groups, E1 on one side and E2/E3 on the other.

We calculated with a Cox regression analysis the probability of surviving to worsening on MIRS in patients with different CTG expansion size: Kaplan-Meier curve is shown in Figure 1b (p = 0.016 at Log rank test). The latter result was confirmed by a logistic regression analysis, after adjustment with clinically relevant variables: higher than 200 CTG triplet repeat number had an independent prognostic effect on worsening in MIRS (HR 5.09, CI 1.34-19.36, p = 0.017) (Tab. III). Furthermore, we assessed the influence of genotypes on the probability of surviving to worsening in muscle strength assessed by total MRC, as shown in Fig 1d with Kaplan-Meier curve (p = 0.004 at Log rank). Figure 2a and 2c show the probability of being free from worsening in muscle strength for UE and LE in the three genotypes E1, E2, E3 (p < 0.001 at Log rank), with the number at risk and of survivors belonging to each genotype in relation to age. The box plot in Figure 2d shows MIRS measurements at baseline and at 24, 48, 72 and 96 months; a significant difference was found between genotypes E1 *vs* E2, and E1 *vs* E3 (p < 0.01).

Baseline age

Seventeen patients were older than 30.1 years; the oldest subjects carried either genotype E1 (7, 21.2%) or genotype E2 (9, 27.2%), and only 1 (3%) had genotype E3. At baseline, the youngest and the oldest subjects were

Table III. Results from univariate and multivariate Cox regression analysis of worsening on MIRS (≥ 1 point).

Worsening ≥ 1 point in MIRS			
	HR	**95% CI**	*P*
Gender (female)	1.13	0.46-2.77	0.78
	(0.55)	(0.19-1.53)	(0.25)
Age at onset (> 30.1 y)	**0.26**	**0.10-0.68**	**0.006**
	(0.26)	**(0.09-0.78)**	**(0.01)**
CTG repeat number > 200 (i.e E2, E3)	**3.9**	**1.28-11.8**	**0.016**
	(5.09)	**(1.34-19.36)**	**(0.017)**

HR: hazard ratio. 95% CI: 95% confidence interval. *p*: p-value. MIRS score. Age at onset > 30.1 years (y). CK: creatine kinase level ≥ upper limit of normal. Genotypes are classified according to CTG repeat number. Adjusted values are reported in brackets. Significance: p < 0.05 two tailed. Significant results are in bold.

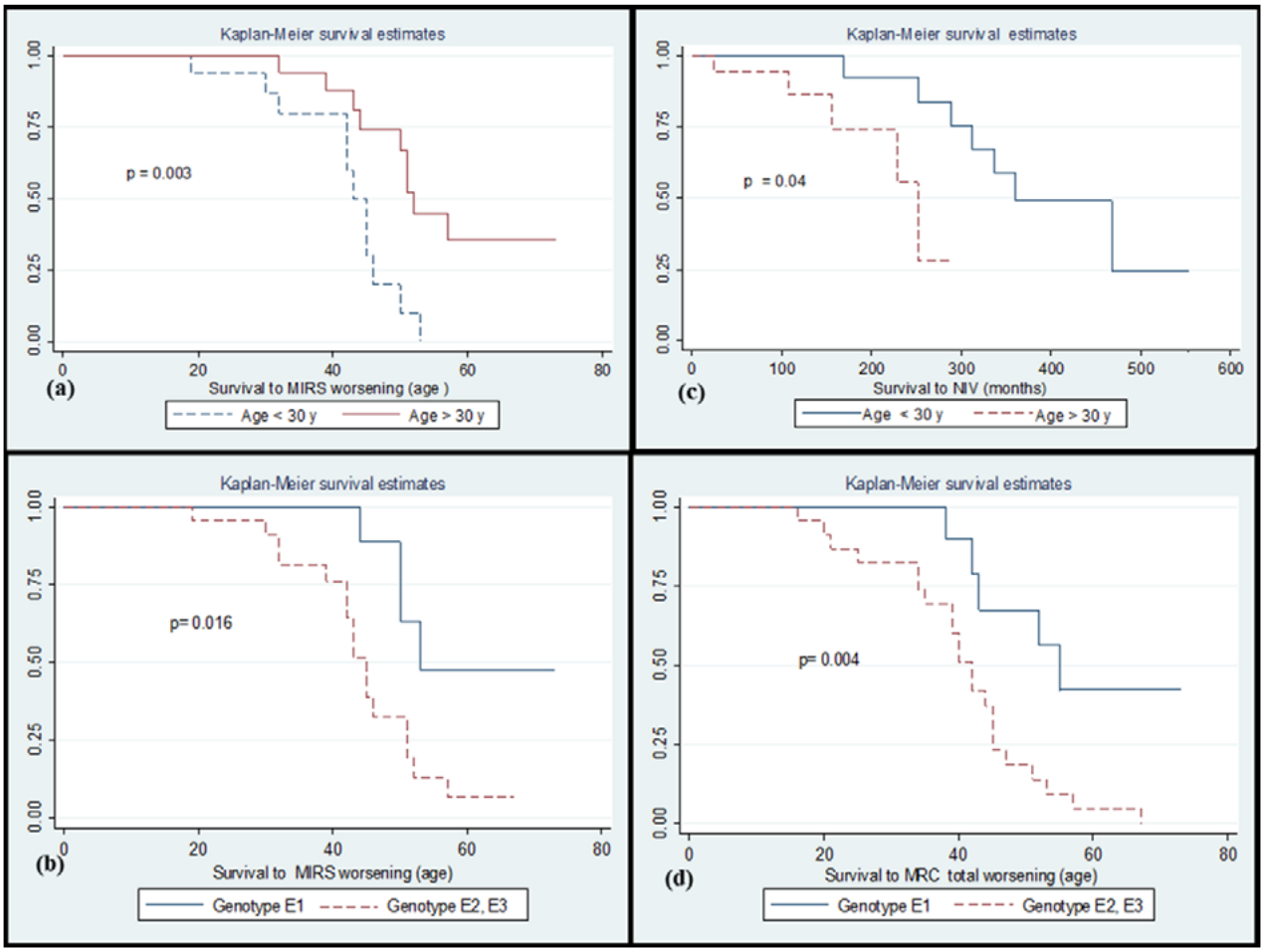

Figure 1. Cox analysis and Log rank test. **Fig 1a)** Kaplan-Meier survival curves expressing the probability of worsening in MIRS from age of onset in subjects with age either above or below the mean age $p = 0.003$, at Log rank test; **b)** Kaplan-Meier survival curves expressing the probability of worsening in MIRS from age of onset in genotypes E1 or E2 and E3, $p = 0.016$ at Log rank test; **c)** Kaplan-Meier survival curves expressing the risk of NIV from age of onset in subjects with age above or below the mean age, $p < 0.04$ at Log rank test; **d)** Kaplan-Meier survival curves expressing the probability of worsening in MRC total scores in genotypes E1 or E2 and E3, $p < 0.004$ at Log rank test.

not significantly different as measured by MIRS, mRS and muscle strength both in total ($p > 0.05$) and in UE ($p = 0.1$) and LE ($p = 0.09$).

Univariate Cox proportional hazard analysis showed that worsening in MIRS was significantly predicted by younger age at baseline. Kaplan Meier survival curves in Fig 1a show the probability of worsening on MIRS in subjects aged either above or below the mean of 30.1 years (Log rank test $p = 0.003$). Multivariate Cox regression analysis, as shown in Table III, confirmed lower risk of progression (HR 0.26, CI 0.09-0.78, $p = 0.01$) in the oldest patients. This result was further validated by a logistic model with multiple imputed data, where old age of onset (OR 0.30, CI 0.15-0.59, $p < 0.001$) and female gender (OR 0.15, CI 0.075-0.30, $p = 0.001$) showed a protective effect towards the risk of worsening on MIRS (Tab. IV).

Gender

At the end of follow-up, muscle force in UE was diminished by 22% in male patients versus 17% in females. In LE, the decrease from baseline was 29% in males versus 23% in females. MIRS scores worsened by 17% in males versus 10% in females, and mRS decline reached 50% in males versus 32% in females. However, the proportion of worsening was never statistically significant between genders, and males did not differ from females in assessment scale scores at the end of follow-up (data not shown).

Cardiac and vascular involvement

In our cohort, during follow-up, cardiac involvement occurred in 75% of patients aged below 30.1 years *vs*

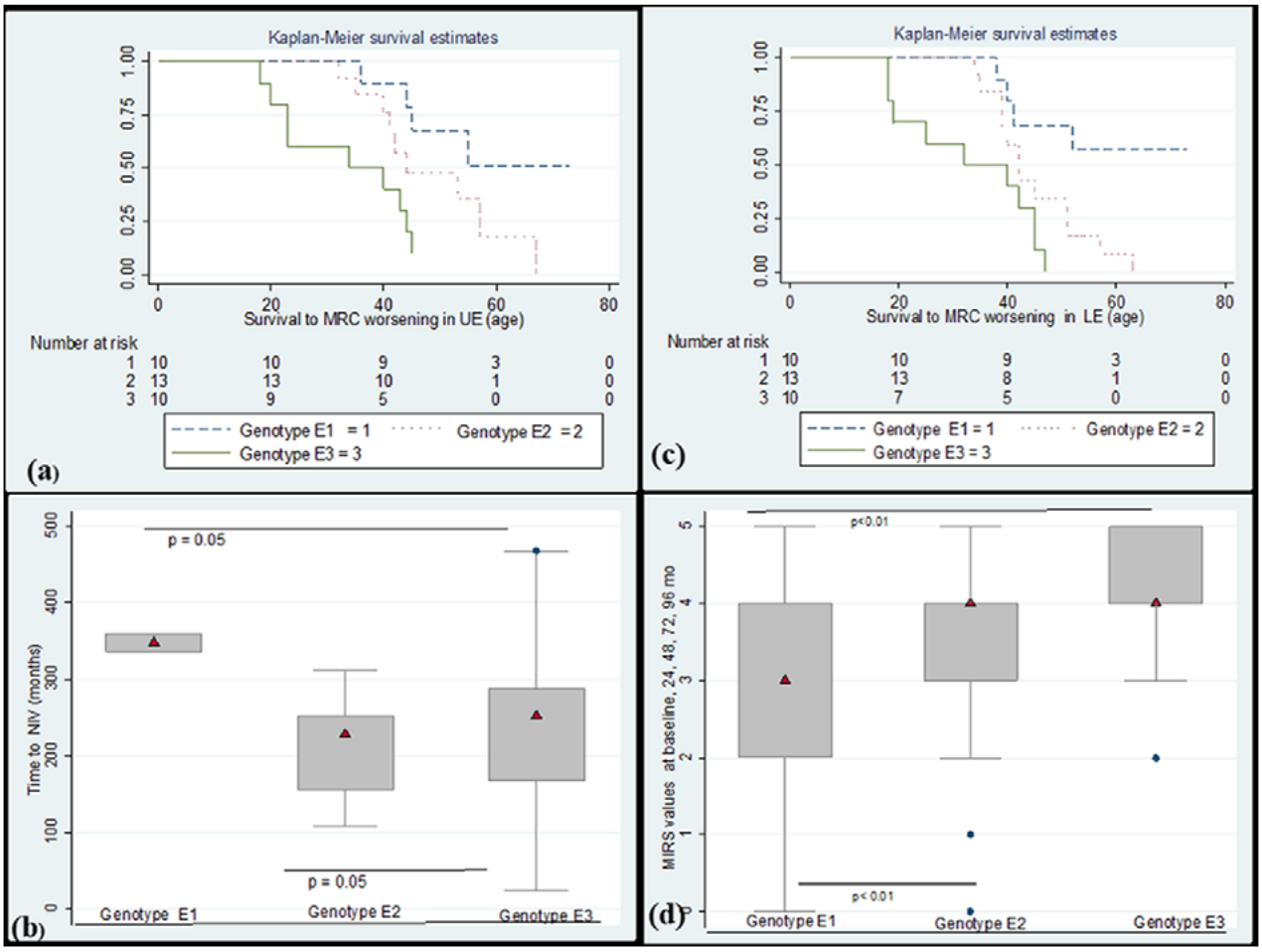

Figure 2. Cox analysis and Log rank test. **a) and c)** Kaplan-Meier survival curves expressing the probability of being free of worsening in strength, assessed by MRC in UE and in LE in the three genotypes. For both analysis $p < 0.001$, at Log rank test; **Anova model: b)** Box plot showing the time to NIV in months in the three genotypes. The boxes represent 25th, 50th and 75th percentiles. The diamond inside each box shows the median and the wriskers shows the range. Two comparaisons highlighted with lines are significant at TK comp test; **d)** Box plot showing the changes in MIRS at baseline and during follow-up at 24, 48, 72 and 96 months since onset in patients carrying different genotypes. The diamond inside each box shows the median and the wriskers show the range. Two comparisons highlighted with the lines are significant; p-value < 0.01.

52.9% in older patients, without statistically significant difference between groups.

The presence of cardiac and vascular morbidities pooled together confirmed at 8-years' follow-up a significant impact on worsening in MIRS scores (OR 3.57, CI 2.00 -6.37, p < 0.002) (Tab. IV).

Progression to NIV

NIV, either CPAP or BIPAP, was initiated during follow-up in 12 cases (36.4%) with equal occurrence between genders. The median age at NIV start was 50.5 years (Range 33-54, IQR12.5; mean 48.0 ± 9.41) and the median time from onset/diagnosis to NIV was 195 months (Range 24- 553, IQR 200; mean 214.9 ± 130.1).

Expansion size and need for NIV

Median time to NIV in genotype E1 was 348 months *versus* 240 months in genotype E3. The times to start NIV differed significantly among genotypes E1 *vs* E3, and E2 *vs* E3 (p < 0.05) as shown in Figure 2b. Regarding blood gas analysis, only pCO2 on last assessment differed in E2 and E3 group from basal pCO2 (p = 0.04), whereas among E1 patients the worsening was not significant (Tab. II). A significant difference between FVC value was detected between group E1, E2 and E3 already at baseline

(p basal = 0.03), and more obviously on last assessment (p = 0.006), confirming that FVC is a reliable indicator of progression [31].

Influence of baseline age, gender and cardiac involvement on the need for NIV

Among the 12 patients who received NIV, 41% (5) were older and 58% (7) younger than mean age. The median survival time to NIV was 324 months (Range 88-553) in the youngest, and 123 months (range 24-288) in the oldest subjects. Kaplan-Meier curve (Fig. 1c) indicated that the age of onset influenced survival to NIV: younger patients showed longer survival, but higher risk of NIV requirement, as demonstrated in univariate (HR 4.96, CI 1.07-22.8, p = 0.04) and multivariate Cox regression analysis (HR 7.54, CI 1.43-39.7, p = 0.01)(unshown results).

Regarding gender, the median time to NIV initiation did not show a statistically significant difference: 187 months in males (range 55-553), and 217 months in females (range 24-362).

The presence of cardiac involvement was independently associated with an increased risk of NIV requirement at 96 months, as resulted in MI data analysis (OR 11.5, CI 1.17-113.7, p = 0.03) (Tab. IV).

Discussion

In the present study we describe the effect of clinical and genetic parameters on neurological and respiratory outcome in a group of DM1 patients followed-up to 18 years.

Knowledge about the progression of strength decline is crucial in DM1 [1-4,9,24-27]. Only a few longitudinal studies of DM1 have documented quantitatively the decline of muscle strength with repeated measurements [9,25-27,42]. We demonstrated a significant worsening at the end of follow-up in all selected clinical outcome measures. Regarding the progression in the distribution of strength loss, we could not find a statistically significant difference of decline in UE as compared to LE. This result differs from that obtained by other authors [1,9,25,27] and could be due to our sample size, to the key muscle group chosen, or to bias related to the measurement method. Interestingly, we recorded a difference in strength of UE and LE limbs among ventilated as compared to non-ventilated subjects (p = 0.01 and 0.02, respectively).

Role of expansion size

Although caution should be kept in using CTG repeat size to predict future symptoms, there is reliable consensus that patients with small CTG expansions generally have milder symptoms, whereas increased expansion size is broadly associated with earlier disease onset and increased clinical severity [1,4,8,9-12,24,27,30,31]. Vivekanand et al. [31] suggested a cumulative influence on disease severity of size of trinucleotide repeat and length of patient exposure to the expanded CTG, i.e. their age at presentation.

In our study, we confirm a significant association between worsening in all outcome measures and expansion size, as shown by survival graphs in Figure 1b and 1d. Furthermore, patients with high number of CTG repeats showed lower muscle strength as well as worse disability scores at baseline. Moreover, we found a statistically significant difference in extremity strength bewteen ventilated and non-ventilated subjects, meaning that respiratory impairment is linked to strength loss in the limbs [33]. Rossi et al. [30] concluded that CTG expansion is an independent predictor of respiratory restriction, and Boussaïd et al. [2,3] found that a higher CTG repeat number was associated with larger decreases over time in PFTs. Hawkins et al. [43] highlighted the issue of central versus peripheral respiratory control, where alveolar hypoventilation could be partially related to respiratory muscle weakness, and partially to involvement of the respiratory center in the brain stem, causing chronic hypercapnia. On the contrary, Thil

Table IV. Results from univariate and multivariate logistic regression analysis expressing the risk of NIV and of worsening on MIRS (≥ 1 point) as outcome.

	NIV			Worsening on MIRS (≥ 1 point)		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
	1.1	0.26-4.54	0.89	**0.35**	**0.20-0.59**	**< 0.001**
Gender (female)	(0.71)	(0.13-3.74)	0.69	**(0.15)**	**(0.075-0.30)**	**(< 0.001)**
	0.53	0.12-2.2	0.39	**0.34**	**0.10-0.60**	**< 0.001**
Age at onset (> 30.1 y)	(0.89)	(0.16-4.72)	0.89	**(0.30)**	**(0.15-0.59)**	**(0.001)**
	12.1	**1.31-111.2**	**0.028**	**3.73**	**2.15-6.48**	**< 0.001**
Cardiac /vascular comorbidities	**(11.5)**	**(1.17-113.7)**	**(0.03)**	**(3.57)**	**(2.00-6.37)**	**(< 0.002)**

OR: odds ratio. 95% CI: 95% confidence interval. In brackets, adjusted results.
The last three columns display results obtained at 8-years'of follow-up with multiple imputation method (MI). (see methods for details) p significant < 0.05 two tailed. Significant results *are* in bold.

et al. [44] found no association between longitudinal lung function impairment and number of CTG repeats or blood gas analysis. Our results on respiratory impairment confirm that CTG expansion size showed a significant effect on respiratory impairment and NIV need.

Role of baseline age

Different clinical phenotypes are recognized according to age of onset. De Antonio et al. [24] provided strong evidence for a disease classification model based on five clinical forms; their data demonstrated that all forms of DM1 differ in terms of CTG expansion size, frequency of symptoms and age of onset of disease manifestations. In our cohort, all the patients were older than 14 years at the time of enrollment, therefore they could be included into juvenile or adult form of the disease. We made the choice of splitting our sample into two groups, based on age of onset. Our patients, either younger or older than mean age, were not different at baseline in MIRS and muscle strength scores. However, as shown by the survival curve (Fig. 1a), we found an expected effect of younger age on progression: longer survival to MIRS worsening in terms of age for older patients as compared to younger ones. Regarding NIV requirement as end point, youngest subjects exhibited higher risk of occurrence, but longer survival to the event.

Effect of gender

At baseline neither muscle strength measures nor disability scores significantly differed between genders, except for MIRS where females were significantly worse than males at baseline. The latter finding is interesting and could be due to an uneven prevalence of some clinical signs in males and females. According to Dogan et al. [8], men more frequently exhibit myotonia, cardiac signs, restrictive syndrome and muscle weakness, whereas women more often show cataracts, dysphagia, digestive tract dysfunction, thyroid disorders and obesity.

At the end of follow-up the change in strength, MIRS and disability scores did not differ statistically between genders; however, at 8-years of follow-up, the risk of worsening in MIRS was significantly lower in females, suggesting a different rate of progression. Gagnon et al. [25] documented, in a 9-year study on 100 DM1 subjects, a higher loss in distal muscle groups with a decrease over 50%. This significant loss of strength was found for both men and women separately; however, men had greater strength decline over time than women for all muscle groups, suggesting that the stronger the participants were at baseline, the more important was the strength loss at 9 years. Hammaren et al. [26] pooled results from different clinical phenotypes in a 5-years' study on 43 patients with assessment only of lower limb strength: their female patients showed a statistically significant change at five years in hip flexors (-1.3%), whereas in males there was a significant decrease in all examined muscle groups. Mathieu et al. [42], in 50 DM1 subjects studied cross-sectionally showed a decrease of 1.2-1.6% per year for proximal muscle groups and of 2.0-3.0% per year for distal muscle groups with no significant difference between genders (0.99% in females and 1.54% in males per year).

Cardiac and vascular involvement

Cardiac complications are the second leading cause of death in DM1 [4,5,8,22,28, 30,31,37,45-47]. Overall, the cardiac phenotype of DM1 is complex and includes an approximately three-fold higher risk of sudden cardiac death compared to age-matched healthy controls.[29,30] Metabolic abnormalities, including diabetes mellitus, hypertension, atherosclerosis, hyperlipidemia are known risk factors of anticipated mortality in DM1 [4]. Moreover, an autonomic nervous system dysfunction, diagnosed on the basis of heart rate variability and increased temporal dispersion of myocardial repolarization argues in favor of a heart involvement in DM1 that might go beyond the known conduction system involvement [4]. Cardiac arrhythmias are common in DM1 [4,29,46] and have been shown by Kaminsky et al. [29] to have a broad correlation in severity with age, muscular impairment, male gender, lung involvement and extent of the molecular defect.

Cardiac involvement in DM1patients occurs as a degenerative process, with progressive fibrosis and fatty replacement of the myocardium, which involves not only the specialized conduction system, but also other areas, initially unaffected, of the working atrial and ventricular myocardium [46,47]. As pointed out by Russo et al. [47] this pathologic substrate facilitates conduction disorders and systolic dysfunction in populations with DM1. Several clinical, metabolic and endocrine features of DM1 phenotype usually affect the elderly, and signs of accelerated aging in DM1 are cardiac conduction disturbance and endocrine abnormalities, as glucose intolerance and dyslipidemia [29]. Cardiac symptoms and signs and other vascular morbidities in our patients had an incidence similar to previous reports [4,7,29,30]. Another interesting finding to be further investigated was the increased risk for NIV requirement in patients with cardiac involvement, possibly reflecting the interrelated multisystem nature of the disease [29,30].

Limitations of the study

Inherent limitations of this study lie in the design based on a retrospective analysis of clinical medical records although most of the patients were followed pro-

spectively at our Center since the time of the diagnosis for a very long longitudinal care. A further limitation might the small sample size which is due the fact that we included only subjects with a diagnosis confirmed by genetic molecular testing in the subjects. However, our data are comprehensive and repeatidly validated by three neurologists

Conclusions

By concluding, large CTG expansions and age of disease onset were significantly associated with neurologic and respiratory impairment during a follow-up period of more than 24 months. Moreover, our study suggests that females showed lower relative risk of neurological worsening at 8 years. Finally, multisystem involvement, especially through cardiac diseases, exerts a significant negative effect on neurological progression and respiratory impairment. These results should be confirmed in prospective trials on a larger population of DM1 patients**.**

In a clinical setting, the management of DM1 patients should be carried out with a multidisciplinary approach which includes a periodic cardiac and respiratory assessment [4,29-31,46,47,51-54]. Particular attention should be paid especially to those patients who carry large CTG expansions.

Disclosure statements

The authors declare no conflict of interest or sources of funding

The authors alone are responsible for the content and writing of the paper

The study was approved by the Ethic Committee AVEN of Modena.

Informed Consent was obtained from the patients involved in the study.

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Respiratory function and therapeutic expectations in DMD: families experience and perspective

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Conflict of interest
Study participants did not receive any form of compensation.
All the authors are involved in several studies in Duchenne muscular dystrophy (Sarepta, Santhera, PTC, Pfizer, Italfarmaco, Roche). EM has participated to advisory boards from the same companies.

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Objective. The aim of this study was to use a structured questionnaire in a large cohort of Duchenne Muscular Dystrophy (DMD) patients to assess caregivers and patients views on respiratory function and to establish if their responses were related to the patients' age or level of functional impairment.

Methods. Questionnaires were administered to caregivers in 205 DMD patients of age between 3 and 36 years (115 ambulant, 90 non-ambulant), and to 64 DMD patients (3 ambulant, 61 non-ambulant) older than 18 years, subdivided into groups according to age, FVC, ambulatory and ventilatory status.

Results. Some differences were found in relation to FVC % values ($p = 0.014$), ambulatory ($p = 0.043$) and ventilatory status ($p = 0.014$). Nearly half of the caregivers expected deterioration over the next years, with the perspective of deterioration more often reported by caregivers of non-ambulant ($p = 0.018$) and ventilated patients ($p = 0.004$). Caregivers appeared to be aware of the relevance of respiratory function on quality of life (84%) showing willingness to enter possible clinical trials if these were aiming to stabilize the progression of respiratory function with a very high number of positive responses across the spectrum of age, FVC, ambulatory and ventilatory status. The boys older than 18 years showed similar results.

Conclusions. Our study showed that the concern for respiratory function increases with age and with the reduction of FVC or the need for ventilation, but the need for intervention was acknowledged across the whole spectrum of age and functional status.

Key words: Duchenne muscular dystrophy, respiratory, quality of life, patient reported outcome measures

Introduction

Over the last few years, there has been increasing attention to the natural history of respiratory function in Duchenne Muscular dystrophy

(DMD). It has become increasingly obvious that after the age of 10 years percent predicted Forced Vital Capacity (% FVC) show progressively reduced values [1-3]. Steroid naïve DMD patients have an earlier onset of deterioration, approximately 2 years before steroid treated patients, but in both groups, once established, the rate of progression is similar [1-3].

The changes are relatively regular and, with increasing age, the decrease in % FVC reaches values that are generally associated with nocturnal hypoventilation and subsequent need for noninvasive ventilation (NIV), initially restricted to nighttime and, later on in life, increasingly used also during the day [4]. This data has been particularly useful at the time of designing or interpreting the results of clinical trials targeting respiratory function as primary or secondary measures [5-8].

While several studies have explored patient and caregivers' perspective about quality of life, care burden or motor aspects [9], less has been investigated in relation to clinical relevance of respiratory function at different ages [10-12].

As recently suggested by the United States Food and Drug Administration (FDA) the use of patient reported scales should be strongly encouraged to include the patient and caregivers perspective to determine the relevance of observed functional changes [13].

Assessing the relevance of respiratory function in DMD at different ages, including patients in the first decade can however be more challenging than when assessing motor function. While clinical signs of motor deterioration are increasingly present in the first decade, especially after the age of 7 years, overt signs of respiratory impairment often become obvious only in the second part of the second decade 14. As a constant decrease in % FVC and more generally a progressive respiratory impairment already start by the age of 10 years [1,3,14], it would be of interest to understand if and how DMD patients and their families are already concerned about the early changes in % FVC and, more generally, how their level of concern varies at different ages and in relation to different functional respiratory levels.

The aim of this study has been to investigate caregivers/patients' views on respiratory function using a structured questionnaire investigating different aspects of respiratory function, including rate of infections or use of antibiotics. More specifically we wished to assess their relevance as meaningful indicators of the progression of the disease and whether the level of responses changes according to age or functional based on their FVC % values and forced expiratory volume (FEV) scores. We also wished to assess caregivers/patients' expectations regarding clinical trials targeting primarily or secondarily respiratory function.

Materials and methods

This is a multicentric study conducted in Italy in three centers (Nemo Center, Policlinico Gemelli, Catholic University, Rome; Nemo Center, University of Messina; Nemo Center, Milan).

The study was approved by the Ethical Committees of all the participating centers. Parents/caregivers of participants (minor/children) and patients above age of 18 were asked to sign a dedicated consent form that also includes consent for sharing academic data and for publication.

A face to face or telephone interview based on a structured questionnaire was administered to caregivers of DMD patients, irrespective of the patients' age. Patients older than 18 years used a self-reported version of the questionnaire. Telephone interviews were conducted only if patients had been seen within the previous 3 months and the results of their respiratory assessments were available. A trained clinician conducted the in-person interviews and telephone interviews using the same semi-structured data collection sheet.

A number of questions were asked to investigate specific respiratory aspects and caregivers/patients' view on possible changes over the next 5 years and the impact of respiratory function on quality of life. In the second part caregivers/patients were asked about their expectations regarding the possibility to enter clinical trials focusing on respiratory function by investigating what would be the minimal change in respiratory function (slowing deterioration, stability, improvement) that would justify the participation into a clinical trial. The interviews lasted 10-15 min on average.

Table I reports details on the questions asked in both the caregivers and self-reported questionnaire.

FVC

From the age of 6 years all DMD patients are routinely asked to perform, depending on their compliance, FVC. FVC was assessed by qualified and certified evaluators according to a standard protocol, which reflects, established international guidelines for lung function testing (American Thoracic Society, European Respiratory Society). The patients were appropriately instructed on the use of the spirometer before the FVC assessments were initiated. In cases where the patient could not perform a mouth seal reliably with the clinic-based Spirometer, a scuba mouthpiece or a facemask should be used. In agreement with natural history studies, reporting % predicted FVC, we will also focus on this measure as this is more comparable with previous studies [1-3].

For all respiratory assessments, the patient was requested to repeat each test 3 to 5 times and the highest value was used.

Table I. Question asked in the caregivers and self-reported questionnaire.

Caregivers /self-reported questionnaire	
Question 1:	How many respiratory infections did your child have/*did you have*, over the past last year?
Question 2:	How many times did your child/*did you* need to take antibiotics for respiratory problems, over the last year?
Question 3:	How do you expect your child's/*your* breathing capacity will change over the next 5 years, according to the evolution of the disease and growth?
Question 4:	Could an improvement in your child's /*your* respiratory function have a positive effect on him quality of life?
Question 5:	Would you consider enrolling/*to be enrolled* in a clinical trial with drugs targeting respiratory function?
Question 6:	What reason would convince you to consider enrolling/*to be enrolled* in a clinical trial with drugs targeting respiratory function?
Question 7:	Would you consider enrolling/*to be enrolled* in a clinical trial with drugs that could reduce the number of respiratory infections?

Key to legend: Words in italic reports the self-reported version of the questionnaire.

Statistical analysis

Descriptive analysis, with absolute and percentage frequencies, was performed to establish the range of responses in relation to the different age, ventilation assistance, motor and respiratory functional levels. Responses between groups were compared for significant difference using the Chi-square test. A p-value of < 0.05 was considered significant.

Results

Caregivers' questionnaires

Questionnaires from the main caregiver for 205 DMD patients (115 ambulant and 90 non ambulant) of age between 3 and 36 years were collected (mean 13.48 ± 6.06 SD). With a few exceptions the main caregiver was the mother.

Caregivers' questionnaires were subdivided in 5 groups according to the age of the patients: group 1 included 18 patients aged 3.0-6.9 years. In this group FVC was recorded only in the 9 patients older than 6 years with a mean % FVC of 81.89%; group 2 included 50 patients aged 7.0-10.9 years. FVC could be reliably recorded in 48/50, with a mean % FVC of 84.75%; group 3 included 55 patients aged 11.0-13.9 years. FVC could be reliably recorded in 53/55, with a mean % FVC of 82.08%; group 4 included 42 patients aged 14.0-17.9. FVC could be reliably recorded in 40/42, with a mean % FVC of 57.73%; group 5 included 40 patients 18 years and above. FVC could be reliably recorded in 34/40, with a mean % FVC of 27.42%.

In the 184 patients who were able to perform FVC, 73/184 (39.7%) had FVC% ≥ 80%; 46 (25%) had FVC% between 60-80%; 16 (8.7%) had FVC% between 50-60%; 10 (5.4%) had FVC % between 40-50%; another 10 (5.4%) had FVC% between 30-40%; 7 (4.0%) had FVC% between 20-30% and in 22 (11.9%) had FVC% below 20%. In 8 patients (4.3%), who were too weak and more severely impaired, their FVC was too low to be reliably recorded and was arbitrarily labelled as below 10%. Another 13 patients who were reported as unable to perform FVC, 9 because too young and 4 due to the presence of behavioral or cognitive problems.

Thirty-two of the 205 patients (15.6%) used NIV.

Question 1: number of respiratory infections

Over 88% reported no infections (65.9%) or only one infection (22.4%). Two infections were reported in 8.8% and more than 2 in 3%. The number of infections did not change significantly in relation to age, but some differences were found in relation to FVC% values ($p = 0.014$). There was also a difference according to ambulatory and ventilatory status with more infections found in non-ambulant vs ambulant patients ($p = 0.043$) and in ventilated versus non ventilated patients ($p = 0.014$).

Question 2: number of antibiotics

Over 90 % reported no antibiotics (73.7%) or only one (20%). Two antibiotics were reported in 3.9% and more than 2 in 2.5%. The number of antibiotics did not change significantly in relation to age, ambulatory status or FVC % values, but there was a difference according to ventilatory status with more antibiotics reported in ventilated versus non ventilated patients ($p = 0.001$).

Question 3: possible respiratory changes over the next 5 years

Nearly 48% anticipated a stable course with no major changes, 47.8% a deterioration and 4.4% an improvement. The expectations did not change in relation to age or FVC% but some differences were found in relation to ambulatory and ventilatory status, with the perspective of a deterioration more often reported in non-ambulant vs ambulant patients ($p = 0.018$) and in ventilated *versus* non ventilated patients ($p = 0.004$).

Question 4: effect of respiratory function on quality of life

Nearly 84% felt that an improvement in respiratory function would result in an improvement in quality of life while 2.9% replied no and 13.2 % reported that they did not have a clear opinion about it. The distribution of responses did not change significantly in relation to age, FVC %, ambulatory and ventilatory status.

Table II and Figure 1 show details of the distribution of the responses for questions 1-4.

Question 5: enrolling in a clinical trial with drugs targeting respiratory function

Nearly 71% of the caregivers would consider enrolling in a clinical trial targeting respiratory function, 2% replied they wouldn't and 27.3% replied that they did not have a clear opinion about it as this would depend on a number of variables such as possible side effects, trial burden, etc.

The distribution of responses changed in relation to age ($p = 0.012$), FVC % values ($p = 0.037$) and ventilatory status ($p = 0.044$). There was no difference in relation to ambulatory status.

Question 6: reasons to consider enrolling in a trial targeting respiratory function

Nearly 87% of the caregivers replied that they would consider participation if the treatment would aim to at least slow down deterioration; an additional 3.4% replied that would consider it if the treatment would aim to stop deterioration, and an additional 3.5% if there was the possibility of an improvement. Approximately 5% did not have a clear opinion and 1 % would not consider entering in a trial. The distribution of responses did not change significantly in relation to age, FVC %, ambulatory and ventilatory status.

Question 7: enrolling in a clinical trial that could reduce the number of respiratory infections

Over 72% replied that they would consider participation, 8.3% replied they wouldn't and 19.5% replied that this would depend on a number of variables such as possible side effects, burden of the trial etc. The distribution of responses did not change significantly in relation to age, FVC %, ambulatory and ventilatory status.

Table III and Figure 2 show details of the distribution of the responses for questions 5-7.

Table II. Caregivers' responses distribution (N, %) by age and FVC% subgroups for questions 1 to 4.

		Age (years)						FVC%							
		3-7 (n:18)	7-10 (n:50)	10-14 (n:55)	14-18 (n:42)	> 18 (n:40)	All (n:205)	< 20% (n:22)	20-30% (n:7)	30-40% (n:10)	40-50% (n:10)	50-60% (n:16)	60-80% (n:46)	> 80% (n:73)	All (n:184)
QUESTION 1	0	11 (61.1%)	36 (72.0%)	43 (78.2%)	23 (54.8%)	22 (55.0%)	135 (65.9%)	10 (45.5%)	3 (42.5%)	7 (70.0%)	7 (70.0%)	11 (68.8%)	34 (73.9%)	54 (74.0%)	126 (68.5%)
	1	7 (38,9%)	10 (20.0%)	7 (12.7%)	11 (26.6%)	11 (27.5%)	46 (22.4%)	9 (40.9%)	1 (14.3%)	2 (20.0%)	1 (10.0%)	2 (12.5%)	8 (17.4%)	15 (20.5%)	38 (20.7%)
	2	0 (0,0%)	3 (6.0%)	3 (5.5%)	6 (14.3%)	6 (15.0%)	18 (8.8%)	2 (9.1%)	2 (28.6%)	1 (10.0%)	2 (20.0%)	3 (18.8%)	3 (6.5%)	3 (4.1%)	16 (8.7%)
	3	0 (0.0%)	1 (2.0%)	1 (1.8%)	1 (2.4%)	1 (2.5%)	4 (2.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	1 (1.4%)	3 (1.6%)
	> 3	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (2.4%)	0 (0.0%)	2 (1.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
QUESTION 2	0	11 (61.1%)	40 (80.0%)	45 (81.8%)	29 (69.0%)	26 (65.0%)	151 (73.7%)	12 (54.5%)	3 (42.9%)	9 (90.0%)	9 (90.0%)	14 (87.5%)	37 (80.4%)	57 (78.1%)	141 (76.6%)
	1	7 (38.9%)	8 (16.0%)	8 (14.5%)	8 (19.0%)	10 (25.0%)	41 (20.0%)	7 (31.8%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	2 (12.5%)	7 (15.2%)	16 (21.9%)	34 (18.5%)
	2	0 (0.0%)	1 (2.0%)	1 (1.8%)	4 (9.5%)	2 (5.0%)	8 (3.9%)	2 (9.1%)	1 (14.3%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	2 (4.3%)	0 (0.0%)	7 (3.8%)
	3	0 (0.0%)	1 (2.0%)	1 (1.8%)	0 (0.0%)	2 (5.0%)	4 (2.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
	>3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (5.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
QUESTION 3	Improving	1 (5.6%)	3 (6.0%)	2 (3.6%)	1 (2.4%)	2 (5.0%)	9 (4.4%)	1 (4.5%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)	3 (4.1%)	7 (3.8%)
	No change	12 (66.7%)	32 (64.0%)	24 (43.6%)	16 (38.1%)	14 (35.0%)	98 (47.8%)	7 (31.8%)	2 (28.6%)	6 (60.0%)	6 (60.6%)	4 (25.0%)	24 (52.2%)	38 (52.1%)	87 (47.3%)
	Worsening	5 (27.8%)	15 (30.0%)	29 (52.7%)	25 (59.5%)	24 (60.0%)	98 (47.8%)	14 (63.6%)	5 (71.4%)	3 (30.0%)	4 (40.0%)	10 (62.5%)	22 (47.8%)	32 (43.8%)	90 (48.9%)
QUESTION 4	No	0 (0.0%)	1 (2.0%)	3 (5.5%)	1 (2.4%)	1 (2.5%)	6 (2.9%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	4 (5.5%)	6 (3.3%)
	Don't know	4 (22.2%)	12 (24.0%)	8 (14.5%)	1 (2.4%)	2 (5.0%)	27 (13.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	2 (12.5%)	5 (10.9%)	16 (21.9%)	24 (13.0%)
	Yes	14 (77.8%)	37 (74.0%)	44 (80.0%)	40 (95.2%)	37 (92.5%)	172 (83.9%)	21 (95.5%)	7 (100%)	10 (100%)	9 (90.0%)	13 (81.3%)	41 (89.1%)	53 (72.6%)	154 (83.7%)

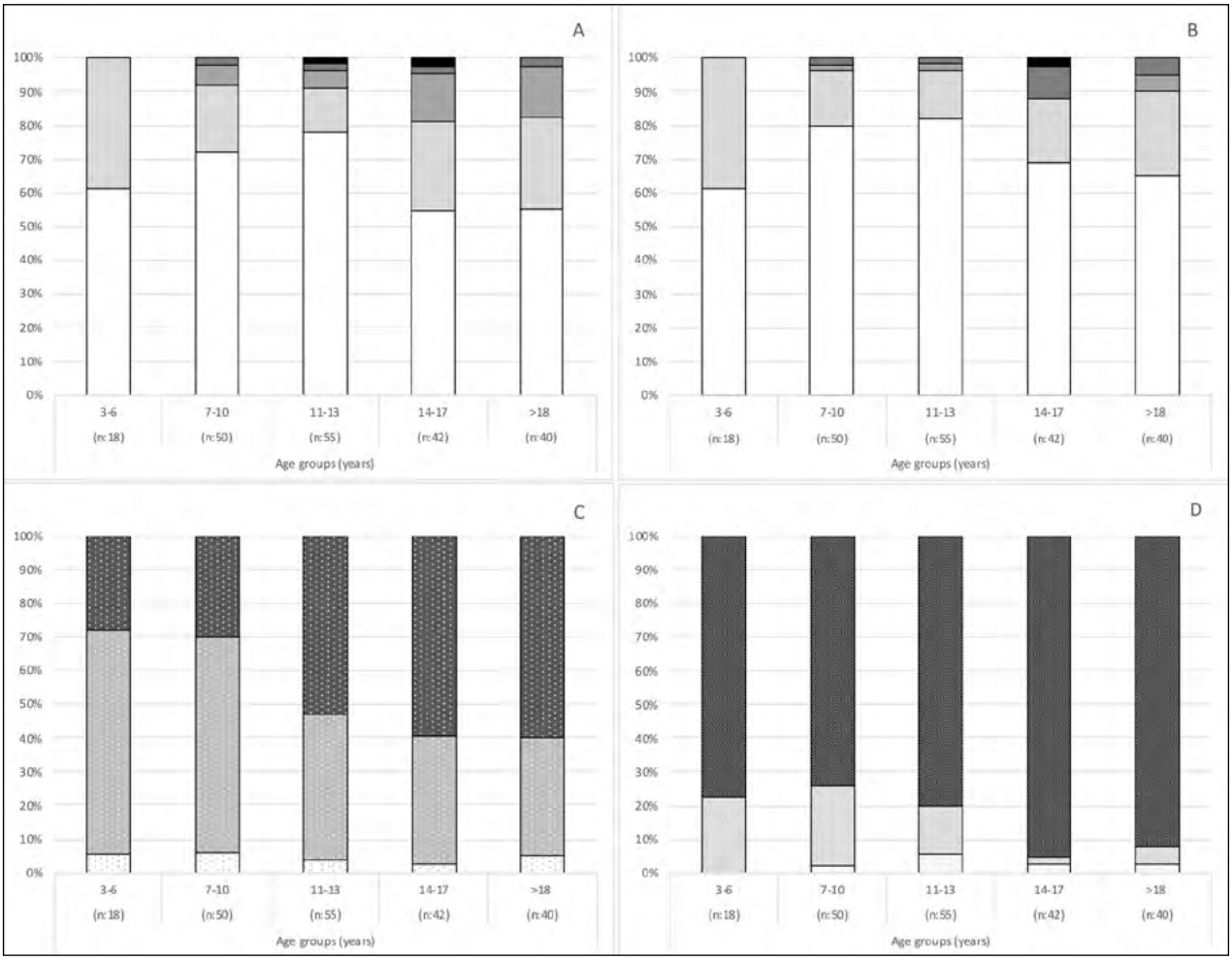

Figure 1. Caregivers' responses distribution by age for questions 1 to 4. (A) Question 1, (B) Question 2, (C) Question 3, (D) Question 4. Key to panels A&B: White= 0; Light grey= 1; Dark grey= 2; Light Black= 3; Black=> 3. Key to panel C: Dotted white= Improvement; Dotted light grey= No change; Dotted black= Worsening. Key to panel D: White texture= No; Light grey texture = I don't know; Black texture= Yes

Self-reported questionnaires in patients older than 18 years

Questionnaires from 64 DMD patients older than 18 years (3 ambulant and 61 non ambulant) were available. These included 45 patients for whom caregivers' questionnaires were also available. Seven patients could not perform FVC because too weak (n:4) or had a tracheostomy (n:3), the remaining 57 were able to perform FVC. Only 2/57 (3.5%) had FVC% ≥ 80; 4 (7%) had FVC% between 60-80, 2 (3.5%) between 50 and 60, 7 (12.3%) between 40 and 50; 8 (14%) between 30 and 40; 4 (7%) between 20-30 and the remaining 30 (52.6%) below 20. Forty-four of the 64 patients (68.7%) used NIV.

Question 1: number of respiratory infections

Over 88 % reported either no infections (59.4%) or only one infection (26.6%). Two infections were reported in 10.9% and more than 2 infections in 3.1%. The number of infections did not change significantly according to ventilatory status, but some differences were found in relation to FVC % values ($p = 0.021$).

Question 2: number of antibiotics

Over 80% reported no (71.9%) or only one (17.2%) antibiotics. Some differences were found in relation to ventilatory status and according to FVC % values ($p = 0.041$).

Question 3: possible respiratory changes over the next 5 years

Nearly 38% anticipated a stable course with no major changes, 53.1% a deterioration and 9.4% an improve-

Table III. Caregivers' responses distribution (N, %) by age and FVC% subgroups for questions 5 to 7.

		Age groups (years)						FVC%							
		3-7 (n:18)	7-10 (n:50)	10-14 (n:55)	14-18 (n:42)	> 18 (n:40)	All (n:205)	< 20% (n:22)	20-30% (n:7)	30-40% (n:10)	40-50% (n:10)	50-60% (n:16)	60-80% (n:46)	> 80% (n:73)	All (n:184)
QUESTION 5	No	2 (11.1%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (2.5%)	4 (2.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	1 (1.4%)	3 (1.6%)
	Don't know	5 (27.8%)	21 (42.0%)	16 (29.1%)	8 (19.0%)	6 (15.0%)	56 (27.3%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	8 (50.0%)	11 (23.9%)	29 (39.7%)	51 (27.7%)
	yes	11 (61.1%)	29 (58.0%)	38 (69.1%)	34 (81.0%)	33 (82.5%)	145 (70.7%)	19 (86.4%)	7 (100%)	10 (100%)	9 (90-0%)	8 (50.0%)	34 (73.9%)	43 (58.9%)	130 (70.7%)
QUESTION 6A	No	1 (5.6%)	0 (0.0%)	1 (1.8%)	1 (2.4%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	2 (1.1%)
	Don't know	2 (11.1%)	6 (12.0%)	8 (14.5%)	3 (7.1%)	5 (12.5%)	24 (11.7%)	2 (9.1%)	1 (14.3%)	0 (0.0%)	1 (10.0%)	6 (37.5%)	5 (10.9%)	7 (9.6%)	22 (12.0%)
	yes	15 (83.3%)	44 (88.0%)	46 (83.6%)	38 (90.5%)	35 (87.5%)	178 (86.8%)	20 (90.9%)	6 (85.7%)	10 (100%)	9 (90.0%)	10 (62.5%)	41 (89.1%)	64 (87.7%)	160 (87.0%)
QUESTION 6B	No	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 0.5%)
	Don't know	2 (11.1%)	3 (6.0%)	5 (9.1%)	4 (9.5%)	5 (12.5%)	19 (9.3%)	2 (9.1%)	1 (14.3%)	1 (10.0%)	1 (10.0%)	4 (25.0%)	4 (8.7%)	4 (5.5%)	17 (9.2%)
	yes	15 (83.3%)	47 (94.0%)	50 (90.9%)	38 (90.5%)	35 (87.5%)	185 (90.2%)	20 (90.9%)	6 (85.7%)	9 (90.0%)	9 (90.0%)	12 (75.0%)	42 (91.3%)	68 (93.2%)	166 (90.2%)
QUESTION 6C	No	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.5%)
	Don't know	1 (5.6%)	3 (6.0%)	2 (3.6%)	2 (4.8%)	4 (10.0%)	12 (5.9%)	1 (4.5%)	1 (14.3%)	0 (0.0%)	1 810.0%)	2 (12.5%)	1 (2.2%)	4 (5.5%)	10 (5.4%)
	yes	16 (88.9%)	47 (94.0%)	53 (96.4%)	40 (95.2%)	36 (90.0%)	192 (93.7%)	21 (95.5%)	6 (85.7%)	10 (100%)	9 (90.0%)	14 (87.5%)	45 (97.8%)	68 (93.2%)	173 (94.0%)
QUESTION 7	No	2 (11.1%)	4 (8.0%)	6 (10.9%)	3 (7.1%)	2 (5.0%)	17 (8.3%)	4 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (4.3%)	9 (12.3%)	16 (8.7%)
	Don't know	4 (22.2%)	14 (28.0%)	12 (21.8%)	5 (11.9%)	5 (12.5%)	40 (19.5%)	2 (9.1%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	4 (25.0%)	9 (19.6%)	21 (28.8%)	37 (20.1%)
	yes	12 (66.7%)	32 (64.0%)	37 (67.3%)	34 (81.0%)	33 (82.5%)	148 (72.2%)	16 (72.7%)	6 (85.7%)	10 (100%)	10 (100%)	11 (68.8%)	35 (76.1%)	43 (58.9%)	131 (71.2%)

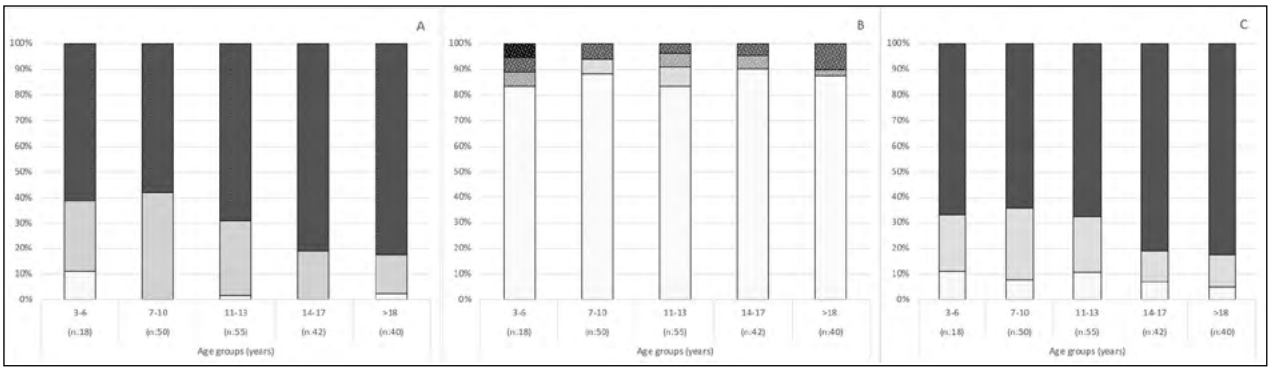

Figure 2. Caregivers' responses distribution by age for questions 5 to 7. (A) Question 5, (B) Question 6, (C) Question 7. Key to panels A&C: White texture= No; Light grey texture= I don't know; Black texture= Yes. Key to panel B: Dotted white= At least slow down; Dotted light grey= At least slow down; Dotted dark grey= At least improve, Dotted light black= I don't know, Dotted black= No.

ment. The distribution of responses did not show significant changes in relation to FVC and ventilatory status.

Question 4: effect of respiratory function on quality of life

Nearly 80% replied yes, 6.3% felt that this would not produce an improvement in Quality of life and 14.1% replied that they did not have a clear opinion about it. Some differences were only found in relation to ventilatory status ($p = 0.028$).

Question 5: enrolling in a clinical trial with drugs targeting respiratory function

Over 70% of patients replied that they would consid-

er participation, 7.8% replied they wouldn't and 20.3% replied that they had not a clear idea. The distribution of responses did not show significant changes in relation to FVC and ventilatory status.

Question 6: reasons to consider enrolling in a trial targeting respiratory function

Nearly 70 % of patients replied that they would consider participation if the treatment targeted to at least slow down deterioration; an additional 17.2% replied that would consider it if the treatment would aim to stop deterioration, and an additional 7.8% if there was the possibility of an improvement. Approximately 5% did not have a clear opinion and 1.6 % would not consider entering in a trial. The distribution of responses did not show significant changes according to FVC or ambulatory status, but some differences were found in relation to ventilatory status ($p = 0.023$).

Question 7: enrolling in a clinical trial that could reduce the number of respiratory infections

Nearly 60 % of patients replied that they would consider participation, 7.8% replied they wouldn't and 32.8% replied that they did not have a clear opinion about it as this would depend on a number of variables such as possible side effects, burden of the trial etc. The distribution of responses did not show significant changes in relation to FVC or ventilatory status.

Discussion

The advent of clinical trials specifically targeting respiratory function or including FVC and other respiratory indexes as secondary measures [5, 6, 8,15] has highlighted the need for better understanding of the progression of respiratory impairment in DMD children. While in the last few years several papers have reported longitudinal natural history data on FVC and FEV, showing concordance on the age when FVC and FEV decline and on their rate of progression [1-3], less has been reported about patient reported outcome measures or, more generally, on the patients' and caregivers' perspective on respiratory function, with the exception of some studies mainly focusing on ventilated patients [10]. One of the aims of our questionnaire was to investigate the awareness of clinical signs in caregivers of DMD patients with a wide range of age and respiratory impairment from very young patients to older adults with severe respiratory impairment. The questionnaire included a first part evaluating the frequency of infections and antibiotics and general questions on the expectations on respiratory function over time and its effect on their quality of life and a second part assessing the willingness of the caregivers to have their children enrolled in studies targeting respiratory function. We were interested in recording what was the general perception from the families and to establish if their responses were related to the patients' age or level of functional impairment, expressed by different parameters FVC, ventilatory and ambulatory status.

When asked to report the number of infections, we found that the overall number of infections was relatively low, with no infections or only one infection in 65.9%. There was an increased number of infections in patients with the lowest FVC and a difference between ambulant and non-ambulant and between ventilated and non-ventilated. The number of patients with frequent infections was however relatively low even in the non-ambulant ventilated patients with very low FVC, probably related to the implementation of care recommendations suggesting the use of vaccinations, In-Exufflator and other recommendations [4]. The number of antibiotics was similar and only slightly lower than the reported number of infections, this suggesting a low number of reported minor infections not requiring antibiotics.

It is of interest that even though in 41.4% of the cases the age of the patients was over 10 years, that is the age when respiratory tests start showing a mild but progressive decline, nearly half of the responders did not foresee a deterioration over the next 5 years. The perspective of deterioration, found in less than half of the patients, was more often reported by caregivers of non-ambulant and ventilated patients or in those with very reduced % FVC. These results suggest that even if caregivers are informed of a possible respiratory impairment in their children as part of the progression of the disease, the progressive deterioration starting at the end of the first decade is in some cases underestimated. This is probably due to the fact that in the first phase respiratory decline is often not associated with any overt clinical respiratory sign, unlike motor difficulties that are obvious since the time of diagnosis. In ambulant patients, loss of ambulation is seen as the major life changing event and is probably the biggest cause of concern, overshadowing other aspects that do not require immediate intervention. Caregivers however appear to be aware of the relevance of respiratory function as demonstrated by their responses on the effect on quality of life and by their willingness to enter possible clinical trials targeting respiratory function. Less that 3% felt that an improvement in respiratory function would not results in an improvement in their quality of life, with a very high number of positive responses (84%) across the spectrum of age, FVC, ambulatory and ventilatory status. In our study we did not use structured assessments to measure quality of life but it is of interest that these results are consistent with previous findings also reporting Quality of life in ventilated patients [10,11].

Similarly, there were a very high percentage (70%) of caregivers considering having their children enrolled in clinical trials targeting respiratory function. The relatively high percentage of caregivers who responded that they did not have a clear idea, was mainly related to the need to have more details about the possible trials, including the severity of possible side effects. It is of interest that despite the results of question 3, with a significant proportion of caregivers reporting a stabilization over the next 5 years, nearly 87% of the caregivers felt that they would consider participating in a clinical trial if, in the absence of significant side effects, the intervention would even only slow down the rate of deterioration. There was a much smaller percentage of patients with no clear idea, mainly in the younger groups with more preserved FVC, but this percentage decreased, with an increase of positive responses to over 90 and nearly 95% if the prospect was stabilization or improvement, therefore including nearly the totality of caregivers, irrespective of age and functional status.

When we asked the DMD patients older than 18 years to fill the same questions of the questionnaire using a self-reported procedure, we observed that the responses were often similar but not identical to the responses recorded by caregivers of patients in the same age group. A correlation between caregivers and patients however was not entirely possible as some adult patients came to clinic not accompanied by their caregivers and in some cases the questionnaire was given only to the caregivers if the patient had moderate or severe cognitive or behavioural problems. The main difference between patients and caregivers was on the question exploring their willingness to participate in a clinical trial. The percentage of patients who would consider a clinical trial if the expectations was slowing down deterioration was overall high but lower in patients than in in caregivers. The percentage increased when the expected result was stabilization.

One of the limitations of this study is that we did not systematically collect economic status or schooling in the caregivers and in the patients. Although we did exclude patients with severe behavioral or cognitive problems, at the time of collecting the questionnaires we felt that patients were often emotionally or cognitively less mature than their age and this may have contributed to their reduced awareness of the severity of their respiratory impairment or on their expectations.

Conclusions

Even with these limitations, our study provides the views of caregivers and older patients on respiratory function in relation to different variables such as age or functional status and is an ideal complement to the recent studies reporting respiratory functional data. Not surprisingly the concern on respiratory function increases with age and with the reduction of % FVC or the need for ventilation but the need for intervention was acknowledged across the whole spectrum of age and functional status. Further studies also using other respiratory measure and more structured assessments of quality of life may help to better define the correlation between these aspects.

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Endocrine myopathies: clinical and histopathological features of the major forms

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Endocrinopathies, such as thyroid and parathyroid diseases, disorders of the adrenal axis, and acromegaly are included among the many causes of myopathy. Muscle disturbances caused by endocrine disorders are mainly due to alterations in the protein and carbohydrate metabolisms. Either a deficiency or excess of hormones produced by the glands can cause muscle dysfunction that can be reversed by starting hormone replacement therapy or acting on hormone dysfunction. The diagnosis is usually easy if a muscle disorder occurs in an overt endocrinopathy; however, in few patients, myopathy could be the first manifestation of the underlying endocrinopathy. In this article we discuss pathophysiology, clinical features and management of muscle involvement related to the major endocrine diseases.

Key words: endocrine myopathies, muscle weakness, creatine kinase, hypothyroidism, myalgia, rhabdomyolysis

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Introduction

Skeletal muscle disorders can arise from a variety of endocrine diseases, including those affecting thyroid, adrenal glands, pituitary, parathyroid. Either a deficiency or excess of hormones produced by the glands can cause muscle dysfunction that can be reversed by starting hormone replacement therapy or acting on hormone dysfunction [1]. The prevalence of neuromuscular diseases as a complication of endocrine disorders is not easily ascertainable and is likely to be underestimated. Non-specific muscular symptoms such as cramps, myalgias, proximal or generalized weakness and exertional pain, may be part of the variable clinical pictures of hypothyroidism, hyperparathyroidism, hyperadrenocorticism [2]. Moreover, in some cases as in hypothyroidism, myopathy becomes evident with increased CK levels, progressive proximal muscle weakness and electromyographic abnormalities [1-3]. Furthermore, some disorders can be considered typical of certain endocrinopathies, such as periodic paralysis in thyrotoxicosis. We review the main endocrine dysfunctions that can cause muscle disorders and their treatment.

Thyroid disorders

Thyroid gland acts on several organ systems working as a metabolic regulatory centre through the secretion of L-thyroxine (T4) and

3,5,3'-triiodo-L-thyroxin (T3) whose production is regulated by thyroid stimulating hormone (TSH) [4].

Hypothyroidism

A thyroid hormone deficiency of is often the result of a lack of dietary iodine, autoimmune thyroiditis or, less commonly, post-treatment ablation [5]. Hypothyroidism is usually more common in women. Symptoms are initially nonspecific and constitutional, with muscle cramps, ideomotor slowdown, later a myxedema may develop, with hair loss, thick skin, and heart enlargement. Hypothyroidism, when suspected, can be confirmed by measuring TSH and T4 blood tests [6].

Hypothyroid Myopathy

The percentage of patients affected by hypothyroidism experiencing neuromuscular symptoms varies from 30 to 80% [4].

Proximal weakness, muscle stiffness and cramping, slow reflexes, and myoedema are the spectrum of neuromuscular symptoms of hypothyroidism and may exhibit also as presenting symptoms of the endocrine disease. Weakness is most common complaint followed by cramps [3,4,7]. Slow reflexes, best seen in the ankle jerk response, also represents a peculiar precocious sign of neuromuscular involvement in hypothyroidism [8]. Another possible acute presentation of hypothyroidism is rhabdomyolysis [9,10].

Myoedema is uncommon and hence often undervalued by clinicians but it is, in most instances, one of classical signs of hypothyroid myopathy. It is a phenomenon of mounding of muscle tissue as a response to pressure or percussion [11]. Hypothyroidism may present as Hoffmann's Syndrome, which is a rare form of hypothyroid myopathy that occurs in adults and is characterized by the presence of hypothyroidism, pseudohypertrophy of muscles and varying degrees of muscle weakness [3,12]. Unusually, it is sometimes observed in children with hypothyroidism a muscular enlargement which is referred to as Kocher-Debre-Semelaigne syndrome [13].

Muscular disturbances in hypothyroidism can be ascribed to the slow or reduced protein turnover and impaired carbohydrate metabolism due to the lack of thyroid hormone [4].

Diagnosis and management

It can be based on the following findings: a low thyroid hormone value, elevated up to ten times normal creatine kinase (CK) levels, possible myopathic pattern at the electromyography (EMG). Establishing a replacing therapy may lead to euthyroid state and muscle symptoms recovery [4].

Morphological changes described in hypothyroid myopathy are largely non-specific and include fiber size variation, type 1 fiber predominance, type 2 atrophy, internal nuclei, sporadic necrosis and regeneration, glycogen accumulation, damaged mitochondria [2,3]. Core-like structures, mainly evident in type 1 fibers, are a frequent feature in long-standing overt hypothyroidism (Fig. 1A). These structures had histochemical and ultrastructural appearances of targetoid fibers and unstructured central cores, with evidence of abnormal deposition of intermediate filament proteins (i.e. desmin) at immunocytochemistry (Fig. 1B). At ultrastructural study, the core areas show disorganized myofibrils, Z-band streaming, rod formation, paucity of mitochondria and glycogen granules (Fig. 1C). Cores often disappear after treatment with levo-thyroxine.

Hyperthyroidism

The prevalence of hyperthyroidism in women is between 0.5-2% and it is 10 times less common in men. The most common causes are Graves' disease, toxic multinodular goiter, and autonomously functioning thyroid adenoma. Rare causes of hyperthyroidisms are: pituitary adenoma, autoimmune thyroiditis (Hashitoxicosis), levothyroxine overdose, inadequate iodine supplementation (amiodaron induced hyperthyroidism, iodine-based contrast media), hCG excess (pregnancy, gestational trophoblastic disease, germ-cell tumors) [14].

Hyperthyroid myopathy

Muscle involvement has been reported to occur in about 80% of thyrotoxic patients [15]. Hyperthyroidism mainly leads to symptoms like muscle wasting and weakness such as proximal muscle weakness, involving both the upper and lower extremities, although distal muscle weakness is also described, associated to brisk reflexes. In addition to muscle weakness, muscle fatigue is often reported and generally described by patients as exercise intolerance.

Various authors have suggested that thyrotoxic myopathy is a result of the overall constellation of weight loss and generalized asthenia of hyperthyroidism [15]. In fact, thyrotoxic myopathy is rarely described as the onset symptom in thyrotoxic patients. However, cases of a fulminating myopathy in hyperthyroidism are reported, due to the involvement of respiratory and bulbar muscles [16,17].

Thyrotoxic periodic paralysis are another rare manifestation of muscular disease in hyperthyroidism characterized by a rapidly progressing paralysis, greater in the proximal segments of lower limbs. This phenomenon occurs in susceptible individuals after an intracellular shift in potassium associated to a dilatation of sarcoplasmic reticulum; however, the underlying relation between dilatation of sarcoplasmic reticulum and excess of thyroid

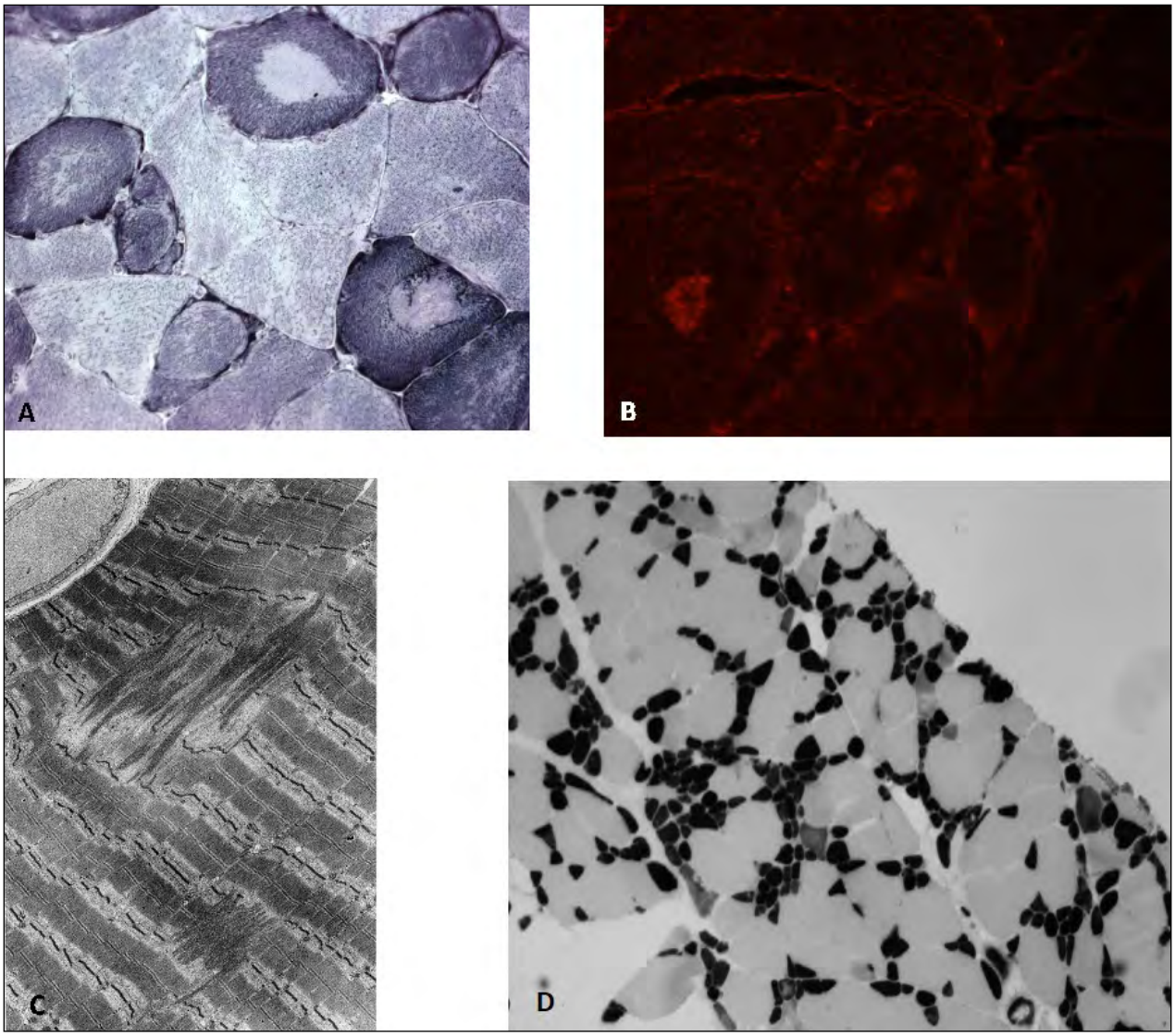

Figure 1. Histopathological findings in hypothyroid and hypercortisolism associated myopathies A: cores in type 1 fibers, NADH-TR (magnification 280 X); B: immunocytochemistry revealing increased desmin binding in two cores (magnification 280 X); C: Electron microscopy showing two core areas with disorganized myofibrils, rod bodies, and lack of mitochondria and glycogen (magnification 6800X); D: ATPase pH 9.4 stain showing a marked type 2 fibers atrophy in steroid myopathy (magnification 110 X).

hormone is not clear. Thyrotoxic periodic paralysis manifests with hypokalemia in the acute state [18].

The pathogenesis of muscle dysfunction in hyperthyroidism is likely due to an upregulation of metabolic activity which leads to increased catabolism in muscle cells, primary target of thyroid hormones.

Diagnosis and management

Muscle enzymes, including CK, are generally normal. At the EMG, a myopathic pattern can be observed. Muscle biopsy is frequently normal.

The management of these myopathies is based on achieving euthyroid state. It is demonstrated that beta-blocker agents, such as propranolol, improve muscle function [4]. On the other hand, it is important to obtain a smooth reduction of FT4 to minimize the risk of a hypothyroidism related myopathy, especially in patients susceptible to hormonal change [19].

Parathyroid disorders

Parathyroid glands are four small glands of the endocrine system located behind the thyroid which have a

regulatory role with action as a thermostat in the systemic calcium homeostasis to ensure tight regulation of serum calcium concentrations and appropriate skeletal mineralization. They produce a hormone called parathyroid hormone (PTH) that raises the blood calcium level by increasing calcium gut absorption, bone resorption and reducing renal clearance of calcium (Ca^{++}) [20].

Hypoparathyroidism

It results from PTH deficiency or end-organ unresponsiveness to PTH. Permanent hypoparathyroidism is the most common long-term complication after total thyroidectomy, but it can also occur as hereditary form, pseudohypoparathyroidism or as a consequence of severe hypomagnesemia. Its incidence varies from 30 to 60% [20,21].

Hypoparathyroidism myopathy

Hypoparathyroidism rarely determines muscle involvement. However, mild CK elevation and muscle weakness have been described. More frequently, hypoparathyroidism results in hypocalcemia which leads to muscle tetany (increased neuromuscular irritability may be demonstrated by eliciting a Chvostek or Trousseau sign and poor reflexes) [21].

Diagnosis and management

Calcium and magnesium serum concentration should be evaluated. CK in hypoparathyroidism can be normal or variably elevated [22,23]. No remarkable findings at EMG and muscle biopsy. A cardiological evaluation with QT interval analysis should be performed [24]. Correcting calcium and magnesium levels is the treatment guideline [24].

Hyperparathyroidism

Hyperparathyroidism should result from primary hyperparathyroidism (HPT), which is due to a growth regulatory disturbance in one or several parathyroid glands (such as hyperplasia or adenomas), or from secondary hyperparathyroidism, which develops in patients with uremia, due to phosphate retention, hypocalcemia, and reduced active vitamin D levels, causing parathyroid hyperplasia and eventually development of parathyroid tumors and hypercalcemia [25].

Hyperparathyroid myopathy

Hyperparathyroidism can develop both central and peripheral neurological symptoms. Muscle typical involvement is a proximal weakness with easy fatiguability, atrophy and hyperreflexia [26]. In some cases, a clinical picture mimicking motor neuron disease has been reported, characterized by muscular atrophy and weakness with hyperreflexia and spasticity [27].

Diagnosis and management

Creatinine kinase levels and EMG in hyperparathyroidism are usually normal. Muscle biopsy shows fibers atrophy usually not associated with degeneration. Surgical approach is considered the way to treat primary hyperparathyroidism leading to a regression of the myopathic disorder. Hyperparathyroidism secondary to renal disease is more difficult to treat, but administration of vitamin D and reduction of phosphorous intake may be helpful [28].

Adrenal glands disorders

Adrenal glands are responsible for glucocorticoids (GCs) production under the hypothalamus-pituitary-adrenal (HPA) axis. These glands are involved in several mechanism for homeostasis and metabolism. In particular, cortisol, whose production is stimulated by adrenocorticotropic hormone (ACTH), acts as suppressant of inflammation, in response to metabolic dysfunction and stress situations [29].

Hypercortisolism

Hypercortisolism can arise from both an iatrogenic condition and an endogenous overproduction. Furthermore, several pathological states associated with muscle damage, such as sepsis, diabetes, acidosis, chronic obstructive pulmonary disease, cancer, are accompanied by an increase of GC production [29].

Iatrogenic hypercortisolism

As a result of an overdosage of steroids, prescribed for therapeutic purposes, an iatrogenic steroid myopathy can occur. The onset is subacute characterized by proximal muscle weakness followed by atrophy [30]. Muscle atrophy results both by a decrease of protein synthesis and by an increase of protein degradation in skeletal muscles. It has also been suggested that GCs impair angiogenesis decreasing capillary number [31].

Diagnosis and management

In corticosteroid myopathy CK value are usually normal. The EMG shows a myophatic pattern with small, polyphasic potentials and no spontaneous activity. A peculiar finding of steroid myopathy is represented by a selective and in some cases marked type 2 muscle fiber atrophy at muscle biopsy which could be useful in diagnosis, in particular to differentiate from an inflammatory myopathy (Fig. 1D) [32].

Steroid myopathy treatment is based on safety steroid dose reduction to the lowest possible dose, using alternate-day dosing or switching to a nonfluorinated steroid [32].

Endogenous hypercortisolism

Endogenous hypercortisolism can be related to an overproduction of ACTH due to pituitary adenomas (Cushing's disease) or to an ectopic hormone secretion of either ACTH or GCs.

Patients affected by endogenous hypercortisolism may complain of muscle weakness, typically proximal. The clinical picture varies from myalgias to severe muscle weakness and atrophy. Patient examination in these cases reveal peculiar signs of steroid excess, such as moon facies, buffalo hump, abdominal striae.

Diagnosis and management

Diagnostic findings in endogenous hypercortisolism are overall the same of those described for the iatrogenic one. Therapy is based on the removal of the oversecreting tissue, leading to a restoration of hormone homeostasis and to the resolution of the myopathy [33,34].

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CASE REPORT

Beneficial effects of one-month sacubitril/valsartan treatment in a patient affected by end-stage dystrophinopathic cardiomyopathy

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Dystrophinopathic cardiomyopathy (DCM) is an almost constant manifestation in Becker muscular dystrophy (BMD) patients significantly contributing to morbidity and mortality. The nearly complete replacement of the myocardium by fibrous and fatty connective tissue results in an irreversible cardiac failure, characterized by progressive reduction of the ejection fraction. According to PARADIGM-HF trial results, the European Society of Cardiology (ESC) guidelines recommend the use of sacubitril/valsartan in ambulatory patients with heart failure and reduced ejection fraction, who remain symptomatic despite an optimal medical therapy. To date, little is still known about the use of sacubitril/valsartan in DCM. We report the case of a patient with dystrophinopathic end stage dilated cardiomyopathy with reduced ejection fraction who successfully responded to sacubitril/valsartan treatment.

Key words: dystrophinopathic cardiomyopathy, heart failure, sacubitril/valsartan, Becker muscular dystrophy

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Introduction

Dystrophynopathies are X-linked recessive disorders characterized by partial (benign dystrophinopathy, BMD) or total (severe dystrophinopathy, DMD) dystrophin deficiency [1]. Cardiac involvement is a common finding in muscular dystrophies [2] and often precedes the skeletal muscle one; in dystrophinopathies, left ventricular systolic dysfunction leading to dilated cardiomyopathy (DCM) and intractable heart failure represents the typical picture [2-4]. Patients may often require the use of mechanical devices [5-6] or need heart transplantation [7]. In late stages, DCM may be complicated by atrial fibrillation or atrial flutter, and/or by ventricular arrhythmias, that predispose the patients to an increased risk of sudden cardiac death [8].

Despite mild muscle symptoms, over 70% of patients with BMD develop dystrophinopathic cardiomyopathy, that evolves toward the picture of an intractable heart failure [3], regardless an appropriate pharmacological treatment [9]. Given the lack of specific guidelines on the issue, the treatment of dystrophinopathic DCM usually follows the general guidelines for treating genetic cardiomyopathies [10].

Sacubitril/valsartan (LCZ696) (SAV) has recently been approved for the treatment of patients with refractory heart failure and reduced ejection fraction (HFrEF), as it showed a reduction in mortality and hospitalization compared with standard drugs [11]. Sacubitril/valsartan belongs to the class of angiotensin receptor-neprilysin inhibitors (ARNi), endopeptidases which cleave natriuretic peptides [11]. The effectiveness and safety of this drug receives constant confirmation in daily practice. However, no data are still available about its possible clinical use in patients affected by dystrophinopathic dilated cardiomyopathy with HFrEF.

We report for the first time the case of a patient with dystrophinopathic dilated cardiomyopathy and HFrEF who successfully responded to sacubitril/valsartan treatment, after just 30 days of therapy.

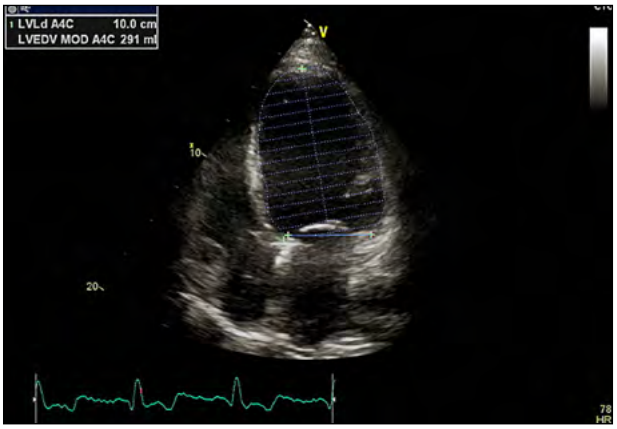

Figure 1. B-mode echocardiography. Enlarged left ventricle with an end-diastolic volume evaluated through the biplane method in apical 4-chambers view (291 ml).

Case report

A 46-year-young man, affected by familial dystrophinopathic cardiomyopathy, was hospitalised for the exacerbation of signs and symptoms of congestive HF. The patient was followed by the age of 23 years for cardiac symptoms characterized by exertional dyspnoea, and several episodes of tachycardia. The diagnosis of dystrophinopathic cardiomyopathy was made because of family history (the older brother died at the age of 28 from intractable heart failure, awaiting heart transplantation) and confirmed by genetic analysis, that showed the deletion of exons 45-49 of the dystrophin gene, typical of BMD phenotype. The patient had no muscle symptoms. The cardiological investigation showed a dilation of the heart chambers and a reduced ejection fraction, consistent with a picture of dystrophinopathic dilated cardiomyopathy, that was confirmed at the endomyocardial biopsy. Treatment with ACE-inhibitors (delapril 45 mg/die), steroids (deflazacort) and antioxidants (vitamin C and E, and Coenzyme Q10) was promptly set up, obtaining a stabilization of the cardiological parameters for about 12 years.

At the age of 40, a bicameral cardioverter defibrillator (ICD) was implanted because the evidence of severely dilated left ventricular cavity with diffuse hypokinesis and onset of symptoms and signs of HFrEF. In that occasion, the pharmacological therapy of HF was titrated according to ESC guidelines: delapride 30 mg/die, carvedilol 25 mg/die, furosemide 25 mg/die and spironolactone 25 mg/die, obtaining relative well-being for about 5 years.

At the age of 45 years, a cardiorespiratory episode of infectious origin, which required hospitalization in health care facility, further compromised the precarious cardiovascular balance of the patient, who experienced after few months dyspnoea on mild exertion and poor tolerability of daily activities (NYHA class III; basal spo2: 96%; heart rate (hr): 95 bpm; arterial blood pressure: 110/70 mmhg). Two-dimensional and M-mode echocardiograms showed reduced systolic indices, including fractional shortening (9%) and ejection fraction (EF) (18%) (Fig. 1). Echocardiography showed high filling pressure (E/E' average 27.3) and a global longitudinal strain (GLS) of -6.4% (Fig. 2). Right ventricle function, tricuspid annular plane systolic excursion (TAPSE = 13 mm) and right ventricle velocity (RVs'= 8 cm/s) were also reduced.

ProBNP was 1578 pg/ml. The patient complained a concomitant involvement of motor abilities, with a reduction of the 6MWT (270 meters), SpO2 (92%), and an increase in HR (110 bpm). Exertion was perceived as hard, rated 4-5 on the Borg scale. According to the current indications in patients with HFrEF [28], the therapy with ACE-inhibitors was switched to SAV, 24/26 mg b.i.d.

After 30 days of SAV therapy, the patient referred a dramatic improvement in his symptoms and functional status, with disappearance of dyspnoea for mild effort. The NYHA class changed from III to II. The motor abilities also improved (6MWT up to 315 meters, and SpO2 up to 98%). The exertion was perceived as slight, according to the Borg scale (rate 2). The ProBNP values decreased significantly to 610 pg/ml (Tab. I). The echocardiography showed an improvement in cardiac function: EF increased to 28% with a concomitant increase in stroke volume; GLS confirmed an improvement in left ventricle function showing an Average of -7.5% (Fig. 2). Left ventricle volume and filling pressure were slightly decreased (E/e' 19.8). An improvement in right ventricle systolic function was also recorded (TAPSE 19 mm; RVs'= 11 cm/s) (Tab. I). The drug was well tolerated; none of the common PARADIGM HF side effects was reported. SAV therapy was confirmed and a new evaluation scheduled, at three-month of treatment.

Table I. Clinical and laboratory data at baseline and after 30 days of therapy with sacubitril/valsartan.

	Baseline	30 days
6MWT		
Heart rate (bpm)		
Baseline	80	75
3 minutes	102	90
6 minutes	110	102
SpO2 (%)		
Baseline	98	98
3 minutes	95	98
6 minutes	92	98
Meters		
3 minutes	136	153
6 minutes	270	315
Dyspnoea	Moderate	Mild
Borg scale	4-5	2
Echocardiographic parameters		
EF (%) **Teicholz** **Biplane**	 14 18	 23 38
LVEDd (mm)	78	74
LVESd (mm)	73	66
IVSd (mm)	8	8
LVPWd (mm)	10	10
LVEDv (ml)	291	230
LVESv (ml)	236	166
LAVI (ml/m²)	76	68
E/e'	27.31	19.88
TAPSE (mm)	13	19
S' (cm/sec)	8	11
GLS Avg (%)	-6.4	-7.5
Laboratory data		
Serum creatinine (mg/dl)	0.76	0.75
Potassium (mg/dl)	4.5	4.9
BUN (mg/dl)	50	57
Pro-BNP (pg/ml)	1578	610

LVEDd: left ventricular end-diastolic diameter; LVESd: left ventricular end-systolic diameter; IVSd: interventricular septum diameter; LVPWd: left ventricular posterior wall diameter; LVEDv: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LAVI: left atrial volume index; TAPSE: Tricuspid annular plane systolic excursion; GLS Avg: global longitudinal strain average; BUN: Blood Urea Nitrogen

Discussion

The treatment of HF related to myocardial involvement in muscular dystrophies is still challenging and no guidelines exist about this issue. As reported in several papers [11-15], SAV improves the effort tolerance, by reducing both end-diastolic and systolic left ventricle volumes, induces reverse remodelling of SAV on left ventricle [12], in turn resulting into a better quality of life. Furthermore, in patients with chronic HFrEF not related to muscular dystrophies, SAV has shown to be superior to enalapril in reducing mortality and HF hospitalizations [13].

However, little is still known about the safety and effectiveness of SAV in patients with dystrophinopathic cardiomyopathy, in which the reduced mobility due to muscular impairment can be aggravated by the heart failure, further limiting their daily activities.

In the case here reported, the use of SAV produced an improvement in symptoms, NYHA class and motor function. The effectiveness of SAV was also demonstrated by the reduction in pro-BNP plasma levels, associated to a reduction in haemodynamic stress and cardiovascular events [14]. Furthermore, an improvement in longitudinal contraction of cardiomyocytes, an event that may contrib-

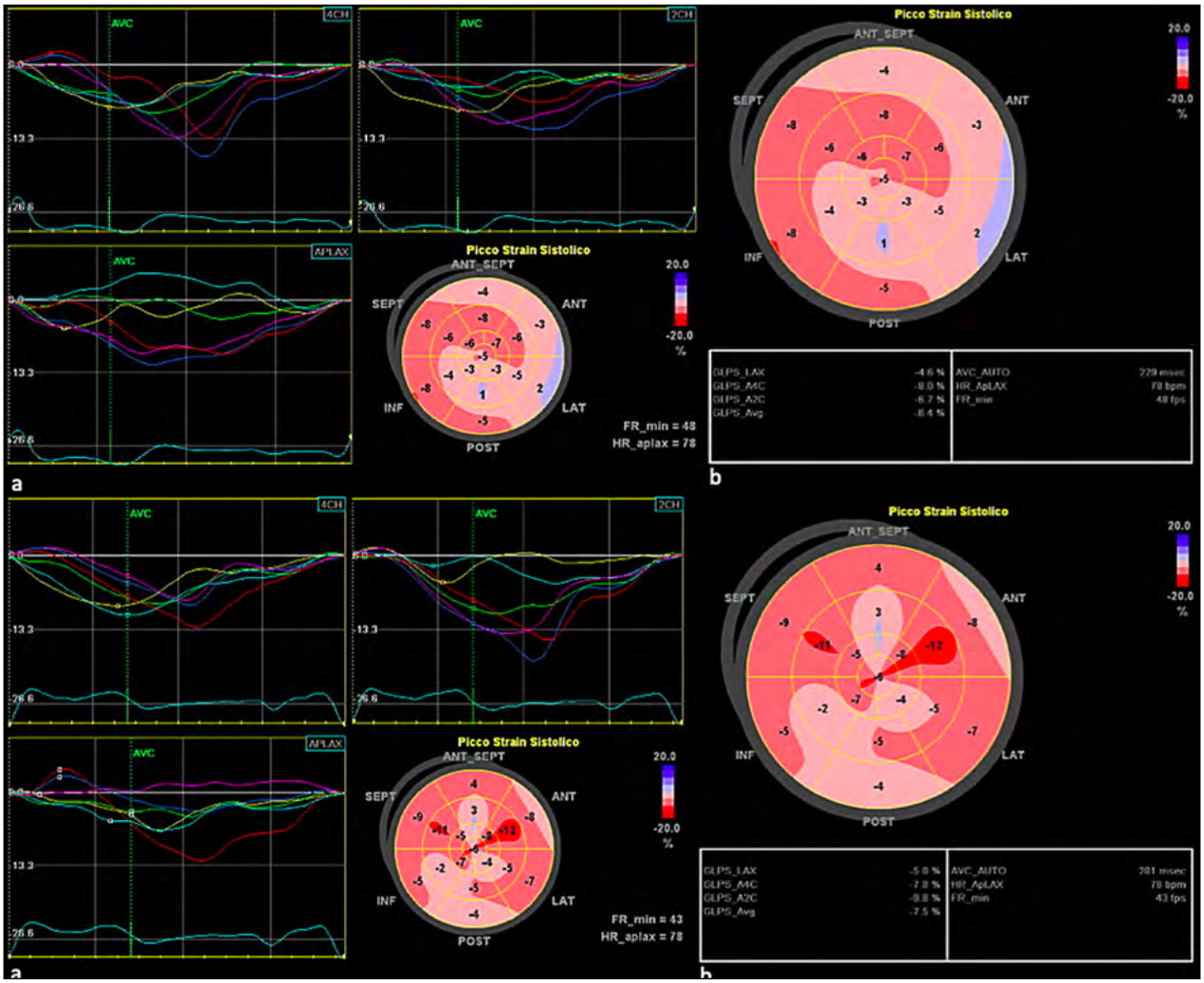

Figure 2. Top. GLS at baseline. Longitudinal strain curves (a) and the 17-segments "Bull's eye" (b). A GLS average of -6.4% with systolic dysfunction involving especially the anterior and lateral walls is shown.; Bottom. GLS after 30 days of SAV. An increase in GLS average (-7.5%) with an improvement of anterior and lateral walls longitudinal strain is shown.

ute to the ejection fraction increasing, was seen by GLS. Interestingly, the improvement was mainly observed in the left ventricle at the antero-lateral wall level, while the earlier and most frequent myocardial involvement is usually observed in the infero-lateral wall in dystrophinopathic patients. This result is not unexpected if we consider that a) the anterolateral wall is later involved in the fibrotic process compared to the inferolateral wall, and so it is still able to better respond to SAV therapy; and b) SAV is able to improve myocardial cell vitality and reduce fibrotic degeneration, as reported in some animal models [15].

To our knowledge, this is the first report on the use of SAV in a patient with dystrophinopathic end stage cardiomyopathy and HFrEF. After only 30 days of therapy, the patient experienced an improvement of clinical symptoms, effort tolerance and cardiac performance, confirmed by a comprehensive echocardiographic assessment that included the strain evaluation. No relevant side effects were reported.

The use of SAV in a larger cohort of patients with dystrophinopathic cardiomyopathy is desirable to confirm its efficacy and safety; moreover, it could be a good pharmacological option for patients with refractory HFrEF not suitable for heart transplantation.

Aknowledgments

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Silent dysphagia in two patients with Steinert disease and recurrent respiratory exacerbations

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We describe two cases of patients with Steinert's dystrophy or myotonic dystrophy type 1 (DM1) who presented with frequent respiratory exacerbations and pneumonia. They did not report any risk factors for asthma, allergy, bronchopathy or dysphagia in their history. The Videofluoroscopic swallow study test allowed to highlight post-swallowing aspiration phenomena responsible for respiratory exacerbations.

Key words: dysphagia, Steinert disease, respiratory exacerbation

Introduction

Myotonic dystrophy type 1 (DM1) is characterized by highly variable clinical manifestations that affect specific tissues, such as distal limbs and facial muscles, smooth muscles, eye (primarily the lens), brain (especially the anterior temporal and frontal lobes), and endocrine function (testosterone deficiency, insulin resistance, thyroid dysfunction). Cardiac involvement is noticed in about 80% of cases [1].

A respiratory dysfunction, predominantly a restrictive ventilatory pattern, is common in myotonic dystrophy and is associated with alveolar hypoventilation, chronic hypercapnia, and sleep disturbance in the form of sleep apnoea and sleep related disordered breathing [2].

Aspiration caused by dysphagia is possible in DM1 [3]. Pulmonary aspiration syndromes refer to a wide spectrum of pulmonary disorders resulting from aspiration of foreign material into the lung. Although aspiration generally triggers coughing, it can be silent, causing difficulties in recognizing aspiration as the cause of undiagnosed respiratory diseases. The severity of aspiration is related to the volume and nature of the aspirate, the chronicity, and the host responses.

Aspiration and its consequences can be divided into 3 forms: a) aspiration pneumonia and diffuse aspiration bronchiolitis; b) aspiration pneumonitis; and c) a foreign body obstruction of a central airway. The first form generally occurs in elderly, debilitated patients with dysphagia, and usually presents as a 'community acquired pneumonia', which tends to be recurrent in patients with diffuse aspiration bronchiolitis. Treatment consists of broad-spectrum antibiotics and management of the underlying dysphagia.

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Conflict of interest
The Authors declare no conflict of interest

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The aspiration pneumonitis is the consequence of the aspiration of regurgitated gastric contents, usually occurring in patients with a marked decreased level of consciousness. Treatment in this form is essentially supportive; however, corticosteroids and other immunomodulating agents may have some effect in these patients [4].

Generally, neuromuscular disorders, esophageal diseases, and the presence of a nasogastric (NG) tube or an endotracheal (ET) tube are factors that may increase the risk of aspiration. Focal or multifocal consolidations in a dependent location is the most common finding on chest X ray [5].

Case report

We describe two patients affected by myotonic dystrophy type 1 (DM1) or Steinert disease, followed at our department for respiratory problems. Both patients - #1 aged 64 and # 2 aged 39 years, were females and on nocturnal mechanical ventilation due to respiratory insufficiency secondary to sleep apnea. The patient #1 had experienced in the previous six months two episodes of pneumonia requiring hospitalization. The patient #2 presented one episode of respiratory exacerbation/month in the past 4 months, the last of which was slowly resolving. When the patients returned to our observation for a clinical-functional re-assessment, both presented a moderate restrictive ventilatory deficit at spirometry, stationary compared to the last checks. The cough peak was 240 L/min in patient # 1, and 220 L/min in patient #2. Both patients did not report dysphagia, difficulty in swallowing, nor did they complain of coughing fits during meals. Allergic tests were negative, as well as the spit test. Both patients were already on home therapy with a cough machine.

Chest CT scan showed in patient #1 the lamellar dysventilation -consolidation of the lower lobe, middle lobe and lingula and incipient tubular ectasias, mainly cleansed, of the air lumen of the segmental bronchi of the middle lobe. In patient # 2 CT scan showed right consolidation of lower lobe and bronchiolitis. Both patients underwent videofluoroscopic swallow study (VFSS). The investigation was performed by digital image acquisition after oral administration of an opaque bolus liquid (gastrografin diluted to 80%), semi-solid (yogurt + gastrografin), and solid (biscuits + gastrografin).

In patient # 1 the VFSS showed stagnation in the pharyngeal valleys and in the piriform sinuses, minimal penetration in the liquid phase of the examination (Fig. 1); in patient # 2, stagnation of the radiological contrast was in the pharyngeal valleys and in the piriform sinuses and determined a sensation of encumbrance, cough and expectoration of the ingested material especially in the solid phase of the examination. The material stagnated after breathing and opening of the epiglottis could be aspirated with post-aspiration swallowing.

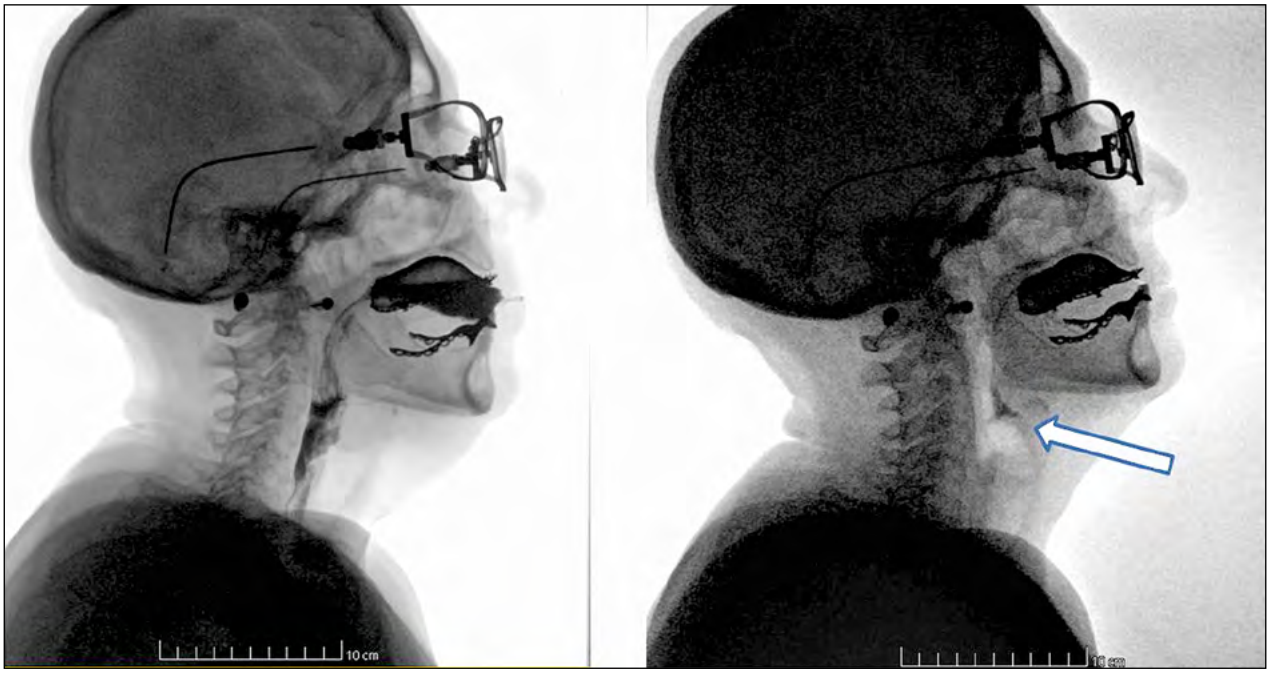

Figure 1. Patient #1. VFSS showing stagnation of the radiological contrast in the pharyngeal valleys and in the piriform sinuses (see arrow).

After the test confirmed the suspicion of dysphagia in both patients, a nutritional counseling was activated to modify the diet, and a course of logotherapy prescribed to re-educate the swallowing muscles. No further episodes of respiratory exacerbation occurred during the following 12 months.

Discussion

Dysphagia is often not recognized in its early stages. It can cause even serious clinical pictures that last in silence for many months [6].

VFSS allows to examine all stages of swallowing, from the preparation stage to the onset of swallowing, the passage of the opaque meal in the oropharynx, and of the bolus in the hypopharynx, so it is considered as the procedure of choice in neuromuscular and NIV-treated patients [2].

The defects mainly detected at VFSS are reduced pharyngeal peristalsis, hypopharyngeal stasis and fragmented swallowing [5]. In recent studies, the aspiration was seen in half of the patients affected by Steinert disease, both adults and infants, and mostly during swallowing [7,8].

In both cases here described, VFSS documented the presence of a swallowing disorder; the correction of the dietary regimen led to no episode of respiratory exacerbation after 12 months.

Data recently appeared in the literature [9] document how the food material stagnated in the pharynx can be aspirated in the post-swallowing phase, even after a few minutes. Aspirated food debris can mimic respiratory exacerbations, and the condition can go silent for many months until it leads to severe respiratory failure.

We agree that a systematic screening of dysphagia should be recommended [10] to achieve an early diagnosis and to set up appropriate dietary modifications and rehabilitation interventions, to avoid aspiration and to prevent severe respiratory complications in these patients.

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NEWS FROM AROUND THE WORLD

AIM

In the period between July and September 2020 the activities of the Italian Association of Myology were limited and reduced due to the pandemic related to SARS-Cov2.

Most of the activities were aimed at the remodeling and organization of the joint congress with the Italian Association for the Study of the Peripheral Nervous System (ASNP), which should have been held in Matera in June, postponed to December 9-12, and which will be carried out in virtual form.

In a joint and commendable effort all the Italian Neuromuscular Centers afferent to the AIM have engaged in the elaboration of a survey estimating the impact of COVID-19 pandemic on services provided by all the Centers. The results of this interesting study have been published in Acta Myologica (2020; XXXIX: p. 57-66 - doi:10.36185-2532-1900-008).

MSM

The 14th Meeting of the Mediterranean Society of Myology (MSM) meeting is moved to spring 2021, Sars-Cov2 permiting. Proposals to organize and host the event are welcome.

WMS

The virtual 25th Congress of the WMS will be held, as announced, from 30th September – 2nd October 2020. The registration is free so that as many of our members who might not have been able to travel to Canada this year as possible can join the WMS spirit of Education, Enjoyment and Excitement!

For more information it is possible to contact Clare Beach, WMS Secretariat and 2020 Congress Manager E: office@worldmusclesociety.org W: www.wms2020.com

The WMS continue to add valuable information about COVID-19 and people with neuromuscular disorders: World Muscle Society position and advice to the website: https://www.worldmusclesociety.org/news/view/150

Once again, we thank all the attendees and our members for the support that has been shown to us and we are here to support others in the field as we all work through these difficult times".

FORTHCOMING MEETINGS

2020

September 25

Stride Registry virtual Investigator Meeting for the Southern European Region. Information: website: *www.ptcbio.com*

September 25-29

Muscle Study Group Annual Scientific Meeting, Washington, US. Information: website: *https://musclestudygroup.org/events/2020-annual-meeting*

September 30 - October 4

25th Congress of World Muscle Society. Vitual Edition. Information: website: *www.wms2020.com*

October 27-31

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

November 2-3

Progeria Research Foundation 10th International Research Congress.Webinar Version. Information: website: *www.progeriaresearch.org/it/2020/07/20/2020-workshop*

December 9-12

20th National Congress of Italian Association of Myology and 10th Annual Congress of the Italian Association for the Study of the Peripheral Nerve. Virtual edition. Information: website: *https://www.miologia.org*

2021

February 20

2nd Annual Conference on Genetics, Paris, France

June 12-15

The European Human Genetics Conference. Glasgow, United Kingdom. Information: website: *https://www.eshg.org*

September 21-25

26th Congress of World Muscle Society. Prague, Czech Republic. Information: website: *www.worldmusclesociety.org*

October 19-23

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

CONGRESSO CONGIUNTO AIM/ASNP
Digital Edition
9-12 Dicembre 2020

PROGRAMME

Mercoledì 9 Dicembre
Streaming on CHANNEL 1

14.00 – 14.20 | Greetings and introduction

14.20 - 15.20 Workshop:
Innovative therapeutic strategies in genetic neuromuscular diseases (Part I)

14.20 – 14.40 An "antisense" approach for neuromuscular diseases | *Toby Ferguson*
14.40 - 15.00 Gene therapy for SMA: from an innovative mechanism of action to clinical data| *M. Pane*
15.00 – 15.20 In vivo gene therapy for Pompe disease | *F. Mingozzi*

15.20 - 16.40 | Workshop:
New tools in the management of patients with neuromuscular disorders

15.20 - 15.40 Genetic modifiers as a tool for personalized treatment of neuromuscular disorders
L. Bello
15.40 – 16.00 Animal models as a tool to design novel therapeutical strategies | *S. Previtali*
16.00 – 16.20 Computation Neurology: devices, data and models for characterization and modelling of neuromuscular diseases | V. *Sanguineti*
16.20 – 16.40 Digital health solutions to increase sensitivity of outcome measures in clinical and trial settings in neuromuscular disorders | *S. Messina*

16.40 - 16.50 | Pausa

16.50 - 18.20 | Oral communications 1: "Updating diagnostic tools in neuromuscular disorders**"**

16.50 – 17.05 Automatic recognition of ragged red fibers in muscle's histological images of patients affected by mithocondrial disorders
J. Baldacci, M. Calderisi, A. Rubegni, C. Fiorillo, F.M. Santorelli (Pisa; Genova)

17.05 – 17.20 Ultra-high frequency ultrasound of median nerve. Comparison of different frequencies and correlation with clinical and neurophysiological findings
D. Coraci, A. De Luna, A. Fusco, S. Giovannini, L. Padua (Roma; Milano)

17.20 – 17.35 Muscle MRI in Myotonic Dystrophy type1 (DM1) *M. Garibaldi, T. Nicoletti, L. Fionda, E. Bucci, T. Tartaglione, G. Tasca, A. Perna, A. Petrucci, G. Silvestri, G. Antonini (Roma)*

17.35 – 17.50 Virtual genetic counselling in Neuromuscular diseases: a pilot telegenetics project
F. Gualandi, M. Neri, M. Farnè, F. Fortunato, G. Vita, M. Pane, G. Rocchi, T. Evangelista, A. Ferlini (Ferrara; Messina; Roma; Pesaro; Paris, France)

17.50 – 18.05 Whole exome and genome sequencing for the genetic diagnosis of dystrophinopathies
R. Selvatici, R. Rossi, F. Mingyan, M.S. Falzarano, P. Rimessi, M. Neri, F. Gualandi, S. Delin, S. Bensemmane, A. Shatillo, L. Bello, E. Pegoraro, A. Ferlini (Ferrara; Shenzhen, China; Zadar, Croatia; Alger; Kharkiv, Ukraine; Padova)

18.05 – 18.20 Skin biopsy may help to distinguish Multiple System Atrophy-parkinsonism type from Parkinson disease with orthostatic hypotension
V. Donadio, A. Incensi, G. Rizzo, R. De Micco, A. Tessitore, G. Devigili, F. Del Sorbo, S. Bonvegna, M. Magnani, C. Zenesini, L. Vignatelli, R. Cilia, R. Eleopra, G. Tedeschi, R. Liguori (Bologna; Napoli; Milano)

18.20 – 18.50 | Lecture:
Neuromuscular disorders prevention: newborn screening, prenatal and pre-implantation diagnosis and counseling | *L. Stuppia*

18.50 – 20.10 | Workshop:
Innovative diagnostic aspects in neuromuscular disorders

18.50 – 19.10 New histopathological markers for the diagnosis of the myopathies: the vintage that is updated | *C. Fiorillo*
19.10 – 19.30 Skin biopsy: beyond the intraepidermal nerve fiber (IENF) density | *M. Nolano*
19.30 – 19.50 Genome analyses in muscular disorders | *V. Nigro*
19.50 – 20.10 NGS in CMT-related disorders | *F. Taroni*

Giovedì 10 Dicembre
Streaming on CHANNEL 1

08.30 – 9.30 | **Breakfast Seminar:**
Transthyretin-related Amyloidosis
Chairmen:

8.30 – 8.50 - Molecular mechanisms | L*. Obici*
8.50 – 9.10 Clinical presentation, diagnosis and treatment of peripheral neuropathy | *G. Vita*
9.10 – 9.30 Clinical and therapeutic aspects of cardiomyopathy | G. *Limongelli*

9.30 - 11.30 | **Oral communications 2: "**Inherited neuromuscular disorders"

9.30 - 9.45 Clinical, morphological and genetic data of patients with distal and myofibrillar myopathies: report from the Italian network.
S. Bortolani, S. Bonanno, G. Vattemi, P. Tonin, M. Monforte, E. Ricci, G. Primiano, S. Servidei, G. Greco, R. Massa, C. Gemelli, M. Grandis, C. Fiorillo, A. Petrucci, M. Filosto, M.L. Valentino, R. Liguori, T. Mongini, M. Garibaldi, G. Antonini, M. Lucchini, M. Mirabella, A. Rubegni, F. M. Santorelli, G. Siciliano, G. Ricci, C. Angelini, A. Ariatti, L. Maggi, G. Tasca (Roma; Verona; Milano; Genova; Brescia; Bologna; Torino; Pisa; Venezia; Modena)

9.45 - 10.00 Phenotypic and genetic characterization of childhood Charcot-Marie-Tooth disease
F.R. Danti, S. Magri, S. Genitrini, E. Pagliano, M. Foscan, A. Ardissone, C. Ciano, P. Saveri, F. Balistreri, D. Di Bella, D. Pareyson, F. Taroni, I. Moroni (Milano)

10.00 - 10.15 Mutations in Supervillin cause myopathy with myofibrillar disorganization and autophagic vacuoles
C. Hedberg-Oldfors, R. Meyer, K. Nolte, Y. Abdul Rahim, C. Lindberg, K. Karason, I. J. Thuestad, K. Visuttijai, M. Geijer, M. Begemann, F. Kraft, E. Lausberg, L. Hitpaß, R. Götzl, E.J. Luna, H. Lochmüller, S. Koschmieder, M. Gramlich, B. Gess, M. Elbracht, J. Weis, I. Kurth, A. Oldfors, C. Knopp (Gothenburg, Sweden; Aachen, Germany; Malmo, Sweden; Worcester, United States; Ottawa, Canada)

10.15 - 10.30 Clinical and biological characterization of a large series of late-onset CMT2I patients carrying the MPZ P70S mutation
P. Saveri, C. Pisciotta, M. Grandis, V. Prada, P. Fossa, R. Mastrangelo, C. Ferri, G. Shackleford, F. Veneri, R. Baldi, G. Lauria, R. Lombardi, C. Ciano, S. Magri, F. Taroni, L. Richard, J.M. Vallat, M. D'Antonio, D. Pareyson (Milano; Genova; Limoges Cedex, France)

10.30 - 10.45 Long-term follow-up and clinical features in an Italian cohort of patients with GNE myopathy.
A. Pugliese, C. Bonanno, G. Nicocia, A. Lupica, S. Messina, GL. Vita, G. Vita, A. Toscano, C. Rodolico (Messina)

10.45 - 11.00 Peripheral nerve involvement in VCP-related multisystem proteinopathy.
S. Testi, M. Filosto, A. Mazzeo, M. Sabatelli, M. Luigetti, E. Pancheri, G. Vattemi, P. Tonin, T. Cavallaro, G.M. Fabrizi (Verona; Brescia; Messina; Roma)

11.00 - 11.15 Congenital Myasthenic Syndromes: a large Italian cohort of patients
A. Gallone, R. Brugnoni, A. Ardissone, E. Terlizzi, R. Masson, G. Ricci, F. Magri, F. Guidolin, M.L. Valentino, D. Frattini, C. Bonanno , M. Catteruccia, A. Malandrini, G. Primiano, C. Antozzi, P. Confalonieri, G. Tasca, M. Monforte, E. Ricci, G. Astrea, C. Ticci, M. Garibaldi, D. Orsucci, F. Ricci, M.T. Ferrò, V.A. Donadio, A. Gentili, E. Bertini, G. Siciliano, D. Piga, G.P. Comi, R. Liguori, I. Moroni, F.M. Santorelli, S. Servidei, A. D'Amico, G. Antonini, A. Evoli, D. Sternberg, D. Beeson, A. Engel, H. Lochmüller, R. Mantegazza, P. Bernasconi, C. Rodolico, L. Maggi (Milano; Piacenza; Pisa; Trieste; Bologna; Reggio Emila; Messina; Roma; Siena; Lucca; Torino; Crema; Paris, France; Oxford, UK; Rochester, MN, USA; Freiburg, Germany; Ottawa, Canada)

11.15 - 11.30 Preliminary results of rank approach for improving quality of life in Charcot-Marie- Tooth type 1A patients
S. Tozza, D. Severi, D. Bruzzese, R. Iodice, L. Ruggiero, R. Dubbioso, E. Spina, A. Iovino, F. Aruta, M. Bellofatto, M. Nolano, L. Santoro, F. Manganelli (Napoli)

11.30 - 12.00 | **Lecture: "High-cost drugs economic sustainability for the National Health Service. How long can we afford them?"** | R. Tarricone

12.00 – 12.15 | **Pausa**

12.15 -13.15 | Workshop:
Imaging techniques in muscle and peripheral nerve diseases

12.15- 12.35 Ultrasound as a multi-tool for Muscle and Nerve | *L. Padua*
12.35 -12.55 MRI in peripheral nerve disorders | *S. Gerevini*
12.55 - 13.15 Imaging vs morphology in the current diagnostic workup of muscle disorders
M. Garibaldi

13.15 – 14.00 – POSTER SESSION (Streaming on Channel 2, 3, 4, 5 ,6 ,7 ,8, 9)

13.15 – 14.00 - CHANNEL 2 – Updating diagnostic tools in neuromuscular disorders

13.15 – 13.20 Muscle MRI pattern recognition: a sample study using a MRI-based tool

M. Maffei, M. Giannotta, G. Scarpini, L. Cirignotta, A. Pini (Bologna)

13.20 – 13.25 Guillain Barrè syndrome chameleon: gadolinium magnetic resonance helps in early diagnosis
Salvalaggio, F. Castellani, M. Anglani, M. Campagnolo, R. Manara, C. Briani (Padova)

13.25 – 13.30 Six muscular MRI patterns in search for an author: clinical, genetic and imaging characterization of six myopathic/dystrophic case reports without a definite diagnosis
M. Rossi, M. Paoletti, V. Vacchini, A. Ferrero, S. Parravicini, A. Gardani, A. Asaro, A. Pichiecchio, A. Berardinelli (Pavia)

13.30 – 13.35 Genilam, an Italian Project to shorten the time of molecular diagnosis for ATTR amyloidosis patients
D. Bonvissuto, E. Rizzo, F. Franchini, A. Nuccitelli, A. Biricik, C. Grillo, L. Barbetta, F. Fiorentino (Roma)

13.35 – 13.40 Unusual findings detected by diagnostic gene panel sequencing applied to heterogenous neuromuscular disorders
F. Magri, G. Manenti, R. Brusa, P. Ciscato, R. Del Bo, F. Fortunato, S. Lucchiari, S. Pagliarani, D. Piga, D. Velardo, V. Sansone, T. Mongini, S. Gandossini, S. Corti, M. Moggio, G.P.Comi, D. Ronchi (Milano; Lecco; Torino; Bosisio Parini)

13.40 – 13.45 NEUROMIO a custom NGS based panel for neuromuscular disorders diagnosis: results of the analysis in a cohort of patients
M. Neri, F. Fortunato, C. Trabanelli, P. Rimessi, R. Selvatici, D. Ognibene, S. Bigoni, S. Fini, E. Terlizzi, D. Giachino, ML Valentino, LM Rocchetti, I. Donati, V. Uliana, E. Pegoraro, A. Pini, M. Pane, F. Gualandi, A. Ferlini (Ferrara; Piacenza; Torino, Orbassano; Bologna; Cesena; Parma; Padova; Roma)

13.45 – 13.50 Whole genome sequencing in a pair of siblings affected with Duchenne muscular dystrophy with discordant cognitive phenotype
D. Sabbatini, M. Alexander, S. Vianello, A. Fusto, B. Merlo, M. Villa, V. Zangaro, F. De Pascale, G. Sorarù, E. Pegoraro, L. Bello (Padova; Birmingham AL, U.S.A.; Padova)

13.50 – 13.55 Promoting Early DIagnoses in Neuromuscolar disease (PEDINE). A pilot study
M. Vacchetti, C. Brusa, R. D'Alessandro, M. Bobbio, M. Spada, R. Turra, F. Ricci, T. Mongini, PEDINE working group (Torino)

13.55 – 14.00 Abnormal α-synuclein deposits in skin nerves: inter and intra-laboratory reproducibility
V. Donadio, K. Doppler, A. Incensi, A. Kuzkina, A. Janzen, J. Volkmann, G. Rizzo, E. Antelmi, G. Plazzi, C. Sommer, WH Oertel, R. Liguori (Bologna; Marburg, Germany)

13.15 – 14.00 CHANNEL 3 - Inherited neuromuscular disorders

13.15 – 13.20 A genotyping and clinical neurophysiological study of early-onset Charcot-Marie-Tooth disease
C. Croci, P. Mandich, I. Meola, A. Geroldi, E. Bellone, A. Accogli, C. Bruno, M. Pedemonte, C. Minetti, C. Fiorillo, P. Lanteri (Genova; Alessandria; Milano)

13.20 – 13.25 Pilot study in phenotypic variability of cardiac involvement in a cohort of patients with Becker muscular dystrophy
V. Castiglione, G. Ricci, A. Govoni, G. Astrea, A. Rocchi, F. Baldinotti, A. Giannoni, C. Passino, M. Emdin, G. Siciliano (Pisa)

13.25 – 13.30 Clinical and genetic characteristics of NEFL-related Charcot – Marie Tooth disease due to P440L mutation in a large Italian family
A. Petrucci, L. Lispi, M. Garibaldi, E. Frezza, R. Massa, F. Moro, F.M. Santorelli (Roma; Pisa)

13.30 – 13.35 Expanding the phenotype of p.R1460W mutation in SCN4A gene: a family report
S. Cotti Piccinelli, B. Risi, E. Baldelli, N. Necchini, A. Galvagni, A. Padovani, R. Brugnoni, L. Maggi, M. Filosto (Brescia; Milano)

13.35 – 13.40 Charcot – Marie – Tooths disease and pregnancy: data from the Italian CMT national registry *C. Pisciotta, D. Calabrese, L. Santoro, I. Tramacere, F. Manganelli, G.M. Fabrizi, A. Schenone, T. Cavallaro, M. Grandis, S. Previtali, I. Allegri, L. Padua, C. Pazzaglia, A. Quattrone, P. Valentino, S. Tozza, A. Mazzeo, M.C. Trapasso, F. Parazzini, G. Vita, D. Pareyson; for the Italian CMT Network (Milano; Napoli; Verona; Genova; Parma; Catanzaro; Messina)*

13.40 – 13.45 Alpha-sarcoglycanopathy presenting as myalgia and hyperckemia in two adults with a long-term follow-up
C. Dosi, A. Rubegni, D. Cassandrini, A. Malandrini, L. Maggi, F.M. Santorelli (Pisa; Siena; Milano)

13.45 – 13.50 A new Italian family with PMP2-related Charcot-Marie-Tooth Disease type 1G
S. Spolverato, F. Taioli, G. Zanette, S. Romito, M. Ferrarini, L. Roncari, G. Cantalupo, G.M. Fabrizi (Verona; Pescheria del Garda)

13.50 – 13.55 Exon 1 nonsense mutation of dystrophin gene and exception to the reading-frame rule
A. Govoni, G. Ricci, A. Lo Gerfo, V. Castiglione, L. Calì, F. Baldinotti, A. Rocchi, M. Emdin, G. Siciliano (Pisa)

13.55 – 14.00 Severe Charcot-Marie-Tooth disease type 1A in a patient with PMP22 tetrasomy
F. Taioli, G.P. Zanette, M. Ferrarini, S. Testi, T. Cavallaro, G.M. Fabrizi (Verona; Peschiera del Garda)

13.15 – 14.00 - CHANNEL 4 - Inherited neuromuscular disorders

13.15 – 13.20 Clinical presentations of two rare mutations of TTR

D. Cardellini, F. Taioli, M. Cappellari, M. Milan, L. Bertolasi, G.M. Fabrizi, T. Cavallaro (Verona; Venezia)

13.20 – 13.25 Mutations in ASCC3 are associated with severe congenital myopathy, arthrogryposis and bone fractures *M. Catteruccia, D. Diodato, F. Fattori, G. Colia, F. De Mitri, A. D'Amico, E. Bertini (Roma)*

13.25 – 13.30 Sensorimotor axonal polyneuropathy and a VUS mutation in Transthyretin gene
F. Gragnani, F. Gilio, R. Iulianella, I.F. Pestalozza, F. Cortese, A.M. Cipriani, E.M. Pennisi (Roma)

13.30 – 13.35 A de novo in-frame deletion in MYOT causes an early adult onset severe distal myopathy
E. Pancheri, V. Guglielmi, V. Nigro, S. Aurino, A. Torella, M. Malatesta, A. Vettore, A. Giorgetti, G. Tomelleri, P. Tonin, G. Vattemi (Verona; Napoli)

13.35 – 13.40 Description of the first cohort of V122I ATTRv amyloidosis patients from non-endemic areas *M. Russo, L. Gentile, G. Di Bella, F. Minutoli, F. Cucinotta, L. Obici, R. Mussinelli, A. Toscano, G. Vita, A. Mazzeo (Messina; Pavia)*

13.40 – 13.45 Whole Exome Sequencing identifies two novel candidate genes and extends the diagnostic spectrum of patients with neuromuscular diseases
R.Rossi, M.S. Falzarano, M Pinotti, D Balestra, M. Neri, F. Fortunato, E. Mercuri, M. Pane, F. Gualandi, R. Selvatici, A. Ferlini (Ferrara; Roma)

13.45 – 13.50 Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: experience from a single center
D. Severi, S. Tozza, E. Spina, M. Bellofatto, M. Nolano, L. Santoro, F. Manganelli (Napoli)

13.50 – 13.55 Tubular aggregate myopathy: clinical and molecular characterization in STIM1 and ORAI1 mutated patients
S. Tripodi, L. Bello, G. Minervini, C. Reggiani, S. Vianello, V. Bozzoni, L. Caumo, P. Riguzzi, A. Lupi, C. Bertolin, G. Sorarù, E. Pegoraro (Padova)

13.55 – 14.00 Clinical features in ATTRv patients
S.Tozza, D. Severi, P. Origone, A. Geroldi, E. Bellone, P. Mandich, M. Nolano, L. Santoro, F. Manganelli (Napoli; Genova)

13.15 – 14.00 CHANNEL 5 - Inherited neuromuscular disorders

13.15 – 13.20 Recommendations for presymptomatic genetic testing for ATTRv in the era of effective therapy: a multicenter Italian study
M. Grandis, L. Obici, G. Ferrandes, D. Pareyson, C. Briani, C. Danesino, M. Canepa, A. Mazzeo, L. Trevisan, S. Fenu, F. Cappelli, F. Perfetto, L. G. Pradotto, F. Benedicenti, G.M. Fabrizi, G. Bisogni, M. Luigetti, P. Rimessi, L. Melchiorri, G. Tini, C. Gemelli, S. Tozza, D. Severi, P. Mandich (Genova; Pavia; Milano; Padova; Messina; Firenze; Oggebbio (Verbania); Bolzano; Verona; Roma; Ferrara; Napoli)

13.20 – 13.25 Molecular and clinical characterization in asymptomatic and symptomatic DMD carriers
V. Zangaro, P. Riguzzi, B. Merlo, S. Vianello, R. Bariani, L. Lamagna, B. Bauce, G. Sorarù, L. Bello, E. Pegoraro (Padova)

13.25 – 13.30 Hereditary neuropathy with liability to pressure palsy: two pediatric symptomatic cases with acute monoliteral foot drop
G. Scarpini, M. Giannotta, F. Pastorelli, A. Pini (Bologna)

13.30 – 13.35 UNC-45B mutations in congenital axial myopathy with cores and multiple internalised nuclei *C. Fiorillo, C. Panicucci, S. Donkervoort, M. Traverso, P. Broda, R. Falsaperla, V. Salpietro, C. Minetti (Genova*

13.35 – 13.40 A case of a Heterozygous Kv1.1 N255D Mutation with Normal Serum Magnesium Levels *F. Bianchi, C. Simoncini, G. Ricci, P. Bernasconi, G. Siciliano (Pisa; Milano)*

13.40 – 13.45 Clinical and electrophysiological features of seipinopathy in an Italian family: an example of spontaneous regressive course of the disease - a case report
S. Parravicini, A. Asaro, C. Cereda, A. Lozza, A. Berardinelli (Pavia)

13.45 – 13.50 Familial Progressive Cardiac Conduction Disease caused by a TRPM4 gene mutation
A. Palladino, Torella, R. Petillo, A. M. Scutifero, S. Morra, P. D'Ambrosio, L. Passamano, V. Nigro, L. Politano (Napoli)

13.50 – 13.55 Combined genetic causes of rhabdomyolysis in a family: can it be a double trouble?
F. Torri, G. Ricci, C. Simoncini, P. Annoscia, G. Alì, L. Chico, D. Cassandrini, Di Muzio, G. Siciliano (Pisa; Chieti)

13.55 – 14.00 Myotonic dystrophy type 1: daytime pulmonary function and sleep related breathing disorders *S. De Pasqua, F. Pizza, P. Avoni C. Quarta, G. Plazzi, R. Liguori (Bologna)*

13.15 – 13.50 - CHANNEL 6 - Biomarkers and outcome measures in neuromuscular disorders

13.15 – 13.20 Fatigue and sleepiness in myotonic dystrophy type 1: motor, neuropsychological and sleep correlates
E. Frezza, C. Galluzzi, G. Greco, P. Proserpio, L. Mauro, G. Sannicolò, A. Pirola, E. Falcier, E. Roma, A. Zanolini, A. Lizio C. Liguori, F. Placidi, V.A. Sansone, R. Massa (Roma; Milano)

13.20 – 13.25 A possible biomarker for paclitaxel-induced peripheral neurotoxicity: Neurofilament light chain serum levels monitoring
P. Alberti, F. Cicchiello, F. Riva, G. Cavaletti, M.E. Cazzaniga (Monza)

13.25 – 13.30 Gender effect on cardiac involvement in Myotonic Dystrophy type 1 (DM1)
M. Garibaldi, L. Fionda, E. Bucci, F. Vanoli, L. Leonardi, A. Lauletta, G. Alfieri, G. Merlonghi, S. Morino, M. Testa, G. Antonini (Roma)

13.30 – 13.35 Serum neurofilament light chain (sNfL) correlate with sural nerve pathological findings
F. Castellani, S. Mariotto, M. Campagnolo, S. Ferrari, C. Briani (Padova; Verona)

13.35 – 13.40 Cognitive and personality involvement in DM1 patients: is there an age at onset related effect?
E. Lai, G. Spadoni, C. Simoncini, G. Ricci, G. Siciliano (Pisa)

13.40 – 13.45 Definition of a new ICF core-set for the upper limbs of hereditary neuropathies
V. Prada, B. Mazzarino, A. Mazzeo, D. Pareyson, L. Santoro, L. Padua, G. Fabrizi, A. Schenone and ULNA group (I. Poggi, L. Mori, M. Grandis, C. Gemelli, L. Gentile, A. Tisano, F. Cavallaro, C. Pisciotta, M. Montesano, F. Manganelli, S. Tozza, G. Aceto, D. Dellaventura, C. Pazzaglia, C. Erra, D. Coraci, T. Cavallaro, A. Peretti, L. Roncari) (Genova; Messina; Milano; Napoli; Roma; Verona)

13.45 – 13.50 Myotonic Dystrophy type 2 unmasked by physical exercise following COVID-19 lockdown
S. Lucchiari, F. Magri, G.P. Comi, M. Sciacco (Milano)

13.15 – 13.50 CHANNEL 7 - Biomarkers and outcome measures in neuromuscular disorders

13.15 – 13.20 Gait and balance evaluation in patients with different myopathies: correlation between imaging data and functional aspects
A. Modenese, A. Picelli, N. Mattiuz, E. Pancheri, N. Smania, G. Vattemi, P. Tonin (Verona)

13.20 – 13.25 Issues in the management of hereditary transthyretin-mediated amyloidosis (hATTR)
A. Parachini, B. Valzasina, M. Grandis, M. Oliverio, A. Schenone, L. Obici (Pavia)

13.25 – 13. 30 Capturing the patient-reported impact of myasthenia gravis in the real-world setting using a smartphone application
F. Saccà, S. Berrih-Aknin, K.G. Claeys, R. Mantegazza, H. Murai, E. Bagshaw, H. Kousoulakou, M. Larkin, T. Leighton, S. Paci (Napoli; Paris, France; Leuven, Belgium; Milano; Narita, Japan; Oxford, United Kingdom; Ghent, Belgium)

13.30 – 13.35 Spinal cord volumetry as a biomarker for monitoring drug treatment in spinal muscular atrophy patients: a pilot MRI study
G. Savini, C. Asteggiano, L.M. Farina, C.A.M. Gandini Wheeler-Kingshott, S. Bastianello, A. Berardinelli, A. Pichiecchio (Pavia; London, UK)

13.35 – 13.40 Muscle MRI of upper girdle in GNE myopathy
E. Torchia, M. Lucchini, S. Bortolani, M. Monforte, M. Mirabella, E. Ricci, G. Tasca (Roma)

13.40 – 13.45 Real-World Treatment Patterns and Outcomes in Patients With Spinal Muscular Atrophy Collected From the RESTORE Registry
L. Servais, J.W. Day, D.C. De Vivo, J. Kirschner, E. Mercuri, F. Muntoni, P.B. Shieh, E. Tizzano, I. Desguerre, S. Quijano-Roy, K. Saito, M. Droege, O. Dabbous, R. Cerbini, F. Baldinetti, A. Shah, F. Khan, F.A. Anderson, R.S. Finkel (Oxford, United Kingdom; Stanford, CA, United States; New York,

NY, United States; Freiburg, Germany; Roma; London, United Kingdom; Los Angeles, CA, United States; Barcelona, Spain; Paris, France; Garches, France; Tokyo, Japan; Bannockburn, IL, United States; Worcester, MA, United States; Orlando, FL, United States)

13.45 – 13.50 Hind limb unloading as a model of skeletal muscle atrophy: validation of in vivo and ex vivo readouts for preclinical translational research
P. Mantuano, F. Sanarica, O. Cappellari, B. Boccanegra, N. Tarantino, E. Conte, M. De Bellis, G. M. Camerino, S. Pierno, A. De Luca (Bari)

13.15 – 13.50 CHANNEL 8 - Biomarkers and outcome measures in neuromuscular disorders

13.15 – 13.20 HyperCKemia and viral infections: a lesson from COVID-19
C. Terracciano, D. Zaino, P. Immovilli, E. Terlizzi, D. Guidetti (Piacenza)

13.20 – 13.25 Creatine kinase and progression rate in amyotrophic lateral sclerosis
M. Ceccanti, C. Cambieri, L. Libonati, E. Onesti, M. Inghilleri (Roma)

13.25 – 13.30 Light-Chain Neurofilaments (Nf-L) assessment in type 3 Spinal Muscular Atrophy patients treated with nusinersen
V. Bozzoni, G. Musso, L. Caumo, L. Bello, S. Tripodi, P. Riguzzi, F. Causin, J. Gabrieli, G. Cester, G. Sorarù, M. Plebani, E. Pegoraro (Padova)

13.30 – 13.35 Improvement of skin biopsy findings after treatment with azatioprina in a case of small fiber neuropathy
R. Milani, ID. Lopez, A. Quattrini, R. Fazio (Milano)

13.35 – 13.40 Discordant clinical outcome in two cousins with X-linked myotubular myopathy
P. D'Ambrosio, M.G. Esposito, S. Morra, A. Palladino, L. Passamano, R. Petillo, E. Picillo, V. Torre, L. Politano (Napoli)

13.40 – 13.45 Validation of the Italian version of the Charcot-Marie-Tooth Health Index (CMT-HI)
C. Pisciotta, E. Ciafaloni , R. Zuccarino, D. Calabrese, P. Saveri, S. Fenu, I. Tramacere, F. Genovese, N. Dilek, N.E. Johnson, C. Heatwole, D.N. Herrmann, D. Pareyson, on behalf of the ACT-CMT study (Milano; Rochester, NY, USA; Iowa City, IA, USA; Arenzano (GE); Bologna; Richmond, VA, USA; Rochester, NY, USA)

13.45 – 13.50 Neuropsychological profile of Becker Muscular Dystrophy
R. Brusa, F. Magri, T. Difonzo, D. Velardo, S. Corti, M. Moggio, M.C. Saetti, G.P. Comi (Milano)

13.50 – 13.55 Long-term respiratory function in SMA type 2 and non-ambulant SMA type 3, longitudinal data from the international SMA consortium (iSMAc)
F. Trucco, M. Scoto, D. Ridout, D. C. De Vivo, B. Darras, E. Bertini, G. Coratti, M. Main, A. Mayhew, J. Montes, R. S. Finkel, E. Mercuri, F. Muntoni on behalf of the international SMA consortium (iSMAc) (Genova; London, UK; New York, USA; Boston,MA, USA; Roma; Newcastle, UK; Orlando, Florida, USA)

13.15 – 13.50 CHANNEL 9 - Emerging neuromuscular entities

13.15 – 13.20 Epidemiological study of HEV prevalence in patients with CIDP and ALS
C. Cambieri, M. Ceccanti, L. Libonati, I. Fiorini, V. Frasca, E. Onesti, G. Taliani, M. Inghilleri (Roma)

13.20 – 13.25 Benign monomelic amyotrophy of upper limb (Hirayama disease): a single center analysis *M.G. Rispoli, L. Ferri, M. Di Pietro, V. Di Stefano, A. Di Muzio (Chieti; Palermo)*

13.25 – 13.30 Neurolymphomatosis as the main presentation of relapse of extranodal diffuse large B-cell lymphoma (DLBCL)
M. Campagnolo, M. Cacciavillani, T. Cavallaro, S. Ferrari, L. Pavan, G. Barilà, A. Salvalaggio, F. Castellani, R. Zambello, C. Briani (Padova; Verona)

13.30 – 13.35 An overlapping case of myasthenia gravis, Guillan- Barré syndrome and autoimmune polyglandular syndrome type III
L. Ferri, M.G. Rispoli, V. Falzano, P. Ajdinaj, V. Di Stefano, A. Di Muzio (Chieti; Palermo)

14.00 – 14.15 | Pausa

14.15 - 15.15 | **New treatment horizons in the management of SMA**
Moderatore – G. Vita
- Recent scientific evidences in the context of early onset SMA | *R. Masson*
- What's new in the landscape of later onset SMA? | *M.C. Pera*

15.15 – 17.15 - Oral communications 3: Biomarkers and outcome measures in neuromuscular disorders

15.15 – 15.30 Long-term functional changes in Becker muscular dystrophy
L. Bello, S. Mastellaro, L. Caumo, P. Riguzzi, V. Zangaro, M. Villa, D. Sabbatini, A. Fusto, B. Merlo, S. Vianello, E. Pegoraro (Padova)

15.30 – 15.45 Sphingomyelin: a novel diagnostic and disease activity biomarker for the management of acquired demyelinating neuropathies
G. Capodivento, C. De Michelis, M. Carpo, R. Fancellu, E. Schirinzi, D. Severi, D. Visigalli, D. Franciotta, G. Siciliano, F. Manganelli, A. Beronio, E. Capello, P. Lanteri, E. Nobile-Orazio, A. Schenone, L. Benedetti, L. Nobbio (Genova; Bergamo; Pisa; Napoli; Pavia; La Spezia; Milano; Rozzano (MI))

15.45 – 16.00 Morphological analysis of TNPO3 and SRSF1 interaction during myogenesis: a super resolution study
R. Costa, M.T. Rodia, N. Zini, V. Pegoraro, R. Marozzo, C. Capanni, C. Angelini, G. Lattanzi, S. Santi, G. Cenacchi (Bologna; Venezia)

16.00 – 16.15 Intraepidermal nerve fiber density as a biomarker of disease severity in hereditary transthyretin amyloidosis with polyneuropathy: data from an Italian cohort

L. Leonardi, A. Truini, A. Fasolino, E. Galosi, M. Luigetti, L. Fionda, F. Vanoli, S. Morino, M. Garibaldi, G. Antonini (Roma)

16.15 – 16.30 Proposal of new functional motor scales to evaluate muscle fatigue in adult SMA patients
G. Ricci, A. Govoni, I. Bortone, L. Billeci, A. Borelli, L. Manca, R. Liguori, M. Coccia, G. Comi, G. Siciliano (Pisa; Milano; Bari; Bologna; Ancona)

16.30 – 16.45 Validation of a new Hand Function Outcome Measure in individuals with Charcot-Marie-Tooth
V. Prada, M. Hamedani, G. Robbiano, G. Mennella, A. Geroldi, A. Zuppa, S. Massucco, R. Zuccarino, L. Mori, E. Bellone, P. Mandich, M. Grandis, A. Schenone (Genova; Coralville, IA, USA)

16.45 – 17.00 Proteomic profiling of cerebrospinal fluid of nusinersen-treated SMA1 patients
M. Sframeli, L. Bianchi, G.L. Vita, R. Oteri, F. Polito, L. Vantaggiato, C. Landi, E. Gitto, S. Messina, L. Bini, M. Aguennouz, G. Vita (Messina; Siena)

17.00 – 17.15 Muscle MRI as a novel outcome measure of hereditary transthyretin amyloidosis: a cross-sectional cohort study
E. Vegezzi, A. Cortese, N. Bergsland, R. Mussinelli, M. Paoletti, F. Solazzo, R. Currò, A. Lozza, X. Deligianni, F. Santini, S. Bastianello, G. Merlini, G. Palladini, L. Obici, A. Pichiecchio (Pavia; London, UK; New York, USA; Pavia; Basel, Switzerland)

17.15 – 18.00 - Oral communications 4: "Innovative therapeutic approaches"

17.15 – 17.30 RNAi therapeutic Patisiran in hATTR amyloidosis: tolerability and management from two centre experience
L. Gentile, M. Russo, M. Luigetti, G. Bisogni, A. Di Paolantonio, A. Romano, V. Guglielmino, M. Sabatelli, A. Toscano, G. Vita, A. Mazzeo (Messina; Roma)

17.30 – 17.45 Pharmacological chaperone to treat myotonia congenita caused by trafficking-defective ClC-1 chloride channel mutants: proof-of-concept with niflumic acid
C. Altamura, E. Conte, D. Sahbani, G.M. Camerino, F. Girolamo, MR. Carratù, P. Imbrici, JF. Desaphy (Bari)

17.45 – 18.00 Inotersen to treat hATTR polyneuropathy: tolerability and management from two centre experience.
M. Luigetti, A. Romano, A. Mazzeo, A. Di Paolantonio, G. Bisogni, V. Guglielmino, M. Russo, L. Gentile, A. Toscano, G. Vita, M. Sabatelli (Roma; Messina)

18.00 - 19.20 | **Workshop: Autophagy and other pathogenic mechanisms in NMDs**

18.00 - 18.20 IGF-1 mediated signalling to counteract muscle atrophy | *A. Musarò*
18.20 – 18.40 New insights of autophagy regulation and involvement in muscle to neurons communication | *M. Sandri*
18.40 – 19.00 Autophagy in peripheral neuropathies: mechanisms and treatment options *V. Timmerman*
19.00 – 19.20 When glycogen becomes insoluble: clinical features and pathobiology of polyglucosan storage disorders | *A. Oldfors*

19.20 - 20.20 | Assemblee AIM e ASNP

Venerdì 11 Dicembre
Streaming on CHANNEL 1

8.30 – 10.00 | **Neuromuscular club**

8.30 – 8.45 Myoglobinuria as unexpected onset of disease in an asymptomatic 75-years-old man
C. Bonanno, A. Pugliese, G. Nicocia, C. Rodolico, A. Toscano (Messina)

8.45 – 9.00 Brown-Vialetto-Van Laere Syndrome: a clinical report
S. Cotti Piccinelli, F. Novara, B. Risi, E. Baldelli , N. Necchini, A. Galvagni, R. Ciccone, A. Padovani, M. Filosto (Brescia; Pavia)

9.00 – 9.15 Pure neuritic leprosy: a clinical and neuropathological report
N. Necchini, S. Cotti Piccinelli, T. Cavallaro, S. Ferrari, B. Risi, E. Baldelli, A. Padovani, M. Filosto (Brescia; Verona)

9.15 – 9.30 Neuromuscular features in Chorea-Acanthocytosis: a clinical and histopathological report
B. Risi, S. Cotti Piccinelli, F. Novara, E. Baldelli, N. Necchini, A. Galvagni, R. Ciccone, A. Padovani, M. Filosto (Brescia; Pavia)

9.30 – 9.45 A case of intraneurial perineurioma. Limits and advantages of imaging techniques.
M. Romano, D. Coraci, S. Cottone, R. Gasparotti, S. Ferraresi, S. Realmuto, E. Cammarata, L. Padua (Palermo; Roma; Brescia; Rovigo, Milano)

9.45 – 10.00 Adult-onset Krabbe's disease: clinical presentation and characterization of peripheral nerve involvement
M. Tagliapietra, F. Crescenzo, D. Polo, S. Ferrari, T. Cavallaro, G. Zanette, G.M. Fabrizi (Verona; Pescheria del Garda)

10.00 - 11.40 | Workshop:
Innovative therapeutic strategies in genetic neuromuscular diseases (Part II)

10.00 – 10.20 Innovative strategies therapeutic in Muscle dystrophies | *G. P. Comi*
10.20 – 10.40 Advances in the treatment of hereditary ATTR amyloidosis | *A. Mazzeo*
10.40 – 11.00 Challenges in treating CMT: do we see daylight? | *D. Pareyson*
11.00 – 11.20 New Therapeutic approaches in SMA | *E. Mercuri*
11.20 - 11.40 New therapeutic strategies in metabolic myopathies | *O. Musumeci*

11.40 - 12.00 | **Pausa**

12.00 – 12.45 – POSTER SESSION (Streaming on Channel 2, 3, 4, 5 ,6 ,7 ,8, 9)

12.00 – 12.45 CHANNEL 2 - Innovative therapeutic approaches

12.00 – 12.05 Long-Term Safety and Efficacy of Patisiran: Global Open-label Extension 24-month Data in Patients with Hereditary Transthyretin-mediated Amyloidosis
D. Adams, A. González-Duarte, E. Mauricio, T. Brannagan, T. Coelho, J. Wixner, H. Schmidt, A. Mazzeo, E. Berber, M.T. Sweetser, M.T. White, J.J. Wang, M. Polydefkis (Le Kremlin-Bicêtre, France; Mexico City, Mexico; Jacksonville, FL, USA; New York City, NY, USA; Porto, Portugal; Umeå, Sweden; Muenster, Germany; Messina; Cambridge, USA; Baltimore, USA)

12.05 – 12.10 FIREFISH Part 2: Efficacy and safety of risdiplam (RG7916) in infants with Type 1 spinal muscular atrophy (SMA)
G. Baranello, L. Servais, R. Masson, M. Mazurkiewicz-Bełdzińska, K. Rose, D. Vlodavets, H. Xiong, E. Zanoteli, M. El-Khairi, S. Fuerst-Recktenwald, M. Gerber, K. Gorni, H. Kletzl, R. Scalco, B. T. Darras on behalf of the FIREFISH Working Group (Milano; London, UK; Liège, Belgium; Oxford, UK; Gdańsk, Poland; Sydney, Australia; Moscow, Russia; Beijing, China; São Paulo, Brazil; Welwyn Garden City, UK; Basel, Switzerland; Boston, MA, USA)

12.10 – 12.15 Systemic Gene Transfer With rAAVrh74.MHCK7.SGCB Increased β-Sarcoglycan Expression in Patients With Limb Girdle Muscular Dystrophy Type 2E
L.R. Rodino-Klapac, E.R. Pozsgai, S. Lewis, D.A. Griffin, A.S. Meadows, P. Roncon, K.J. Lehman, K. Church, N.F. Miller, M.A. Iammarino, L.P. Lowes, J.R. Mendell (Columbus, Ohio, USA; Cambridge, MA, USA)

12.15 – 12.20 Intravenous Onasemnogene Abeparvovec Clinical Development Programs in Spinal Muscular Atrophy (SMA): Integrated Safety Report
D. Chand, R.S. Finkel, E. Mercuri, R. Masson, J. Parsons, R. Cerbini, F. Baldinetti, A. Kleyn, M. Menier, K. Montgomery, D.M. Sproule, S.P. Reyna, D.E. Feltner, S. Tauscher-Wisniewski, J.R. Mendell (Bannockburn, IL, United States; Orlando, FL, United States; Roma; Milano; Aurora, CO, United States; Columbus, OH, United States)

12.20 – 12.25 Unravelling combined RNA interference and gene therapy in vitro and in vivo disease models as a potential therapeutic strategy for CMT2A
R. De Gioia, M. Nizzardo, S. Bono, S. Salani, V. Melzi, S. Pagliarani, E. Abati, N. Bresolin, G. Comi, S. Corti, F. Rizzo (Milano)

12.25 – 12.30 Testing a novel dasatinib formulation in mdx mouse model: towards the repurposing of Src tyrosine kinase inhibitors in Duchenne muscular dystrophy
F. Sanarica, P. Mantuano, B. Boccanegra, O. Cappellari, E. Conte, G.M. Camerino, A. Cutrignelli, N. Denora, A. Mele, M. De Bellis, A. De Luca (Bari)

12.30 – 12.35 Long-Term Follow-Up (LTFU) of Onasemnogene Abeparvovec Gene Therapy in Spinal Muscular Atrophy Type 1 (SMA1) From Phase 1 START Trial
J.R. Mendell, R. Shell, K.J. Lehman, M. McColly, L.P. Lowes, L.N. Alfano, N.F. Miller, M.A. Iammarino, K. Church, R. Cerbini, S.P. Reyna, F.G. Ogrinc, H. Ouyang, D.M. Sproule, M. Meriggioli, D.E. Feltner, S. Al-Zaidy (Columbus, OH, United States; Bannockburn, IL, United States)

12.35– 12.40 Histopathological features in ambulant patients with Becker Muscular Dystrophy: preliminary data from the Givinostat trial cohort
D. Velardo, M. Ripolone, F. Magri, R. Brusa, A. Govoni, S. Cazzaniga, L. Peverelli, P. Ciscato, S. Zanotti, M. Sciacco, M. Moggio, P. Bettica, G.P. Comi (Milano; Pisa; Lodi)

12.40 – 12.40 SUNFISH Part 2: Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA)
E. Mercuri, N. Barisic, O. Boespflug-Tanguy, N. Deconinck, A. Kostera-Pruszczyk, R. Masson, E. Mazzone, A. Nascimento, K. Saito, D. Vlodavets, C. Vuillerot, S. Fuerst-Recktenwald, S. Fuhrer, M. Gerber, K. Gorni, H. Kletzl, C. Martin, W.Y. Yeung, J.W. Day on behalf of the SUNFISH Working Group (Roma; Zagreb, Croatia; Paris, France; Gent, Ghent; Brussels, Belgium; Warsaw, Poland; Milano; Barcelona , Spain; Tokyo, Japan; Moscow, Russia; Lyon, France; Basel, Switzerland; Basel, Switzerland; Welwyn Garden City, UK; Palo Alto, CA, USA)

12.00 – 12.40 CHANNEL 3 - Innovative therapeutic approaches

12.00 – 12.05 Ocrelizumab in a case of refractory Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) with antibodies anti Rituximab
S. Casertano, E. Signoriello, F. Rossi, A. Di Pietro, F Tuccillo, S. Bonavita, G. Lus (Napoli)

12.05 – 12.10 Identification and characterization of urine-derived stem cells (USCs) by the novel technology Celector®
M.S. Falzarano, N. Spedicato, A. Margutti, R. El Dani, R. Rossi, S. Zia, P. Reschiglian, B. Roda, A. Grilli, S. Bicciato, A. Ferlini (Ferrara; Bologna; Modena)

12.10 – 12.15 Mutational profile in patients with anti-myelin-associated glycoprotein (MAG) antibody neuropathy identifies new therapeutic target
F. Castellani, A. Visentin, M. Campagnolo, A. Salvalaggio, C. Candiotto, R. Zambello, F. Piazza, L. Trentin, R. Bertorelle, C. Briani (Padova)

12.15 – 12.20 Efgartigimod in Autoimmune Neuromuscular Diseases
A. Guglietta, P. Ulrichts, S. Schmidt, J. Beauchamp, H. de Haard, W. Parys (Zwinjaarde, Belgium)

12.20 – 12.25 CPPs-conjugated antisense nucleotides: a new therapeutic strategy for Spinal Muscular Atrophy symptomatic patients
E. Pagliari, M. Bersani, M. Rizzuti, A. Bordoni, D. Saccomanno, N. Bresolin, GP. Comi, S. Corti, M. Nizzardo (Milano)

12.25 – 12.30 Open-label Study of Patisiran in Patients with hATTR Amyloidosis Post-Orthotopic Liver Transplant
T. Coelho, J. Gillmore, D. Adams, F. Muñoz-Beamud, A. Mazzeo, J. Wixner, V. Planté-Bordeneuve, L. Lladó, S. Arum, J.J. Wang, X. Li, H. Schmid (Porto, Portugal; London, UK; Le Kremlin Bicêtre, France; Huelva, Spain; Messina; Umeå, Sweden; Créteil, France; Barcelona, Spain; Cambridge, MA, USA; Münster, Germany)

12.30 – 12.35 Onasemnogene Abeparvovec Gene Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update
K.A. Strauss, M.A. Farrar, K.J. Swoboda, K. Saito, C.A. Chiriboga, R.S. Finkel, S.T. Iannaccone, J.M. Krueger, J.M. Kwon, H.J. McMillan, L. Servais, J.R. Mendell, J. Parsons, M. Scoto, P.B. Shieh, C. Zaidman, F. Baldinetti, M. Schultz, S.P. Reyna, F.G. Ogrinc, S. Kavanagh, D. Chand, D.E. Feltner, S. Tauscher-Wisniewski, B.E. McGill, D.M. Sproule, F. Muntoni (Strasburg, PA, USA; Sydney, NSW, Australia; MA, USA; Tokyo, Japan; New York, NY, USA; Orlando, FL, USA; Dallas, TX, USA; Grand Rapids, MI, USA; Madison, WI, USA; Ottawa, ON, Canada; Oxford, UK; Columbus, OH, USA; Aurora, CO, USA; London, UK; Los Angeles, CA, USA; St. Louis, MO, USA; Bannockburn, IL, USA)

12.35 – 12.40 Long-term impact of inotersen on neuropathy quality of life (QoL) for hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN): NEURO-TTR open-label extension at 2 years
L. Obici, A. Lovely, T. Coelho, A. Yarlas, M. Pollock, K. McCausland, I. Conceição, C. Karam, S. Khella, G.Vita, M. Waddington-Cruz, M.V. Llonch (Pavia; Porto, Portugal; Akcea Therapeutics; Lisboa, Portugal; Portland, Oregon, United States; Philadelphia, PA, Unites States: Messina; Rio de Janeiro, Brasil)

12.00 – 12.30 CHANNEL 4 - Current therapies in neuromuscular disorders

12.00 – 12.05 CMV primary infection and GBS, a treatment open question. Report of two cases and review
S. Dallagiacoma, S. Bocci, S. Bartalini, S. Ferrone, L. Franci, F. Ginanneschi, F. Giannini (Siena)

12.05 – 12.10 Systemic Gene Transfer With rAAVrh74.MHCK7.micro-dystrophin in patients with Duchenne Muscular Dystrophy
J.R. Mendell, Z. Sahenk, K. Lehman, C. Nease, L.P. Lowes, N.F. Miller, M.A. Iammarino, L.N. Alfano, J. Vaiea, S. Al-Zaidy, S. Lewis, K. Church, R. Shell, L. Picaro, R.A. Potter, D.A. Griffin, E.R. Pozsgai, M. Hogan, L.R. Rodino-Klapac (Columbus, Ohio, USA; Cambridge, MA, USA)

12.10 – 12.15 Home monitoring of different outcome measures during dose adjustment of intravenous immunoglobulin (IVIg) in patients with chronic inflammatory neuropathies
P.E. Doneddu, D. Mandia, F. Gentile, F. Gallia, G. Liberatore, F. Terenghi, M. Ruiz, E. Nobile-Orazio (Milano)

12.15 – 12.20 Efficacy of Rituximab in refractory Myastenia gravis
F. Tuccillo, B.M. De Martino, M. Pezzella, M. Esposito, F. Habetswallner (Napoli)

12.20 – 12.25 First and second line treatment in chronic inflammatory demyelinating polyradiculoneuropathy in children: 10 years experience of tertiary pediatric neurology centre
F. Ursitti, L. Papetti, M.A.N. Ferilli, R. Moavero, G. Sforza, F. Vigevano, M. Valeriani (Roma; Aalborg, Denmark)

12.25 – 12.30 Sub cutaneous Immunoglobulin in two patients affected by Stiff person syndrome: a comparison study with intravenous Immunoglobulin
V. Donadio, E. Fileccia, R. Rinaldi, G.M. Minicuci, R. D'Angelo, L. Bartolomei, R. Liguori (Bologna; Vicenza; Mirano (Ve); Bologna)

12.00 – 12.30 CHANNEL 5 - Disimmune and inflammatory neuromuscular disorders

12.00 – 12.05 Higher muscle damage in patients with anti-Mi2-positive dermatomyositis: a single centre retrospective cohort
F. Girolamo, M. Fornaro, M. Giannini, A. Amati, A. Lia, M. Tampoia, D. Dabbicco, L. Coladonato, M. Trojano, L. Serlenga, F. Iannone (Bari; Strasbourg, France)

12.05 – 12.10 Atypical Acute Motor-Sensitive Axonal Neuropathy (AMSAN) during Acute Hepatitis B Virus (HBV) infection
N. De Angelis, P. Galluzzi, F. Parodi, S. Bocci, F. Ginanneschi, C. Battisti, F. Giannini (Siena)

12.10 – 12.15 Clinico-pathological features in patients with anti-HMGCR immune-mediated necrotizing myopathy: a single-center experience
M. Meneri, D. Velardo,M.Magri, L. Andreoli, A. De Rosa,R. Brusa, M. Mauri, C. Matinato, L. Peverelli, P. Ciscato, S. Corti, C. Cinnante, M. Moggio, M. Sciacco, G.P. Comi (Milano; Lodi)

12.15 – 12.20 Long-term Prognosis in Guillain-Barré Syndrome and Clinical Variants: Focus on Motor and Sensory Outcome
S.G. Grisanti, C. Demichelis, A. Zuppa, V. Prada, A. Beronio, V. Dorindo, A. Schenone, L. Benedetti (Genova; Alessandria; La Spezia)

12.20 – 12.25 Characteristics of corneal innervation in patients with myasthenia gravis
G. Nicocia, C. Bonanno, A. Pugliese, D. Montanini, E. Postorino, S. Messina, G. Vita, P. Aragona, A. Toscano, C. Rodolico (Messina)

12.25 – 12.30 A case of COVID19 associated pharyngeal-cervical-brachial variant of Guillain-Barrè Syndrome
G. Liberatore, T. De Santis, P.E. Doneddu, F. Gentile, A. Albanese, E. Nobile-Orazio (Milano)

12.00 – 12.35 CHANNEL 6 - Disimmune and inflammatory neuromuscular disorders

12.00 – 12.05 Anti-AChR Myasthenia Gravis presenting with early predominant left triceps weakness, associated with reversible muscular atrophy
A. Rasera, M. Barillari, D. Cavalli, S. Romito (Verona)

12.05 – 12.10 Isolated cranial neuropathy associated with anti-glycolipid antibodies
C. Petrelli, F. Logullo (Macerata)

12.10 – 12.15 Perivascular M1 macrophages expressing VEGF and SDF1 promote angiogenesis in anti-HMGCR immune mediate necrotizing myopathy
F. Girolamo, M. Fornaro, M. Giannini, L. Coladonato, A. Amati, A. Lia, M. Tampoia, D. Dabbicco, R. Tamma, T. Annese, M. Errede, D. Virgintino, D. Ribatti, M. Trojano, F. Iannone, L. Serlenga (Bari; Strasbourg, France)

12.15 – 12.20 Acquired asymmetric brachial plexopathy: a description of a case-series
E. Pezzotti, L. Pasca, A. Gardani, V. Vacchini, E. Rognone, M. Paoletti, G. Cosentino, M. Plumari, C. Cereda, A. Berardinelli (Pavia)

12.20 – 12.25 Myasthenia Gravis and Latent Tuberculosis Infection- A Case Report
M. Sardaro, I. Plasmati, S. Aniello, M. Superbo, D. Liuzzi, S. Altomare, R. Leone R., D. Giorelli D., V. Lucivero (Barletta)

12.25 – 12.30 Report of an unusual course of CANDA (chronic ataxic neuropathy with disialosyl antibodies)
E. Schirinzi, E. Merico, C. Simoncini, A. Govoni, A. Bacci, R. Calabrese, G. Siciliano (Pisa)

12.30 – 12.35 Inflammation in Children with Neuromuscular Disorders and Sleep Disordered Breathing
F. Trucco, E. Carruthers, J.C. Davies, A. Simonds, A. Bush, H. Tan (Genova; London, UK)

12.00 – 12.30 CHANNEL 7 - Disimmune and inflammatory neuromuscular disorders

12.00 – 12.05 Early neurophysiological abnormalities in Guillain-Barré Syndrome: 4-year experience of Verona center
A. Rasera, S. Romito, A. Segatti, E. Concon, L. Alessandrini, F. Basaldella, A. Badari, C. Arcaro, B. Bonetti, G. Squintani (Verona)

12.05 – 12.10 Severe inflammatory myopathy in a pulmonary carcinoma patient treated with Pembrolizumab: an alert for myologists
D. Velardo, L. Peverelli, A. De Rosa, E. Domina, P. Ciscato, G. Sita, M. Sciacco, M. Moggio, G.P. Comi (Milano; Lodi)

12.10 – 12.15 Recurrent Variant of Miller Fisher Syndrome: is a ganglionopathy? - A Case Report

M. Sardaro, I. Plasmati, C. Santoro, R. Calabrese, S. Aniello, S. Altomare, R. Leone, V. Lucivero (Barletta)

12.15 – 12.20 Subcutaneous immunoglobulins in Myasthenia Gravis and anti-HMGCR myositis
A. Zuppa, C. Demichelis, S.G. Grisanti, C. Cabona, A. Schenone, L. Benedetti, M. Grandis (Genova)

12.20 – 12.25 Childhood Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Case Series
A. Tozzo, A. Ardissone, C. Ciano, FR. Danti, E. Pagliano, I. Moroni (Milano)

12.25 – 12.30 A case of progressive, stepwise, asymmetrical pure motor neuropathy: MMN versus motor CIDP
S. Tronci, U. Del Carro, M. Filippi, R. Fazio (Milano)

12.00 – 12.35 CHANNEL 8 - Toxic and metabolic neuromuscular disorders

12.00 – 12.05 A diagnostic delay of case of neurogastrointestinal encephalopathy (MNGIE)
F. Aruta, G. Capaldo, C. Pelosi, A. Iovino, M. Giaquinto, P. Romano, R. Rinaldi, S. Trimarco, F. Vitale, L. Ruggiero (Napoli; Avellino; Benevento; Bologna)

12.05 – 12.10 Topiramate in Oxaliplatin-Induced Peripheral Neurotoxicity: more than neuroprotection
P. Alberti, A. Malacrida, S. Semperboni, C. Meregalli, E. Ballarini, G. Cavaletti (Monza; Milano)

12.10 – 12.15 Movement disorders in children with a mitochondrial disease: a cross-sectional survey from the Nationwide Italian Collaborative Network of Mitochondrial Diseases
C. Ticci, D. Orsucci, A. Ardissone, E. Bertini, C. Bruno, V. Carelli, D. Diodato, A.M. Donati, M. Filosto, C. La Morgia, C. Lamperti, D. Martinelli, C. Minetti, M. Moggio, T. Mongini, V. Montano, I. Moroni, O. Musumeci, E. Pegoraro, G.Primiano, E. Procopio, A. Rubegni, M. Sciacco, S. Servidei, G. Siciliano, C. Simoncini, P. Tonin, A. Toscano, M. Mancuso, R. Battini, F.M. Santorelli (Pisa; Lucca; Milano; Roma; Genova; Bologna; Firenze; Brescia; Torino; Messina; Padova; Verona)

12.15 – 12.20 Mapping the neurotoxic effect of Oxaliplatin on dorsal root ganglia: MALDI mass spectrometry imaging highlights alterations to the tissue proteome
E. Ballarini, P. Alberti, V. Carozzi, V. Rodriguez-Menendez, A. Smith, G. Cavaletti, F. Magni (Monza)

12.20 – 12.25 Early onset recurrent muscle dysfunction associated with novel POGLUT1 mutation
A. Cavaliere, S. Gibertini, A. Ruggieri, F. Blasevich, F.R. Danti, L. Maggi, I. Moroni (Milano)

12.25 – 12.30 Different effects of oxaliplatin and cisplatin incubation on the electrophysiological properties of differentiated F-11 cells
L. Monza, V. Pastori, A. Becchetti, G Cavaletti, M. Lecchi (Monza; Milano)

12.30 – 12.35 Mitochondrial abnormalities with mtDNA single deletion in association with a LMNA gene frameshift variant: a case report

C. Simoncini, V. Montano, G. Ricci, G. Ali, A. Logerfo, F. Baldinotti, M. Caligo, G. Lattanzi, G. Cenacchi, A Barison, M. Mancuso, G. Siciliano

12.00 – 12.35 CHANNEL 9 - Toxic and metabolic neuromuscular disorders

12.00 – 12.05 Clinical and genetic study in a patient with Neutral Lipid Storage Disease with Myopathy (NLSD-M)
E. Baldelli, S. Cotti Piccinelli, B. Risi, N. Necchini, A. Galvagni, A. Padovani, M. Filosto (Brescia)

12.05 – 12.10 Unusual case of motor and dysautonomic neuropathy due to Thallium intoxication
A. Petruzzellis, E. Vecchio, L. Gallicchio, V. Recchia, L. Didonna, P. Lovreglio, G. De Palma, F. Tamma (Bari; Brescia)

12.10 – 12.15 Next generation sequencing-based gene panel tests for the management of diagnosis of lipid myopathies
E.M. Pennisi, F. Cortese, F. Gragnani, L. De Giglio, M. Garibaldi, A. D'amico, E. Bertini, F. Fattori (Roma)

12.15 – 12.20 Assessment of oxaliplatin-induced peripheral neurotoxicity in different mouse models
E. Pozzi, A. Canta, N. Oggioni, M. Bossi, G. Cavaletti, P. Marmiroli (Monza)

12.20 – 12.25 Whole-exome sequencing identifies recessive RDH11 mutations in a new glycogen storage myopathy with retinitis pigmentosa
O. Musumeci, A. Torella, M. Savarese, C. Rodolico, A. Ciranni, R. Oteri , F. Del Vecchio Blanco, G. Esposito, V. Nigro, A. Toscano (Messina; Napoli; Pazzuoli (NA); Helsinki, Finland)

12.25 – 12.30 Evaluation of muscle involvement in Acromegaly and Cushing's syndrome
L. Ruggiero, M.C. De Martino, E. Spina, R. Dubbioso, S. Tozza, C. Pivonello, C. Simeoli, R. Ferrigno, N. Di Paola, R. Iodice, L. Santoro, R. Pivonello, F. Manganelli (Napoli)

12.30 – 12.35 Familial mitochondrial myopathy and renal failure due to biallelic MGME1 mutations
M. Sciacco, M. Ripolone, L. Napoli, D. Piga, D. Velardo, P. Ciscato, M. Moggio, G.P. Comi, D. Ronchi (Milano)

12.45– 13.05 | Clinical and therapeutic updates on Pompe Disease | A. Toscano

13.05 – 14.20 - Oral communications 5: "Emerging neuromuscular entities"

13.05 – 13.20 Biallelic mutations in sord cause a common and potentially treatable neuropathy
A. Cortese, Y. Zhu, A. Rebelo, S. Negri, S. Courel, L. Abreu, C.J. Bacon, Y. Bai, D.M. Bis-Brewer, E. Bugiardini, E. Buglo, M.C. Danzi, S. ME Feely, A. A. Fragkouli, N. A Haridy, R. Isasi, A. Khan, M. Laurà, S. Magri, M. Pipis, C. Pisciotta, E. Powell, A. M. Rossor, J. Sowden, S. Tozza, J. Vandrovcova, J. Dallman, E. Grignani, E. Marchioni, S.S. Scherer, B. Tang, Z. Lin, A. Al-Ajmi, R. Schüle, M. Synofzik, T. Maisonobe, T. Stojkovic, M. Auer-Grumbach, M. A.

Abdelhamed, S.A. Hamed, R. Zhang, F. Manganelli, L. Santoro, P. Saveri, F. Taroni, D. Pareyson, H. Houlden, D.N. Herrmann, M.M. Reilly, M.E. Shy, G. Zhai, S. Zuchner (Miami, Florida, USA; London, UK; Pavia; Iowa City, Iowa, USA; Assiut, Egypt; Milano; Rochester, NY, USA; Napoli, Italy; Coral Gables, Florida, USA; Pavia; Philadelphia, Pennsylvania USA; Hunan Province, China; Al-Jahra, Kuwait; Tübingen, Germany; Paris, France; Vienna, Austria)

13.20 – 13.35 Natural history course of DNM2-related congenital centronuclear myopathy: a retrospective multicentre Italian Study.
D. Diodato, M. Catteruccia, L. Maggi, I. Moroni, E. Pegoraro, P. Riguzzi, L. Ruggiero, M. Garibaldi, A. Berardinelli, M. Pane, G. Atrea, F. Santorelli, E. Bertini, A. D'Amico (Roma; Milano; Padova; Napoli; Pavia; Pisa)

13.35 – 13.50 Biallelic RFC1 expansion is a common cause of idiopathic sensory neuropathy and ganglionopathy
R. Currò, A. Salvalaggio, S. Tozza, C. Gemelli, N. Dominik, V. Galassi Deforie, F. Castellani, E. Vegezzi, S. Efthymiou, G. Cosentino, E. Alfonsi, E. Marchioni, S. Colnaghi, EM. Valente, C. Tassorelli, MM. Reilly, H. Houlden, P. Mandich, E. Bellone, M. Grandis, A. Schenone, L. Santoro, F. Manganelli, C. Briani, A. Cortese (Pavia; Padova; Napoli; Genova; London, UK)

13.50 – 14.05 TYMP mutations result in late onset mitochondrial myopathy with altered muscle mtDNA homeostasis
D. Ronchi, L. Caporali, G. Manenti, M. Meneri, S. Mohamed, M. Contin, D. Piga, V. Mancinelli, S. Corti, M. Sciacco, V. Carelli, G.P. Comi (Milano; Bologna)

14.05 – 14.20 Neuromuscular sarcoidosis: single center experience in 209 consecutive patients.
B. Labella, F. Cinetto, R. Scarpa, R. Manara, E. Pegoraro, C. Agostini, C. Briani (Padova; Treviso)

14.20 - 16.00 |Round table: New suggestions for managing patients with Neuromuscular Disorders
Neuromuscular experts, Patients and Associations

16.00 - 17.00 | Workshop: Paraneoplastic diseases of muscle, NM junction and peripheral nerve: diagnostics and therapy

16.00 – 16.20 Paraneoplastic neuropathies | *S. Ferrari*
16.20 – 16.40 Presynaptic paraneoplastic disorders of the neuromuscular junction: an update |*R. Liguori*
16.40 – 17.00 Paraneoplastic disorders of skeletal muscles | *C. Rodolico*

17.00 – 18.15| Oral communications 6: "Current therapies in neuromuscular disorders **"**

17.00 – 17.15 Tubular Aggregate Myopathy caused by activating mutation in STIM1: a functional study in myoblasts and myotubes deriving from affected patients toward the identification of new therapeutic targets

E. Conte, G.M. Camerino, A. Pannunzio, M. Coluccia, M. Mora, L. Maggi, O. Cappellari, A. De Luca, P. Imbrici, A. Liantonio (Bari; Milano)

17.15 – 17.30 An Italian Database to assess the diagnosis, pathogenesis and effect of therapy in Multifocal Motor Neuropathy (MMN) and its variants: a prospective collaborative study

P.E. Doneddu, D. Cocito, A. Mazzeo, L. Benedetti,M. Luigetti, Fazio, C. Briani, G. Siciliano, M.Filosto, G. Antonini, G. Cosentino, R. F. Manganelli, M. Inghilleri, M. Carpo, G.A. Marfia, G.M Minicuci, L. Gentile, E. Peci, A. Schenone,M. Sabatelli, Tronci, M. Campagnolo, Schirinzi E, G. Liberatore, E. Nobile-Orazio for the MMN Study Group (Milano; Torino; Messina; Genova; La Spezia; Roma; Padova; Pisa; Brescia; Napoli; Roma; Bergamo; Treviglio; Vicenza)

17.30 – 17.45 Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3

L. Maggi, L. Bello, S. Bonanno, A. Govoni, M. Grandis, L. Passamano, F. Trojsi, F. Cerri, V. Bozzoni, L. Caumo, R. Piras, R. Tanel, E. Saccani, M. Meneri, V. Vacchiano, G. Ricci, E. D'Errico, S. Bortolani, R. Zanin, L. Politano, A. Schenone, S. Previtali, A. Berardinelli, M. Turri, L. Verriello, M. Coccia, R. Liguori, M. Filosto, G. Marrosu, G. Siciliano, I.L. Simone, T. Mongini, G.P. Comi, E. Pegoraro "(Milano; Padova; Pisa; Genova; Napoli; Cagliari; Trento; Parma; Bologna; Bari; Torino; Pavia; Bolzano; Udine; Ancona; Brescia)

17.45 – 18.00 Response to treatment and outcome in late versus early onset MG

F. Pasqualin, S.V. Guidoni, M. Ermani, E. Pegoraro, D.M. Bonifati (Trevisa; Padova)

18.00 – 18.15 Short- and long-term efficacy of lenalidomide therapy in patients with POEMS syndrome

F. Terenghi, F. Gentile, F. Gallia, P.E. Doneddu, R. Mazza, M. Ruiz, A. Nozza, E. Nobile-Orazio (Milano; Pavia)

Sabato 12 Dicembre

Streaming on CHANNEL 1

8.30 – 9.30 | **Breakfast seminar:**
"New perspectives for Myotubular Myopathies"

8.30 – 8.50 XLMTM: clinical spectrum, epidemiology, Nat-His MTM1 Study | *A. D'Amico*
8.50 – 9.10 Histopathology of centronuclear myopathies | *C. Bruno*
9.10 – 9.30 Gene therapy | *W. Müller-Felber*

9.30 – 11.30 | Oral communications 7: "Disimmune and inflammatory neuromuscular disorders"

9.30 – 9.45 Immune-mediated necrotizing myopathies: clinical-serological features of a large Italian cohort of patients
S. Bonanno, M. Lucchini, E. Pancheri, P. Rovere Querini, R. De Lorenzo, A. Biglia, C. Gemelli, P. Riguzzi, L. Bello, A. Pugliese, L. Ruggiero, G. Ricci, C. Fiorillo, G. Vattemi, G. Siciliano, C. Rodolico, M. Filosto, M. Garibaldi, E. Pegoraro, S. Previtali, P. Tonin, G. Antonini, L. Cavagna, M. Mirabella, L. Maggi (Milano; Roma; Verona; Pavia; Genova; Padova; Messina; Napoli; Pisa)

9.45 – 10.00 Serum pattern of metalloproteinases-2 and-9 and tissue inhibitors in patients with chronic inflammatory demyelinating polyneuropathy
G. Cosentino, V. Di Stefano, M. Montana, E. Alfonsi, C. Tassorelli, F. Brighina, B. Fierro, G. Caimi (Pavia; Palermo)

10.00 – 10.15 Muscle manifestations and CK levels in COVID infection: results of a large cohort of patients inside a Pandemic COVID-19 Area
A. De Rosa, E. Pinuccia Verrengia, I.Merlo, F. Rea, G. Siciliano, G. Corrao, A. Prelle (Legnano; Pisa; Milano)

10.15 – 10.30 Guillain-Barré Syndrome and COVID-19: an observational multicenter study from Lombardy and Veneto (Italy)
S. Cotti Piccinelli, S. Gazzina, C. Foresti, B. Frigeni, C. Servalli, M. Sessa, G. Cosentino, E. Marchioni, S. Ravaglia, C. Briani, F. Castellani, G. Zara, F. Bianchi, U. Del Carro, R. Fazio, M. Filippi, E. Magni, G. Natalini, F. Palmerini, A. M. Perotti, A. Bellomo, M. Osio, G. Scopelliti, M. Carpo, A. Rasera, G. Squintani, P. E. Doneddu, V. Bertasi, M.S. Cotelli, G.M. Fabrizi, S. Ferrari, L. Bertolasi, F. Ranieri, F. Caprioli, E. Grappa, L. Broglio, G. De Maria, U. Leggio, L. Poli, F. Rasulo, N. Latronico, E. Nobile-Orazio, A. Padovani, A. Uncini, M. Filosto (Brescia; Bergamo; Pavia; Padova; Milano; Treviglio; Verona; Esine; Cremona, Chieti-Pescara)

10.30 – 10.45 Muscle MRI findings and correlation with clinical and immunological parameters in a cohort of IMNM patients

L. Fionda, F. Vanoli, L. Leonardi, J. Alonso Perez, J. Diaz Manera, G. Merlonghi, S. Morino, E. Bucci, G. Alfieri, A. Lauletta, G. Antonini, M. Garibaldi (Roma; Barcelona, Spain)

10.45 – 11.00 Prevalence and relevance of diabetes mellitus in chronic inflammatory demyelinating polyneuropathy
P.E. Doneddu, D. Cocito, F. Manganelli, R. Fazio, C. Briani, M. Filosto, L. Benedetti, E. Bianchi, S. Jann, A. Mazzeo, G. Antonini, G. Cosentino, G.A. Marfia, A. Cortese, A.M. Clerici, M. Carpo, A. Schenone, G. Siciliano, M. Luigetti, G. Lauria, T. Rosso, G. Cavaletti, E. Beghi, G. Liberatore, L. Santoro, E. Spina, E. Peci, S. Tronci, M. Ruiz, S. Cotti Piccinelli, E.P. Verrengia, L. Gentile, L. Leonardi, G. Mataluni, L. Piccolo, E. Nobile-Orazio, on the behalf of the Italian CIDP Database Study Group (Milano; Torino; Napoli; Padova; Brescia; Genova; Messina; Roma; Pavia; Varese; Treviglio; Pisa; Treviso; Monza)

11.00 – 11.15 Distinguishing features of Acute- and Chronic-Onset Chronic Inflammatory Demyelinating Polyradiculoneuropathy
G. Liberatore, F. Manganelli, D. Cocito, R. Fazio, C. Briani, M. Filosto, L. Benedetti, G. Antonini, G. Cosentino, S. Jann, A. Mazzeo, A. Cortese, G. A. Marfia, A. M. Clerici, G. Siciliano, M. Carpo, M. Luigetti, G. Lauria, T. Rosso, G. Cavaletti, P. E. Doneddu, L. Santoro, E. Peci, S. Tronci, M. Ruiz, S. Cotti Piccinelli, A. Schenone, L. Leonardi, A. Toscano, L. Piccolo, G. Mataluni, E. Nobile-Orazio (Milano; Napoli; Torino; Padova; Brescia; Genova; La Spezia; Roma; Palermo; Messina; Pavia; London, UK; Varese; Pisa; Treviglio; Treviso; Monza)

11.15 – 11.30 The neurophysiological lesson from the Italian CIDP database
E. Spina, S. Tozza, P. E. Doneddu, D. Cocito, R. Fazio, C. Briani, M. Filosto, L. Benedetti, G. Cavaletti, S. Jann, A. Mazzeo, G. Antonini, G. Cosentino, G. A. Marfia, A. Cortese, A.M. Clerici, M. Carpo, A. Schenone, G. Siciliano, M. Luigetti, G. Lauria, T. Rosso, G. Liberatore, E. Peci, S. Tronci, M. Ruiz, S. Cotti Piccinelli, E. Pinuccia Verrengia, L. Gentile, L. Leonardi, G. Mataluni, F. Manganelli, L. Santoro, E. Nobile-Orazio (Napoli; Torino; Milano; Padova; Brescia; Genova; Monza; Messina; Roma; Pavia; Varese; Treviglio; Pisa; Treviso)

11.30 - 11.45 | Pausa

11.45- 12.45 | **Workshop:**
New therapeutic frontiers in dysimmune diseases of muscle, NM junction and peripheral nerve disorders

11.45 – 12.05 Drug-induced worsening in myasthenia gravis" -| *A. Evoli*
12.05 – 12.25 New immunomodulatory treatment for immune-mediated neuropathies | *L. Benedetti*
12.25 – 12.45 State of the art on the therapy of autoimmune myopathies | *M. Mirabella*

12.45 -14.30 | Oral communications 8: "Toxic and metabolic neuromuscular disorders"

12.45 -13.00 Long-term follow up in presymptomatic LOPD patients (PRELOPD STUDY). An Italian Neuromuscular Centers Experience
O. Musumeci, S. Servidei, T. Mongini, S. Ravaglia, G.P. Comi, F. Santorelli,V. Tugnoli, G. Antonini, E. Pennisi, L. Ruggero, G. Siciliano, C. Sancricca, F. Ricci, R. Brusa, A. Rubegni, E. Sette, M. Garibaldi, G. Ricci, A. Toscano (Messina; Roma; Torino; Pavia; Milano; Pisa; Ferrara; Napoli)

13.00 -13.15 Peripheral Nervous System (PNS) toxicity induced by immune-checkpoint inhibitors in cancer patients: single centre experience
S. Bocci, L. Insana, R. Danielli, F. Ginanneschi, L. Franci, L. Calabrò, A. M. Di Giacomo, M. Maio, F. Giannini (Siena)

13.15 -13.30 Clinical, pathological and prognostic heterogeneity in immune-checkpoint inhibitors-induced myositis
S. Bocci, N. Volpi, R. Danielli, S. Bartalini, L. Calabrò, A.M. Di Giacomo, M. Maio, F. Giannini (Siena)

13.30 -13.45 Neurofilament light chain: a possible serum biomarker for axonal damage in chemotherapy-induced peripheral neurotoxicity rat models
G. Fumagalli, A. Chiorazzi, V. Rodriguez-Menendez, K. Blennow, H. Zetterberg, G. Cavaletti, P. Marmiroli (Monza; Mölndal, Sweden; London, UK)

13.45 -14.00 Clinical, laboratory and therapeutic follow-up of large cohort of Late Onset Pompe Disease (LOPD) patients: a single Centre experience
A. Pugliese, G. Nicocia, G. Tavilla, A. Ciranni, R. Oteri, C. Rodolico, G. Vita, O. Musumeci, A. Toscano
(Messina)

14.00 -14.15 Arsenic Trioxide-induced peripheral neuropathy: prospective evaluation in a cohort of patients with acute promyelocytic leukemia.
M. Campagnolo, F. Lessi, M. Cacciavillani, M. Riva, A. Salvalaggio, F. Castellani, C. Briani (Padova)

14.15 -14.30 Lipid composition of cellular membranes in Neutral lipid Storage Disease type M: a possible role in etiology of disease?
E.M. Pennisi, D. Tavian, N.I. Noguera, L. DeGiglio, L., M. Mora, L.Maggi, M. Filosto, F. Cortese, M.Garibaldi, S.Missaglia, C.Angelini, E.Palma, A.Macone (Roma; Milano; Brescia; Venezia)

14.30 - 14.50 | Awards and Conclusions

INSTRUCTIONS FOR AUTHORS

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, case report, and advances in applied (translational) and basic research.

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Starting from 2020, a publication fee of 200 Euros is required. The Corresponding Author must fill in the appropriate form and send it with the corrected proofs. 50% off is offered for members of Associazione Italiana di Miologia (AIM) and/or Mediterranean Society of Myology (MSM) in good standing with dues. A copy of the payment receipt for the current year is mandatory to prove the membership).

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Case Reports, Scientific Letters (maximum 1500 words, 10 references, 3 figures or tables, maximum 5 authors). A summary of 150 words may be included.

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Information concerning new books, congresses and symposia, will be published if conforming to the policy of the Journal.

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Examples of the correct format for citation of references:

Journal articles: Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230-8. doi.org/10.14639/0392-100X-1583

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

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