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Integrated care of muscular dystrophies in Italy. Part 1. Pharmacological treatment and rehabilitative interventions

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This paper describes the pharmacological therapies and rehabilitative interventions received by 502 patients with Muscular Dystrophies, evaluated in relation to patient's socio-demographic and clinical variables, and geographical areas.

Data were collected by the MD-Socio-Demographic and Clinical Schedule (MD-SC-CS) and by the Family Problems Questionnaire (FPQ).

The most part of the enrolled patients were in drug treatment. The number of the medications increased in relation to patient's age, disability degree and duration of illness and was higher among patients with Duchenne Muscular Dystrophy (DMD) compared with Becker (BMD) or Limb-Girdle Muscular Dystrophies (LGMD). Steroids (deflazacort or prednisone) were the drug most frequently used, followed by cardiologic and bone metabolism drugs. In general, patients using steroids were younger and had a shorter duration of illness; patients using cardiac drugs and dietary supplements were older and had a longer duration of illness.

Rehabilitative interventions were provided to about 70% (351/502) of patients, mainly DMD. Of these, physiotherapy was the more frequent treatment (96.6%) and was prevalently performed in rehabilitative centres (about 70% of patients) and at home in only 30%. Hydrokinetic-therapy was practiced by 6.8% of patients. Respiratory rehabilitation was provided to 47.0% of patients (165/351) and assisted mechanical ventilation to 13.1% (46). The amount of rehabilitative interventions increased in relation to the patient's age, level of disability and duration of illness.

Compared to Central and Northern Italy, in Southern Italy there was a higher attention to cardiological impairment as shown by a higher number of patients receiving heart drugs.

No statistically significant differences concerning the possibility to have access to rehabilitative interventions were noted among the three geographical areas. However, patient living in Southern Italy tend to receive rehabilitation more often at home.

Key words: muscular dystrophies, integrated care, pharmacological treatment, rehabilitative intervention

Introduction

Muscular dystrophies (MDs) include a group of inherited disorders characterized by progressive muscle weakness and wasting, and classified according to pattern of inheritance, age of onset, and involvement of specific skeletal muscles (1, 2). The identification of

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dystrophin (3, 4) and the subsequent characterization of the dystrophin-glycoprotein complex (DGC) was the first step towards the clarification of the molecular pathogenesis of MDs (5, 6). Several forms of MD arise from primary mutations in genes encoding the components of DGC complex (7). The most common forms – affecting both children and young adults – are Duchenne (DMD), Becker (BMD) and Limb-Girdle Muscular Dystrophies (LGMDs). Due to the multi-systemic involvement, the management of MDs requires a multifaceted approach and a multidisciplinary expertise (8, 9). The clinical management is mainly based on the use of drugs [steroids (10-12), ace-inhibitors (13, 14) or beta-blockers (15) followed by other cardiological and/or respiratory medication when appropriate (15, 16)] and rehabilitative treatments (9). This integrated approach was able to improve quality and prolong life expectancy even in patients affected by the most severe forms (17, 18). As a consequence, DMD should now be considered as an "adulthood" disease (17, 18) requiring long term family assistance which may be very demanding (family burden) when professional and social supports are poor or lacking (19, 20).

In 2012, a national study on the families of patients with muscular dystrophies was carried out in Italy with the aim to describe the difficulties of the care-giver experience as well as the professional and social supports the relatives may rely on (21, 22). We found that relatives whose children had higher degree of disability, spent more daily hours in caregiving and/or had poor social support experienced a higher burden. Nevertheless, 88% of them reported something positive out of the situation (21, 22).

Based on the same data set, in this paper, we report data on the pharmacological and rehabilitative treatments provided to the 502 patients, and investigate differences in relation to demographic and clinical variables, and geographical areas.

Patients and methods

Design of the study

The study was carried out in 8 specialized centres for MDs, located in Northern (3 centres), Central (3 centres), and Southern Italy (2 centres). The patients' selection criteria were the following: diagnosis of DMD, BMD, or LGMD confirmed by molecular analysis or muscle biopsy; age between 4 and 25 years; in charge to the participating centres for at least 6 months; living with at least one adult relative. For each patient the key-relative was interviewed if he/she was aged between 18 and 80 years and not suffering from illness requiring long-term intensive care (21, 22).

Data were collected concerning: a) family socio-demographic characteristics and patient's clinical variables through the Muscular Dystrophy-Socio-Demographic and Clinical Schedule (MD-SD-CS); b) patient's level of functional autonomy according to the Barthel Index (BI); c) therapies provided to patients and support received by the families, through the MD Care Schedule (MD-CS); d) family burden through the Family Problems Questionnaire (FPQ).

The protocol of the study was approved by the Ethic Committee of the Second University of Naples (coordinating centre), and by the Ethical Committee of each participating Centre.

Instruments description

MD-SD-CS collects information on the main socio-demographic characteristics of the patients and their families, and on patients' clinical variables. Barthel Index (BI) assesses the patient's degree of independence in daily activities. It provides a global 1-100 score (0 "totally dependent"; 100 "totally independent"). Questions ad hoc developed by the researchers for the present study were used to interview the key-relative on patient's functional autonomy in the previous month. The inter-rater reliability in BI scoring was tested preliminary (Cohen's kappa coefficient ranging from 1 to 0.90 for 9 BI items and equal to 0.67 for the lasting BI item).

MD-CS collects information on pharmacological therapies received by the patient in the two months preceding the interview and on psycho-educational interventions and social/welfare support provided to patients and their families in the past six months. The schedule also collects information on where each treatment was provided.

FPQ explores relative's burden, attitudes toward the patient, and professional and social network support in emergencies concerning the patient (23). It contains additional items on expenses sustained by the family in the previous 12 months for care.

The psychometric properties of the FPQ was previously tested in this study sample (21).

Statistical analysis

Differences in pharmacological therapies and rehabilitative interventions related to patients' socio-demographic, clinical and geographic variables were explored by the analysis of variance and χ^2, as appropriate. Correlations between the number of drugs or rehabilitative interventions and patients' age, duration of illness and levels of functional abilities (BI global score) were explored by Spearman's r coefficient. Multiple regression analyses were performed to explore the simultaneous ef-

Table 1. Characteristics of the 502 patients and their key-relatives.

	Patients (N = 502)	**Key-relatives (N = 502)**
Sex, N (%)		
Males	484 (96.4)	74 (14.7)
Females	18 (3.6)	428 (85.2)
Age, mean (SD) years	12.8 (5.6)	43.4 (7.4)
Marital status, N (%)		
Single	502 (100)	61 (12,1)
Cohabitant/spouse	0	441 (87.8)
	Attendance	Degree
Education, N (%) yes	430 (85.6)	502 (100)
Pre-school	50 (11.6)	-
Primary school	148 (34.4)	35 (6.9)
Secondary school	90 (20.9)	184 (36.6)
High school	127 (29.1)	219 (43.6)
University	17 (4.0)	64 (12.7)
Currently employed (adults) N (%) yes	7 (7.4)	264 (52.6)
Relationship with the patient, %		
Mother	-	424 (84.6)
Father	-	70 (14.0)
Others	-	7 (1.4)
Duration of symptoms, mean (SD) years	8.9 (5.5)	-

fects on drugs and rehabilitative interventions (dependent variables) of patients' socio-demographic and clinical characteristics. Only variables related to drugs or rehabilitative interventions statistically significant in the univariate analysis were included in the multivariate ones. Statistical significance was set at $p < 0.01$.

Results

Of the 502 patients consecutively recruited, the most part was male, young, and school attending (Table 1). Three-hundred-thirty-three (66%) of them were DMD, 129 (26%) BMD, and 40 (8%) LGMDs. The mean level of independence in daily activities, measured by the BI, was 68.3 (31.3sd). One-hundred-ninety-four patients (39%) were in wheelchair.

Most of the 502 key-relatives were mothers and married or cohabiting. Almost half of them had received higher education and were employed (Table 1). They spent on average 5.7 (4.6sd) daily hours in patient's care-giving in the previous two months.

Pharmacological treatment

As reported in Table 2, most patients (73.5%) were in drug treatment. The number of the medications increased in relation to patient's age ($r = .32$, $p < .0001$), disability degree (BI global score $r = -.39$, $p < .0001$), and duration of illness ($r = .38$, $p < .0001$). Moreover, it was higher among patients affected by DMD compared with BMD or LGMDs (2.5 ± 1.8 *vs* 1.3 ± 1.8 vs. 1.5 ± 2.4, $F = 23.0$, df 2,499; $p < .0001$).

Steroids were the drug most frequently used, followed by cardiologic and bone metabolism drugs. Patients using corticosteroids were younger (11.6 (5.1) *vs* 13.6 (5.9), $F = 16.0$; df 1,500; $p < .0001$) and had a

Table 2. Pharmacological treatment received by patients with MDs in the past six months (N = 502).

N = 369 (73.5%)				
	DMD	**BMD**	**LGMDs**	**Total sample**
Type of drugs, N (%)				
Corticosteroids	205 (90.3)	14 (6.2)	8 (3.5)c	227 (61.5)
Cardiologic	144 (74.6)	41 (21.2)	8 (4.1) a	193 (52.3)
Bone metabolism	127 (86.4)	13 (8.8)	7 (4.8) c	147 (39.8)
Gastric	63 (84.0)	7 (9.3)	5 (6.7) b	75 (20.3)
Mean number of drugs/patient (sd)	2.5 (1.8)	1.3 (1.8)	1.5 (2.4) c	2.9 (1.7)
Differences among the three groups, a $p < .005$; b $p < .001$; c $p < .0001$				

shorter duration of illness (8.0 (4.9) *vs* 9.6 (5.9), F = 9.9, 1, 460, <. 0001), while patients using cardiac drugs and dietary supplements were older (16.9 (4.4) *vs* 10.0 (4.6), F = 259,6; df 1,500; p < .0001; 14.0 (5.9) *vs* 12.3 (5.0), F = 8.4, df 1,500; .01), and had a longer duration of illness (12.7 (4.8) *vs* 6.3 (4.3), F = 227.9, df 1,460; p < .0001; 10.3 (5.9) *vs* 8.4 (5.3), F = 10.1, df 1,460, p < 0.05).

Patients assuming cardiologic, bone metabolism and/or gastric protective drugs had lower levels of functional abilities (50.5 (31.6) *vs* 79.4 (25.4), F = 126.5, df 1,500, p < .0001; 58.2 (30.2) *vs* 72.5 (30.8), F = 22.5, df 1,500; p < .0001; 59.8 (29.3) *vs* 69.8 (31.4), F = 6.6; 1,500; p < .01).

A higher number of pharmacological prescriptions, particularly those concerning cardiological treatment, was found in centres located in Southern Italy compared with those in Central or Northern Italy (3.0 ± 2.1, vs 1.4 ± 1.5 vs 1.8 ± 1.6, F = 38.1, df 2,499; p < .0001).

Rehabilitative treatments

Three-hundred-fifty-one patients (70%) benefited of rehabilitative interventions. Physiotherapy was the most frequent treatment provided to MD patients, followed by respiratory rehabilitation and assisted mechanical ventilation (Table 3). Hydrokinetic-therapy was performed in only 21/502 (4.2%) patients. Rehabilitation was provided at home in about one-third (107/351, 30.5%) of cases. Although the percentage of rehabilitative interventions received by patients did not differ among the three geographical areas, however the home care rehabilitative treatments were more frequently performed in Southern Italy (24 in North, 31 in Central and 52 in South Italy (p < 0.003).

The complexity of rehabilitation treatment, intended as a number of rehabilitative interventions, increased in relation to patient's age (r = .33, p < .0001), level of disability (BI global score r = -.63, p < .0001), and duration of illness (r = .38, p < .0001).

Multiple regression analyses

Socio-demographic and clinical variables accounted for 23% of variance in pharmacological therapies provided to patients in the previous two months (Table 4). As shown by the standardized beta weights, number of drugs was significantly higher among patients' with longer duration of illness, and suffering from DMD.

Patient's clinical variables accounted for 42% of variance observed in rehabilitative interventions (Table 4) received by the patients in the previous six months, confirming that the number of the interventions was higher among patients with more severe disabilities, and in those suffering from DMD or LGMDs.

Discussion

The study reveals that about 75% of patients, independently from the type of muscular dystrophy, receive a drug treatment. This finding outlines a shift from past views of MDs as "incurable diseases" toward a clinical approach based on effective pharmacotherapy. In line with the current clinical guide-lines, the steroids (deflazacort or prednisone) were the drug more frequently administered in DMD (8, 9); they were more frequently used by patients still ambulant (119/205) compared with those wheelchair-bound (86/205) (X^2 = 55.7 df 1, p < .0001). This result can be explained by the current debate on the use of corticosteroids in the wheelchair stage, although recent studies have shown that the long-term steroid administration is useful to a) preserve upper limb strength (24), b) reduce the progression of scoliosis and the decline of respiratory function (25, 26) and c) delay the onset of heart dysfunction (27).

The higher number of cardiac drugs prescribed in Centres located in Southern Italy, may be related to the long-term expertise in cardiological monitoring of these Centres (28-30) and by the recent adoption of *Treat-NMD and National Council for Rare Diseases guide-lines* (31, 32).

The study also shows that the majority of MD patients in Italy receive rehabilitative interventions, whose complexity increased as the illness progresses. However some differences exist in the modality of provision, as in Southern Italy a higher number of patients receive domiciliary treatment. This condition, probably due to the poor availability of rehabilitative centers in Southern Italy, leads to an indirect benefit, both for patients and families, in terms of comfort of care, time saving and transfer costs.

Table 3. Rehabilitative treatment received by patients with MDs in the past six months (N = 502).

	DMD	BMD	LGMDs	Total sample
Rehabilitation, N (%)				351 (69.9%)
Type of rehabilitation, N (%)				
Physiotherapy	278/339 (82)	35/339 (10.3)	26/339 (7.7)[a]	339 (96.6)
Respiratory rehabilitation	138/165 (83.6)	17/165 (10.3)	10/165 (6.1)[a]	165 (47.0)
Assisted mechanical ventilation	45/46 (97.8)	0	1/ (2.2)[a]	46 (13.1)
Differences among the three groups, [a] p < .0001				

Table 4. Multiple regression analyses: effects of socio-demographic and clinical variables on pharmacological and rehabilitative treatments provided to patients with MDs.

	Drug treatments	Rehabilitative treatments
	Standardized Beta	
Variables		
Patient's age	.08	.05
Barthel Index	-. 04	-.38c
Duration of illness	.33c	.14
Type of MD- BMD	- .26c	-.26c
Type of MD-LGMD	- .15b	- .07
Model's F, df , p<	27.13; 5, 456; .0001	66.4; 5, 456; .0001
R2	.23	.42
[a] = p < .05; [b] = p < .001; [c]= p < .0001		

This study also reveals that in Italy – although with the known different regional shortages – an integrated pharmacological/rehabilitative care is guaranteed to the majority of patients with muscular dystrophies. Hopefully the recent changes in the Italian health care policy will further facilitate the patient's access to evidence based treatment.

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