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SPORT AND NEUROMUSCULAR DISEASES

-PSYCHOSOCIAL IMPACT AND PHYSICAL BENEFITS ON A COHORT OF RARE DISEASES-

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1. LITERATURE REVIEW

1.1 Definition and classification of neuromuscular diseases

Neuromuscular disease is a very broad term that encompasses many diseases and conditions that impair the functioning of the muscles, either directly, being pathologies of the voluntary muscle, or indirectly, being pathologies of nerves or neuromuscular junctions. Genetic neuromuscular conditions are debilitating and often prematurely fatal, and only nowadays few standard treatment options are available. For many neuromuscular disorders, including Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), the genetic cause is well known. Gene therapy holds promise for the treatment of these monogenic neuromuscular diseases, and many such therapies have made substantial strides toward clinical translation (Nelson et al., 2017). A recent review made a state of art on clinical research strength on muscular dystrophy using bibliographic literature. A quantitative literature analysis was carried out on muscular dystrophies (MD) (DMD, Becker Muscular Dystrophy (BMD), Congenital Muscular Dystrophy (CMD), Myotonic Dystrophy, Emery-Dreifuss Muscular Dystrophy, Facioscapulohumeral Muscular Dystrophy, Oculopharyngeal Muscular Dystrophy, and Limb-Girdle Muscular Dystrophy) from 1991 to 2015 for assessing the global research trends. This literature-based study showed an increase interest all over the years for these rare diseases (Ram, 2017).

Among the very high number of neuromuscular diseases, we will focus just on few of them, which will be the subject of this study.

DMD is an X-linked neuromuscular disorder characterized by progressive muscle weakness, mainly in boys. DMD/BMD are allelic muscular diseases responsible for

over 80% of all muscular dystrophies. The incidence of DMD is 1 in 3500 male newborns with a prevalence of 6 in 100,000 males and is characterized by weakness of leg, pelvic and shoulder girdle muscles starting in early childhood. The mean delay between DMD clinical presentation to a health professional and diagnosis around the globe has consistently been approximately 2 years, even if in Italy a lower diagnostic delay of 10 months has been recently reported (D'amico et al, 2017). This diagnostic Odyssey is in itself distressing,and also prevents parents from accessing genetic counselling and prenatal diagnosis in future pregnancies. More recently, late diagnoses may have inappropriately delayed timely access to steroids that prolong ambulation (Ross and Clarke, 2017; Wong et al., 2015). Treatment with Translarn (ataluren) and Exondys51 (eteplirsen) is now available on the market to slow the decline in mobility of patients who have a confirmed nonsense mutation of the dystrophin gene or a mutation amenable to exon 51 skipping. However most DMD patients are still untreatable and many other experimental trials are ongoing (Seto et al. 2012; Sienkiewicz et al., 2015).

BMD is a milder variant of dystrophinopathy with a better prognosis. The incidence of BMD is 1 in 18450 males and prevalence 2.4 per 100,000 in the general population (Mavrogeni et al., 2015).

SMA is a genetic disorder of motor neurons in the anterior horns of the spinal cord and brainstem that results in muscle atrophy and weakness. SMA is an autosomal recessive disease linked to deletions of the survival of motor neuron (SMN1) gene on chromosome 5q. Humans have a duplicate gene (SMN2) whose product can mitigate disease severity, leading to the variability in severity and age of onset of disease, and is therefore a target for drug development. Clinical subgroups have been defined

based upon best motor function attainment during development. Type 1 SMA infants never sit independently. Type 2 SMA children sit at some point during their childhood, but never walk independently. Type 3 SMA children and adults are able to walk independently at some point in their childhood (Kolb and Kissel, 2015).Subsequent modifications divided SMA type 3 category by age of onset, added a SMA type 4 for adult-onset cases and included a SMA type 0 for patients with prenatal onset and death within weeks (Zerres and Davies, 1999; Russman, 2007).

Advances in preclinical and clinical trials have paved the way for novel therapeutic options for SMA patients, including many currently in clinical trials. In 2016, the first treatment for SMA has been approved in the USA, an antisense oligonucleotide (Nusinersen) that increases full-length protein product derived from SMN2. The approval of a first treatment for SMA and the rapid advances in clinical trials provide the prospect for multiple approaches to disease modification. There are several other promising therapeutics in different stages of development, based on approaches such as neuroprotection, or gene therapy (Bharucha-Goebel and Kaufmann 2017).

CMT disease, the most frequent form of inherited neuropathy, is a genetically heterogeneous group of disorders of the peripheral nervous system, but with a quite homogeneous clinical phenotype (progressive distal muscle weakness and atrophy, foot deformities, distal sensory loss and usually decreased tendon reflexes) (Mathis et al., 2015). The use of high-throughput screens, and techniques such as RNAinterference (RNAi) and induced pluripotent stem cell continue to push forward other therapies for specific genetic forms of CMT and are potentially more generalizable to peripheral neuropathies. These developments, along with the development of improved outcome measures and longitudinal natural history data,

advance CMT, making the future for finding treatments and/or cures closer than it has ever been (Gutmann and Shy, 2015).

1.2 Exercise and neuromuscular diseases – State of art

Exercise-based therapy may be helpful for several disabiliting diseases.

Although some papers have been published on physical activity and neuromuscular diseases, we still have no recommendations or evidence-based data (Anziska and Sternberg, 2013).

A recent systematic review to evaluate benefits and risks of exercise in CMT showed that the optimal exercise modality and intensity as well as the long-term safety of exercise still remain unclear (Sman et al., 2015). However, it appears that exercise in CMT patients may be effective in improving some components of health and fitness without harmful effects in the short-term. The majority of published studies investigated resistance training interventions, which were found to result in positive modifications in strength, functional activities, and muscle fiber size. Similarly, aerobic training led to favorable changes in some measures of strength and functional activities, as well as an increase in aerobic capacity. Combined exercise intervention studies found positive changes in ankle flexibility, balance, agility, and mobility (Sman et al., 2015). Respiratory function has been rarely investigated in CMT patients and found minimally abnormal compared to healthy subjects, and with no amelioration after combined rehabilitation treatment (Maggi et al., 2011).

Conversely, neuromuscular recovery after a fatiguing task has been found to be impaired in the vastus lateralis muscle, but not in the biceps brachii muscle, of functionally independent CMT type 1A patients, compared with healthy individuals (Menotti et al., 2012). This difference was thought due to a prevalent involvement of the lower limbs.

The relationship between sport activity and quality of life (QoL) in neuromuscular diseases has been rarely investigated. Padua demonstrated that in CMT1A patients the

ability to ambulate independently is the motor skill most positively affecting the perceived QoL, as assessed by means of questionnaires (Padua et al., 2008).

Menotti et al. studied the energy cost of aerobic activity in CMT1A patients measuring the steady-state oxygen uptake (VO2), the carbon dioxide production (VCO2) and the heart rate (HR) to assess the metabolic and the cardiac cost (Menotti et al., 2015). CMT1Apatients showed a greater metabolic and cardiac cost of walking per unit of distance when compared with healthy individuals. HR depends on the training status of the individuals and it is likely that patients are less trained and have lower cardiopulmonary fitness, so both measurements could be adopted to detect improvements in walking economy of CMT1A patients following the implementations of training interventions specifically targeting walking performance, as successfully shown in paraplegic patients with spinal cord injuries (Felici et a., 1997; Gazzani et al., 1999).

In addition, recent studies on the profile of physical activity and behaviour of CMT patients can allow targeting of rehabilitation intervention to better address mobility and fitness (Ramdharry et al., 2016).

Crossing to another group of neuromuscular diseases, very few studied investigated the relationship between physical activity and myopathies. Maggioni et al. in 2008 assessed the cardiac and autonomic adaptations to sport activities in 30 wheelchair hockey players with different types of muscular dystrophy (DMD and others). They assessed the heart rate variability (HRV) in three different phases: pre-game, game, recovery. Although, an autonomic imbalance between the sympathetic and the parasympathetic tone was found in DMD patients, this paper shows how the autonomic modulation capacity of DMD subjects reacts significantly to physical stress. As it is known that aerobic training mainly influences the vagal control of HR,

these results can mean that there is the possibility to improve cardiac function and cardiac adaptation to exercise by aerobically training, limiting muscle and cardiac deconditioning, that can also play a role in the autonomic imbalance (Maggioni et al., 2008).

In 2013 the randomized controlled trial “no use is disuse” in DMD patients suggested that assisted bicycle training of the legs and arms is feasible and safe for both ambulant and wheelchair-dependent children and may decline muscle deterioration (Jansen et al., 2013). Following this paper, de Valle and collegueas reported the importance of complementary therapies (swimming and other organized sports) in DMD and BMD patients and the physical and psychological benefits of sporting activities. They underlined the lack of proven efficacy and published international standards of care and the need of studies on the effects of these therapies to provide evidence-based advice to families (de Valle et al., 2016).

There are several concerns that exercise may cause overwork weakness (OW), characterized by a progressive muscular weakening due to exercise, work, or daily activities in people with neuromuscular disease, and this topic is the subject of ongoing debate with contradictory results. Piscosquito et al. have tested the OW hypothesis in 271 CMT1A patients recruited in the Italian/UK multicenter trial of ascorbic acid and did not find effect of OW over time resulting in greater weakness in dominant muscles with increasing age or in more severely affected patients (Piscosquito et al, 2014; Piscosquito et al, 2014).The main consequence of these results is that exercise is not harmful for CMT1A patients, and possibly for the overall CMT population. Since a detrimental effect of supramaximal exercise cannot be excluded, most authors encourage physical activity in CMT patients, but recommend aerobic exercises at a submaximal work level (Maggi et al., 2011; Lindeman et al.,

1995; White et al., 2004). By definition, muscular endurance refers to the ability to perform a specific aerobic muscular action for a prolonged period of time, whereas explosive strength refers to the ability to exert strength or force as rapidly as possible in a given action with a short, very high intensity anaerobic exercise (Mikkola et al., 2007).However, the best training to adopt (e.g. endurance? explosive strength?) is still not known. A recent study on two novel outcome measures for CMT disease, the 6-minute walk test and StepWatchTM Activity Monitor (SAM), which is an activity measuring accelerometer, showed that several SAM outputs, all reflecting the higher speed, were significantly related to the main score of physical aspect of QoL: the higher the explosive performance, the better the physical QoL (Padua et al. 2016).

1.3 Psychosocial and emotional effects of sporting activity

Sport activity is a valuable tool to improve sense of wellness, QoL and to break down social barriers of discrimination for disabled individuals. Apart from the issue of autonomy of the individual, many physical, psychological and social benefits arise from sporting participation, which can translate into reduced health-care costs. Available evidence reveal also a positive impact of sports on areas of self-esteem, self-efficacy and mental health (Vita et al., 2016; De Pauw 2005).

The main impairment types in Paralympic sports include amputation or limb deficiency, cerebral palsy, spinal cord-related disability, visual impairment, and intellectual impairment. A sixth group, known as *les autres*, accommodates those athletes with physical impairments who are not covered by the other groups (Webborn et al., 2012). It is commonly accepted that subjects with a single disabled body segment are those preferentially prone to a sport activity. In this context, individuals with a progressive and severe genetic neuromuscular disorder are believed able to perform sports, with the exception of those competitive and with a full-body workout.

Several scientific studies underline a positive correlation between physical activity and reduction of depression and anxiety. It is also true that anxiety trait, depression and low self-esteem are often referred by neuromuscular patients. Neuromuscular experts have not so far directed too much attention to disability sport. Based on available literature, very rarely they suggest patients to perform sport activity and, when they do, they recommend avoiding supramaximal exercise. An intensive muscular training can induce a marked improvement of QoL, removal of depression, and reduced trait anxiety (Brosse et al., 2002; Adams et al., 2015; Kumar et al., 2016;

Cusso et al., 2016).Thanks to sport practice, patients can experience increased self-esteem and self-efficacy leading to interpret existing situations as more autonomy-promoting and to organize their actions on the basis of personal goals and interests rather than controls and constraints (Vita et al., 2016; Donaldson and Ronan, 2006; Bowker, 2006). A quantitative review and synthesis of studies correlating medical patients' treatment noncompliance with their anxiety and depression, made by Di Matteo et al. suggests the importance of recognizing depression as a risk factor for poor outcomes among patients who might not be adhering to medical advice(Di Matteo et al., 2000).Different mechanisms have been taken in count to explain how physical exercise can improve the emotional status.

Previous observational and interventional studies have suggested that regular physical exercise may be associated with reduced symptoms of depression (Blumenthal et al., 1999). A randomized controlled trial on 174 adults engaged in either a walking or stretching/toning program showed how changes in physical fitness, body fat, and self-efficacy were related to improvements in esteem perceptions relative to attractive body, strength, and physical condition (McAuley et al., 2000; McAuley et al., 1997).

Furthermore, physical activity has a positive relationship with the psychological aspects such as self-concept, self-esteem and self-efficacy. Many researches indicate that sport motivation plays a central role in promoting physical activity, and physical activity can be motivated by various reasons and the self-determination theory (SDT) offers a suitable framework for studying exercise behavior (Costa et al., 2013).

SDT is a macro-theory of human motivation which has a significant impact on research regarding motivation in sport. It gives prominence to the distinction in intrinsic and extrinsic motivation, and it has been demonstrated that motivation may have an important role to play in the adoption and maintenance of healthy-promoting

behavior in young adults (Daley and Duda, 2006). SDT has been also studied as related to children and parents relationship, and autonomy achievement. Parents' use of control and autonomy support is posited to influence children by shaping their feelings of autonomy and competence (Florrie Fei-Yin Ng et al., 2004). Lewis and Sutton published a study to test SDT in relation to exercise participation with the aim of identifying whether degree of autonomy mediates the relationship between personality traits and exercise partecipation (Lewis and Sutton, 2011).

2. CASE REPORT

My interest on this research field came from a noteworthy experience we had two years ago with a CMT 4A patient, in our Referral Centre for Rare and Neuromuscular diseases in Messina.

Thanks to this patient, we had the opportunity to document the positive physical, emotional and psychosocial changes induced by sport activity in a Paralympic swimmer with CMT type 4A (Vita el al.).

The patient came to our attention when she was 31-year-old, referring a long history of progressive muscle weakness. At three years of age, because of frequent falls, she was seen by a neuropediatrician who noticed claw hands and a steppage gait. Her gait improved after bilateral Achilles tendon lengthening. By 14 years of age she developed dysphonia. She continued to have progressively increased difficulty and at age 28 she became wheelchair-bound. There were dysphonia for bilateral vocal cord paresis, rare dysphagia for liquids, inability to go from supine to seated position without assistance, severe claw hands and bilateral pes cavus. Genetic study revealed that she was homozygous for a c.173_174 insA mutation in the GDAP1 gene, determining the introduction of a premature stop codon (p.P59AfsX3).

On the occasion of the visit at age 31, the patient was also evaluated by a psychologist. The 36-item short-form questionnaire (SF-36) (Apolone et al., 1998) assessed QoL by eight specific categories of physical and emotional scores, then summarized in two scores: physical composite score (PCS) and mental composite score (MCS). Previous studies in CMT patients showed that very low scores for PCS

indicate severe physical dysfunction, distressful bodily pain, frequent tiredness and unfavorable evaluation of health status. Very low scores for MCS indicate frequent psychological distress and severe social and role disability due to emotional problems (Padua et al., 2006; Padua et al., 2008). Anxiety was evaluated by State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). Beck Depression Inventory II (BDI-II) was used to evaluate depression symptoms (Beck et al., 1996). Rosenberg Self-Esteem Scale measured global self-worth by evaluating both positive and negative feelings about the self (Rosenberg,1965). All SF-36 QoL domains were markedly deteriorated with respect to the Italian normative sample, especially physical function, role physical, social function and mental health. There were also high scores of state and trait anxiety, high level of somatic and cognitive elements of depression, and low self-esteem. We suggested the patient to perform physical activity and she became a Paralympic swimmer (Vita et al., 2016).

Although just anecdotal observations on different debilitating diseases has been published so far, some comments, probably, come straight. Based on available literature, very rarely neuromuscular experts suggest patients to perform sport activity. Nevertheless, our CMT4A patient not only was able to carry out regularly intensive aerobic swimming workout with progressive increase of covered distance, but she also competed in sprint distance events, in which anaerobic activity is prevalent to endurance, with many wins in national championships. After five years of sport activity, in addition to improved quality of life and depression, reduced trait anxiety and enhanced self-esteem, deltoid, biceps and triceps muscle strength increased as well as the ability to propel her wheelchair independently. This might be related to strengthening of deconditioned muscles which were not severely affected. In fact the polymorphic disabilities involving people with CMT disease may lead to

deconditioning and a lower tolerance for physical activities. Even a short physical performance battery is an efficient and safe tool in producing some improvement in proximal limb muscles (De Pauw 2005; Webborn and de Vliet 2012; Ramdharry et al., 2014).

3. STUDY BACKGROUND

Starting from this our single experience and reviewing the available literature on sport practice, not just physical exercise, in neuromuscular disease, I started asking all neuromuscular patients, referred to our Centre, about any leisure activity, any sport and the reasons of their choice, whether they were practicing or not.

During this year, I started a professional collaboration with NEMOSUD Clinical Centre in Messina, always in sinergy with the Unit of Neurology, AOU Policlinico of Messina, for the care and scientific research for neuromuscular patients. I met Francesca Massimino, a 48-year-old woman with a diagnosis of SMA type 2. She is the president of Leoni Sicani wheelchair hockey team based in Sciacca, province of Agrigento. Afterwards I met Alessandro Lopes, administrator of Aquile di Palermo wheelchair hockey team based in Palermo, father of Matteo and Gabriele, respectively a 16 and 14-year-old boys affected by DMD and the president of this team, Salvatore Di Giglia, whose son, affected by DMD, died few years ago.

We realized that in the rare but large scenario of neuromuscular diseases, there is a more rare group that is represented by “neuromuscular athletes” and we decided to propose a multicentre study to most tertiary Neuromuscular Centres in Italy, already in collaboration with Messina Centre for other previous and actual studies, about the sport effects on social life, emotional status and QoL.

Our belief is that, based on clinical and psychological background differences compared to spinal cord injury (SCI) patients, people affected by genetic neuromuscular disorders are not prone and encouraged to start an agonistic activity.

Intensive muscular training might induce increased self-esteem and self-efficacy leading to interpret existing situations as more autonomy-promoting and to organize patient's actions on the basis of personal goals and interests rather than controls and constraints (Ng et al., 2012). Coping strategies together with the beneficial and gratifying effects of sport could lead to a considerable improvement of mental, emotional and psycho-social health in patients with disabling diseases.

However, the scientific literature lacks data of proven efficacy of sport activity as a complementary therapy of neuromuscular diseases.

Main aim of this study is to collect data from a cohort of athletes affected by rare diseases all over the country, with the aim to achieve evidence based guidelines for patients and families.

4. STUDY SUBJECT

This is a multicentre study in which 14 Italian Referral Centres for Neuromuscular diseases have been involved.

A retrospective analysis has been conducted on a sample of athletes with a confirmed diagnosis of neuromuscular diseases (DMD, BMD, CMT, SMA and other muscular dystrophies-MD), matched with a group of pathological control subjects (neuromuscular patients not practicing any sport).

Patients were studied at NEMOSUD Clinical Centre, AOU Policlinico "Gaetano Martino", Messina and they are all athletes.

INVOLVED REFERRAL CENTRES:

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14.Dott. Stefano Previtali, Ospedale San Raffaele, Milano

STUDY AIMS:

Primary: To evaluate the role and benefits of physical activity in general muscle strength, social participation, self-esteem and QoL

Secondary:

- to evaluate the correlation between motivational systems, anxiety disorder and depression, personality trait and QoL in patients practicing agonistic sporting activity;
- to evaluate the presence of neuropathic pain in the clinical picture of neuromuscular disease and how it could be managed with physical activity.

Tertiary: creation of guidelines of standards of care and evidence-based advices for families and patients on the effects of sport on neuromuscular diseases.

STUDY SAMPLE:

30 neuromuscular patients, being athletes, from all the 14 Centres in Italy.

INCLUSION CRITERIA:

- minimum age: 14 years
- confirmed diagnosis (with genetic confirmation if available) of neuromuscular disease
- modified Barthel Index (mBI) ≤ 90.
- practice of agonistic sporting activity (team or single activity) ≥6 months.

EXCLUSION CRITERIA (for patients and pathological controls):

- inability to read, understand, sign off the Informed Consent and fill up the questionnaires;
- participation to any clinical trials with experimental drugs in the 6 months prior to the study enrollment;
- modifications of pharmacological therapy or physical therapy in the 6 months prior to the study enrollment;
- hospitalization for any critical evens or acute illness in the 6 months prior to the study enrollment;
- any concomitant major diseases (neoplasms, cardiovascular and cerebrovascular diseases, etc.).

STUDY DESIGN:

After reviewing all the inclusion and exclusion criteria, every patient enrolled in the study will match pathological controls (neuromuscular patients not practicing any sport) with the following scheme:

Patients/controls = 1:1

They will match for:

- age (± 5 years)
- gender
- mBI (when possible also diagnosis matching)

5. METHODS

All patients and controls underwent questionnaires to assess their mental and emotional health.

They also underwent ID PAIN questionnaire to assess if any neuropathic or mixed pain was present as clinical symptom, whether they have been any benefit on this symptom with sport practicing or not.

In collaboration with Rome Centre-Gemelli University, we decided to use "The lifetime total physical activity questionnaire". This tool is not still available for Italian speaking population, so I translated it to be used in this study and to be validated for future studies.

Here the scales and questionnaires:

- **State-Trait Anxiety Inventory (STAI)** (Spielberger et al. 1983; Pedrabissi and Santinello, 1989 ; Julian LG, 2011). There are 2 subscales within this measure. First, the State Anxiety Scale (S-Anxiety) evaluates the current state of anxiety. The Trait Anxiety Scale (T-Anxiety) evaluates relatively stable aspects of "anxiety proneness," including general states of calmness, confidence, and security. Range score: 20-80 (20-39, mild anxiety; 40-59, moderate anxiety; 60-80, severe anxiety
- **Beck Depression Inventory II (BDI-II)** (Beck et al. 1996; Ghisi et al. 2006). Self-report instrument containing 21 questions, each answer being scored on a scale value of 0 to 3. We obtain a BDI total score where, higher scores indicate more severe depressive symptoms (Range score: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression) and two separated scores: the BDI-II somatic/affective factor (BDI-II FSA) and the BDI-II cognitive

factor (BDI-II FC). Both of them are scored differently for male and female population.

- **Rosenberg Self-Esteem Scale** (Rosenberg, 1965; Prezza et al. 1997). A 10-item scale that measures global self-worth by measuring both positive and negative feelings about the self. Range score: 10-16 low self-esteem; 17-33 not low-not high self-esteem; 34-40 high self-esteem.
- **Eysenck Personality Questionnaire** revised version **(EPQ/R)** (Eysenck and Eysenck, 1975; Eysenck et al., 1985). A questionnaire to assess the personality traits of a person. The personality is conceptualized as three biologically-based independent dimensions of temperament: Extroversion (E), Nevroticism (N) and Psychoticism (P). There is also a fourth scale, Lie/Social Desirability (L) as index of socially conforming behaviour.

Cut-off score range:

EPQ/R-E: cut-off ≥11

EPQ/R-N: cut-off ≥9

EPQ/R-P: cut-off ≥3

EPQ/R-L: cut-off ≥11

- **36-item Short-Form Questionnaire (SF-36)** (Apolone and Mosconi, 1998). To evaluate QoL. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability.

The eight sections are:

- vitality

- physical functioning
- bodily pain
- general health perceptions
- physical role functioning
- emotional role functioning
- social role functioning
- mental health
- **12-Item Short-Form Health Survey (SF-12)** (Ware et al., 1996). Italian version to evaluate QoL in 14-18 years age ranging patients. This questionnaire is scored with two synthetic indexes: Physical Component Summary PCS) and Mental Component Summary (MCS).
- **ID-PAIN** to assess the presence of neuropathic or mixed pain. ID-Pain is a 6-item self-questionnaire whose score ranges from 0 to 5 with higher scores corresponding to neuropathic or mixed pain with neuropathic component. The presence of pain limited to the joints (that is nociceptive pain) is scored -1. The likelihood of pain to be neuropathic based on the ID-Pain score is defined as follows: 4–5 likely, 2–3 probable, 0 or -1 improbable (Portenoy R, 2006; Padua et al., 2013).
- **The lifetime total physical activity questionnaire (**Friedenreich CM et al., 1998).An interview-administered questionnaire that assesses lifetime patterns of total physical activity including occupational, household, and exercise/sports activities. This questionnaire will be used to be validated as an italian version.
- The **Barthel Index** is considered to be the best of the ADL measurement scales (Shah et al., 1989). The modified version (mBI) emphasized scoring based on performance rather than capacity. Range score: 00 – 20 total dependence, 21 – 60

severe dependence, 61 – 90 moderate dependence, 91 – 99 slight dependence, 100 independence.

Only for athletes we used another questionnaire to look at sport motivation:

- **Behavioural Regulation Exercise Questionnaire –2 (BREQ-2**; Costa et al. 2013). The instrument comprises 19 items scored on a five-point scale ranging from 0 to 4. It is synthesized in five scales are: Amotivation, External regulation, Introjected regulation, Identified regulation and Intrinsic regulation.

6. RESULTS AND STATISTICS

PRELIMINARY RESULTS (MONOCENTRIC STUDY)

This study has been approved by our local Ethical Committee.

Surprisingly our referral Centre collected more than1/3 of the study sample (11 athletes), so we decided to report these preliminary results, as a monocentric study, of Messina Centre.

Because of delays of other Centre's ethical Committee approvals and local organizations, we do not have available results to analyse now for this work. We will publish the complete study next year.

6.1 Demographic and clinical results

Informed Consent was signed off by all of the patients (pts) of both groups. Inclusion and exclusion criteria have been verified for both groups.
All the results are reported as mean score of the study sample ± standard deviation (SD).

Demographics

11 athletes (M8, F3; mean age 26 ± 13) and 11 control subjects (M8, F3; mean age 25 ± 13 years).

Diagnosis and mBI

We recruited 11 athletes with the following diagnosis distribution:

5/11 pts (45.4%) DMD

2/11 pts (18.1%) SMA type 2

1/11 pts (9%) SMA type 3

1/11 pts (9%) CMT

1/11 pts (9%) BMD

1/11 pts (9%) MD

matched with the control group where the diagnosis distribution was:

6/11 controls (54.5%) DMD

2/11 controls (18.1%) SMA type 2

2/11 controls (18.1%) SMA type 3

1/11 controls (9%) MD

The mean mBI was 30±8 in athletes group and 38±8 in control group. In both cases we can score it as severe dependence (mBI score: 21 – 60 severe dependence).

Sport activity and The lifetime total physical activity questionnaire

In the athletes group we found this distribution of sport activity:

8/11 (72.7%) wheelchair-hockey players

2/11 (18.1%) swimmers

1/11 (9%) dancer

Duration and intensity of sport activity showed up from the italian version of the "lifetime total physical activity questionnaire".

We had these preliminary results:

8 wheelchair-hockey players exercised themselves 10 months±2 during the past year, 4±2 hours per week.

2 swimmers exercised themselves 12 months±2 during the past year, 3±1 hours per week.

1 dancer exercised himself 9 months during the past year, 4 hours per week.

This questionnaire does not take in account the agonistic competitions and the time spent to perform them. The wheelchair-hockey players from Leoni Sicani and Aquile di Palermo teams have been in A1 and A2 series, respectively. One of the swimmers and the dancer have been in national and regional competitions, respectively.

ID PAIN questionnaire

None of the 11 athletes or controls reported neuropathic pain.

6/11 (54.5%) had a score of -1, meaning presence of nociceptive pain (due to joint issues and bone deformities).

5/11 (45.4%) had a score 0,meaning no pain.

In the control group 11/11 (100%) reported a score -1.

Medications

All the DMD patients (5/11 and 6/11 in the athletes and control group, respectively) were on corticosteroids, as approved support therapy in this disease.

3/11 and 2/11 in the athletes and control group, respectively were on antihypertensive drugs.

1/11 pt in the control group was on antidepressant drugs for reactive depression due to her health issues.

6.2Neurophychological results

Neuropsychological questionnaires results-ATHLETES GROUP

STAI- (S-Anxiety)
The mean score was 35±8.1 (range score of mild level anxiety). The scores in detail showed:

10/11 (90.9%) with mild level of anxiety

1/11 (9%) with moderate level of anxiety

STAI - (T-Anxiety)

The mean score was 33.5±7.9 (range score of mild level of anxiety). The scores in detail showed in 11/11 pts (100%) a mild level of anxiety.

BDI-II- TOTAL SCORE

The mean score was 4.1±4.3 (range score of minimal level of depression).

BDI-II- COGNITIVE FACTOR (BDI-II FC)

In the male population of the group we found a mean score of 1.7±1.8 (normal range).

In the female population of the group we found a mean score 0.6±1.1 (normal range).

BDI-II- SOMATIC/AFFECTIVE FACTOR (BDI-II FSA)

In male population of the group we found a mean score of 2.7±3 (normal range).

In the female population of the group we found a mean score 2.6±4.6 (normal range).

Rosenberg Self-Esteem Scale

The mean score was 32.1±3.9 (range score of not low not high self-esteem). Looking at the scores in detail we found:

3/11 (27.2%) with a range score of high self-esteem

8/11 (72.7%) with a range score of not low not high self-esteem

EPQ/R-E

The mean score was 10±3 (range score of normality).

EPQ/R-N

The mean score was 5±3.7 (range score of normality).

EPQ/R-P

The mean score was 5.8±3.1 (high score of psychoticism).

EPQ/R-L:

The mean score was 12±4.9 (high score of social conformity).

SF-36

7/11 pts were more than 18-year-old and they performed the questionnaire:

Here in details the eight section scores:

- vitality (mean score 63.5±9.8)
- physical functioning (mean score 0)
- bodily pain (mean score 72.5±22.4)
- general health perceptions (mean score 45.1±21.5)
- physical role functioning (mean score 82.1±31.3)
- emotional role functioning (mean score 61.4±23)
- social role functioning (mean score 71.1±28.7)

- mental health (mean score 66.8±25.5)

SF-12

4/11 pts were between 14 and 18-year-old and they performed the questionnaire.

The mean PCS score was 42.8±1.1

The mean MCS score was 59.1±5.4

BREQ-2

Here in details the five scales scoring:

Amotivation: mean score 0.2±0.6

External regulation: mean score 0.2±0.4

Introjected regulation: mean score 1.1±0.9

Identified regulation: mean score 2.8±0.1

Intrinsic regulation: mean score 2.9

Neuropsychological questionnaires results-CONTROL GROUP

STAI (S-Anxiety)

The mean score was 35.3±6.3 (range score of mild anxiety). The scores in detail showed:

8/11 (72.7%) with mild anxiety

3/11 (27.2%) with moderate anxiety

STAI (T-Anxiety)

The mean score was 37.5±8.5 (range score of mild anxiety). The scores in detail showed:

6/11 (54.5%) with mild anxiety

5/11 (45.4%) with moderate anxiety

BDI-II TOTAL SCORE

The mean score was 7.1±7.4 (range score of minimal level of depression)

BDI-II - COGNITIVE FACTOR (BDI-II FC)

In the male population of the group we found a mean score of 2.5±2.9 (normal range), but looking at the single scores, we found 3/8 male pts (37.5%) with high FC, sign of severe depression.

In the female population of the group we found a mean score of4.3±5.8 (borderline range for symptoms of depression). 1/3 of the female pts (33.3%) had an high FC score, sign of severe depression.

BDI-II - SOMATIC/AFFECTIVE FACTOR (BDI-II FSA)

In the male population of the group we found a mean score of3.5±2.4 (normal range).

In the female population of the group we found a mean score of 6±7.8 (normal range), but 1/3 of the female pts (33.3%) had an high FSA score, sign of severe depression.

Rosenberg Self-Esteem Scale

The mean score was 32.8±4.6 (range score of not low not high self-esteem). Looking at the scores in detail we found:

6/11 (54.5%) with a range score of high self-esteem

5/11 (45.4%) with a range score of not low not high self-esteem

EPQ/R-E

The mean score was 9±4 (range score of normality). Looking at the scores in detail we found that 4/11 (36.3%) had an high score of extroversion.

EPQ/R-N

The mean score was 4.3±3.4 (range score of normality).

EPQ/R-P

The mean score was 6±2.3 (high score of psychoticism).

EPQ/R-L:

The mean score was 12.3±4.5 (high score of social conformity).

SF-36

7/11 pts were more than 18-year-old and they performed the questionnaire:

Here in details the eight section scores:

- vitality (mean score 50.7±26)
- physical functioning (mean score 5±11.1)
- bodily pain (mean score 73.5±27)
- general health perceptions (mean score 33.5±28.1)
- physical role functioning (mean score 67.8±37.4)
- emotional role functioning (mean score 90.4±25.3)

- social role functioning (mean score 89.2±19.6)
- mental health (mean score 70.8±14.3)

SF-12

4/11 pts were between 14 and 18-year-old and they performed the questionnaire.

The mean PCS score was 35±9.8

The mean MCS score was 53.7±9

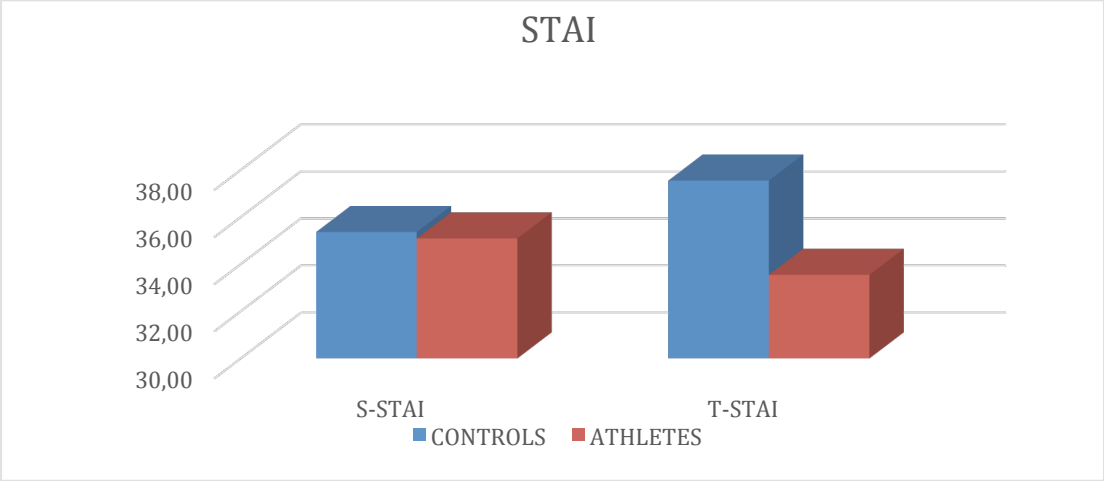
BREQ-2 is not applicable in the control group. It has been used only with athletes to look at their sport motivation.

6.3 Data analysis

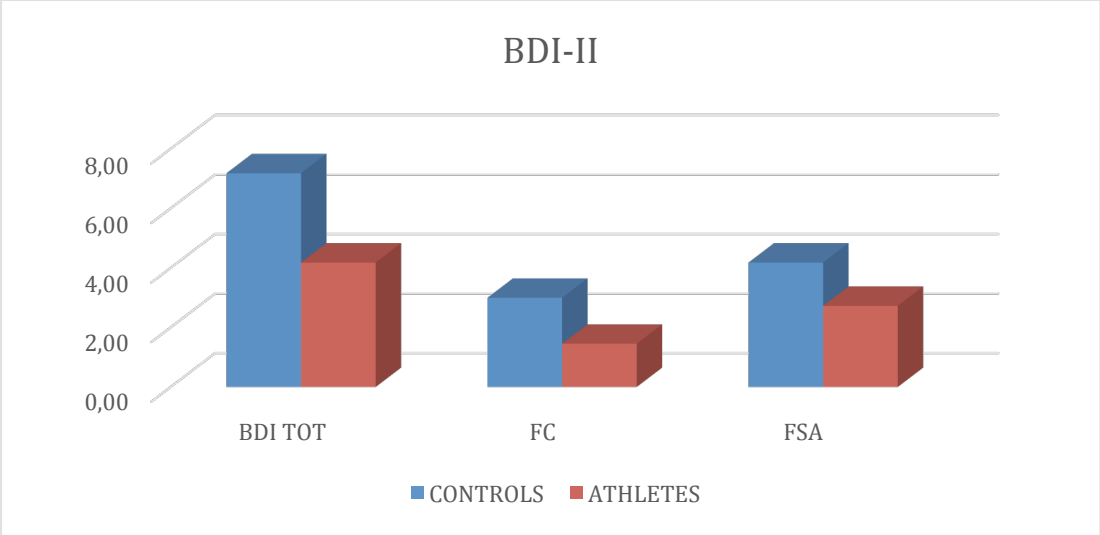
DESCRIPTIVE ANALYSIS

We showed in the previous paragraph all the results as means and SD. We compared the two groups, first summarizing the results in the following graphs.

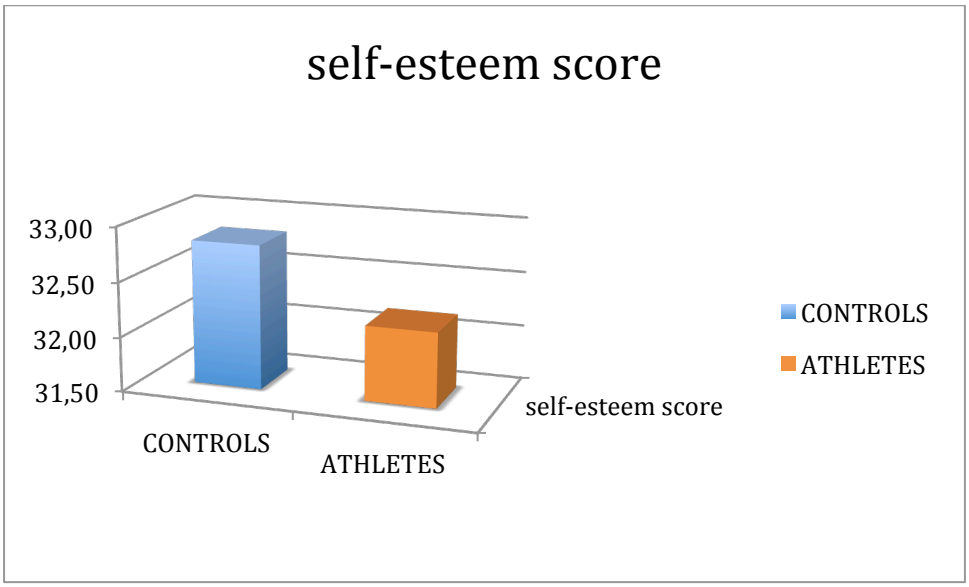
Graph 1. STAI results



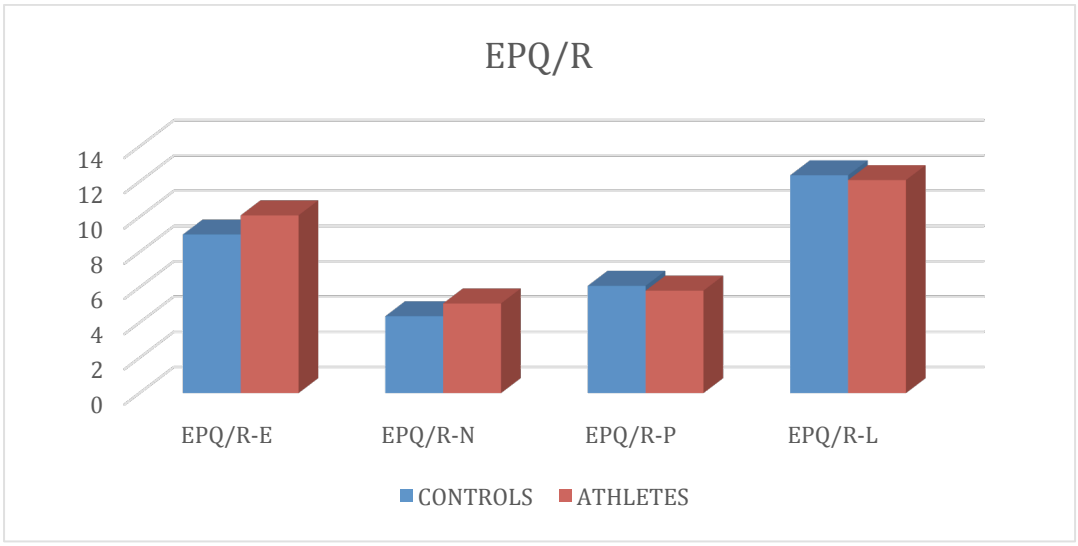
Graph 2. BDI-II results.



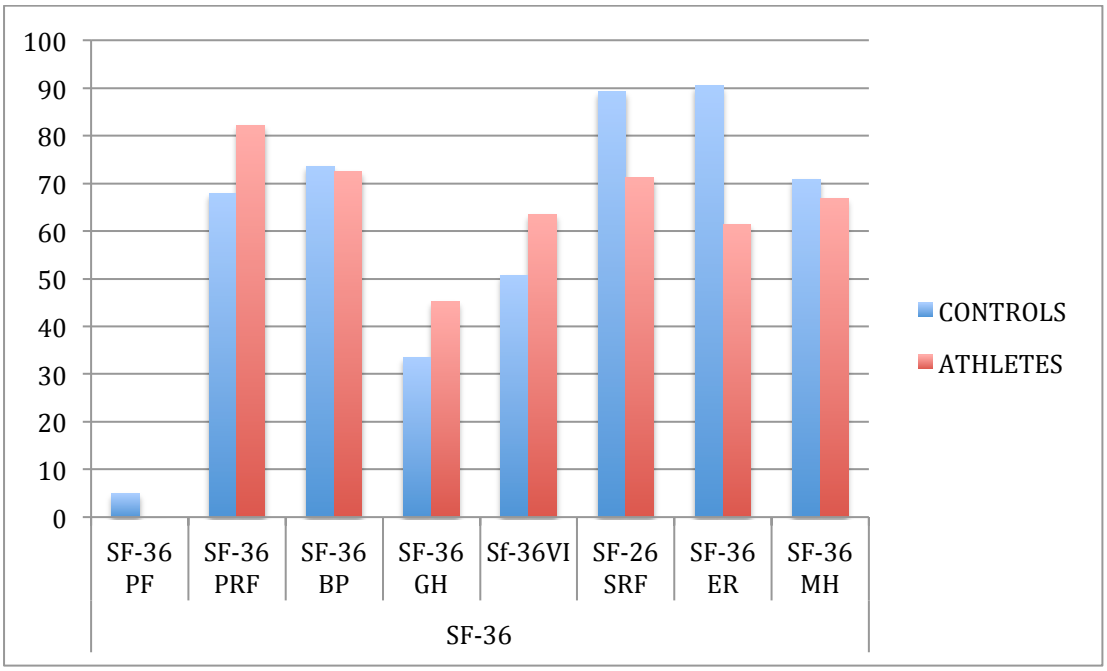
Graph 3. Rosenberg self esteem scale results.



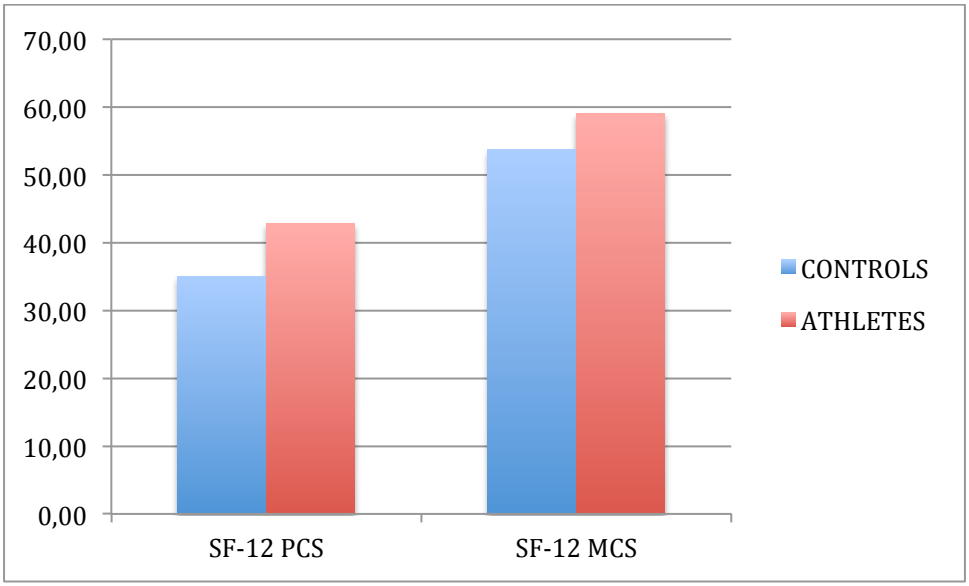
Graph 4. EPQ/R results.



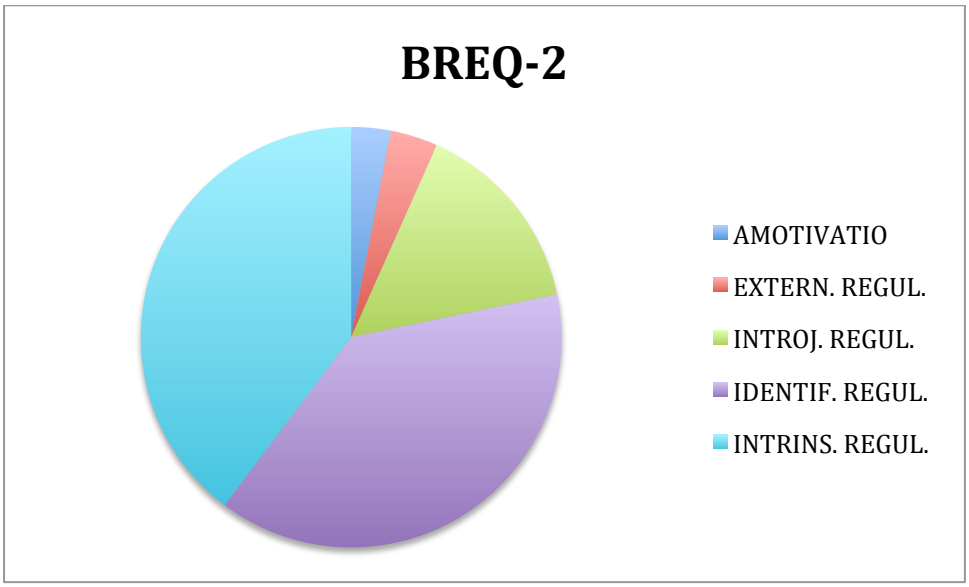
Graph 5. SF-36 results.



Graph 6. SF-12 results.



Graph 7. BREQ-2 results in the athletes group.



STATISTIC ANALYSIS

The Statistical Package for the Social Science (SPSS) was used to carry out whether sport practice determined significant different responses on all the neurophysiological scales. A Mann-Whitney U test was conducted between two unrelated, independent groups on a dependent variable (each questionnaire), where sport practice is the independent variable.

The non-parametric Mann-Whitney test demonstrated non-significant differences between the two groups in all the neurophysiological scales performed ($p > 0.1$), except SF-36 ER.

But, in some of them, the p-value seems to show a significant trend:

BDI-II tot. score $p= 0.1$

BDI-II FSA $p=0.2$

T-STAI $p=0.2$

SF-12 PCS p= 0.2

SF-12 MCS p=0.2

SF-36 ER p=0.03

SF-36 SF p=0.1

7. DISCUSSION

This is the first study on benefits and effects of sport practice, focused just on neuromuscular patients with a heterogeneity of study sample, instead of a single disease group examined. We presented the preliminary data of an Italian multicentric study where University of Messina is the Coordinator Center. 11 athletes affected by different neuromuscular diseases (DMD, BMD, CMT, SMA and MD)have been recruited and compared to a cohort of 11 patients control group, not practicing any sport, matching age, gender, mBI and, when possible, diagnosis. The preliminary data are the results of our Centre (Messina), where a large sample of patients (more than expected) has been recruited and where the psychological effects of sport practice has been investigated and compared to a control group. T-anxiety mean score was lower among athletes than in controls, showing a different personality trait. Anxiety, as stable trait, is lower in athletes, leading them to a major self-efficacy, interpretation of existing situations, problem-solving and more autonomy-promoting. Also, the level of T-anxiety score was different between the two groups. None of the athletes had a level of anxiety higher than mild. In the control group we found both mild and moderate level on T-anxiety score, showing less general states of calmness, confidence, and security. On S-anxiety score, evaluating the current state of anxiety, we did not find substantial differences. Probably because this score measures a transient emotional condition, it is not a stable trait of personality that is involved in daily coping, where sport practice can have an effect. On the other hand, the difference on T-anxiety score confirm this hypothesis. Interesting results have been also found on BDI-II scale, used to evaluate depression symptoms. The graph 2 exhaustively highlights how in all the three sub-scores of the control group scores were higher. The BDI-II total score showed minimal level of depression in both

group, even if with higher score in the control group. But looking at the cognitive and affective/somatic components (BDI-II FC and BDI-II FSA) the athletes group was in the normal range. The control group had borderline/pathological FC and FSA score. These results confirm the correlation between sport practice and treatment and/or prevention of depression.

Self-esteem mean score was similar in both groups, showing a “not low not high” self-esteem. But, as the graph 3 shows and looking at the detailed scores, we found more high self-esteem score in the control group than in the athletes. These findings could be apparently contradictory with the previous results on anxiety and depression scales. The EPQ/R questionnaire results can aid to comment these findings. We tried to correlate personality traits to sport practicing patients, comparing these findings to not sport practicing patients. The aim was to see if specific traits of personality make people more prone to sport practice. The four subscores on EPQ/R did not show significant differences between the two groups (see graph 4). But on EPQ/R-L scale, the control group had a higher score compared to the athletes. EPQ/R-L score is an index of socially conforming behaviour and could explain the contradictory high self-esteem score among controls. A series of earlier studies, conducted in England, Australia and the USA has suggested that the EPQ/R-L scale contains two empirically distinct components, one functioning partly as an index of socially conforming behaviour and the other functioning as a purer index of lying or dissimulation less contaminated by social conformity (Katz and Francis, 1991). It is well known in neuropsychological literature the possibility of the subject “faking” his answers, in order to give a deliberately good impression, answering personality questionnaires having and idea of “ self”. This attitude is not considered a pure form of insincerity or lie, but could the way to adapt to circumstances, maybe unknown or stressful

(Saklofske DH and Eysenck S BG, 1988). Together, these two high scores (EPQ/R L and high self-esteem in control group) could mean “dissimulation”.

Without finding significant differences on EPQ/R subscores, we did not succeed in delineating specific personality traits making more prone subjects to sport practice, but we can wait for the multicentric study analysis results to see if, in a larger study sample, any difference emerges.

Keeping on sport-practicing subject personality, interesting results came from BREQ-2 questionnaire. This tool assesses sport motivation in regular exercisers from the point of view of SDT (Costa et al, 2013). In the latest version of BREQ, developed by Markland and Tobin, we find the five subscales investigated in this study (Markland and Tobin, 2004). In our athletes group the scales “identified regulation”, and “intrinsic regulation” had the higher scores (see graph 7). The first, explains the level of recognizing and accepting the value of sport behaviour, the second, explains the level of involvement in physical activity for the enjoyment and satisfaction inherent in engaging in exercise (Costa et al, 2013). Really low scores have been found in subscales: 1. “amotivation” (“ I don’t see the point in exercising”) and 2. “ external regulation”, meaning that the sport adherence behaviour in our group is not controlled by external contingencies (“ because other people say I should”).

Our athletes showed a better social adherence and self-efficacy compared to the control group. High EPQ/R-L score in control group could also mean lack of social own identity and need of social behaviour controlled by “external reasons”. This probably means how sport practice can improve these emotional aspects as adaptive behavioural achievements. Our athletes recognize their own values and personal

inclinations, as it is shown on BREQ-2 and they do not need social conformity behaviour (low EPQ/R-L score).

QoL results on SF-36 and SF-12 showed differences in the teenager group, assessed with SF-12. MCS and PCS scores, assessing mental and physical component of QoL respectively, were higher in the athletes group, highlighting higher QoL.
Contradictory results showed up from the SF-36 group (adults) in all the eight sections and they not allow us to make any conclusion. Also for QoL we can wait for the multicentre study analysis results to see if, in a larger study sample, any difference emerges, or we can think about dissimulation and social conformity in the adult group that is less present in teenagers.

The statistic analysis with non-parametric Mann-Whitney test demonstrated non-significant differences between the two groups, but these are preliminary data from one single Center so, we will wait for the end of the study to state conclusions on statistic significance.

Last aims of this study were the assessment of presence of any neuropathic or mixed pain as clinical symptom and validation of "The lifetime total physical activity questionnaire". ID PAIN questionnaire concluded that no neuropathic pain was present in both cohorts, practising and not-practising sport. In these diseases we can have different type of pain (nociceptive/osteoarticular due to bone deformities and joint retractions).
100 % of control group reported nociceptive pain, compared to the only 54.5% of athletes group reporting the symptoms.
The importance of sport in reducing physical problems is well known (Crandell et al., 2009). In neuromuscular diseases, weakness and impaired mobility predispose to

numerous musculoskeletal issues. Early recognition and appropriate management are helpful in maintaining function, preventing deterioration in vital capacity, and improving QoL. Physical therapy can reduce these problems or it can help to manage them, especially to avoid or contain increase of adiposity and risk of becoming overweight, worsening the flexibility, contractures and musculoskeletal issues(Kolb and Kissel, 2015). Our aim is to spread the concepts among neuromuscular community of patients and clinicians, about how sport can be helpful not only in managing physical problems but improving emotional health, self-efficacy and self-concept.

Finally, “The lifetime total physical activity questionnaire” will be available for Italian speaking population since our aim is to validate it when all the results from all Centers will be collected, to be used for future studies.

8. CONCLUSIONS

Why just on neuromuscular diseases?

Because neuromuscular diseases as rare, are orphans. There is a lack in knowledge of prognosis, managing daily problems, health issues, psychosocial burden of these patients and even more of their caregivers. We are still looking at etiological and satisfactory therapies, that maybe for some of them are starting to be available, or, at least, are showing encouraging results.

So far, in my clinical experience I realized that being affected by rare diseases, such as DMD, SMA etc. has a totally different emotional and psychological background compared to a patient with SCI where few body segments are severe impaired, compared to other part, perfectly working. We, as neuromuscular clinicians, should be committed to improve QoL of these patients, helping them in their daily life, avoiding reactive anxiety and depression disorders because they feel weaker and without chance to improve on clinical basis.

We coordinate this study because sport practice can help neuromuscular patients improving QoL, reducing trait anxiety, striking improvement of depression and preventing or reducing musculoskeletal issues and pain. In our cohort, both functionally independent and dependent neuromuscular patients were practicing sport. Being functionally dependent does not mean impossible to exercise, and this concept should be supported by clinicians.

We want to proceed in the future with Observational Multicentric studies to look at:

1. To assess the metabolic and cardiac cost of activity in neuromuscular patients

2. To address the type of sporting activity and to verify any improvement in optimizing energy costs.

But first, we will propose longitudinal studies, needed to confirm our data on sport psychological impact and to support provision of evidence-based advice to patients and families.

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