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(with a focus on Duchenne muscular dystrophy)

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Recommendations regarding the early recognition of neuromuscular disorders
(with a focus on Duchenne muscular dystrophy)

Mattia Doria[1], Giuseppina Annicchiarico[1], Carmelo Rachele[1], Carlo Minetti[2], Adele D'Amico[2], Marika Pane[2], Filippo Buccella[3], Marco Rasconi[4]

[1] Italian Federation of Medical Pediatricians; [2] Italian Myology Association; [3] Parent Project Association; [4] Italian Union Against Muscular Dystrophy

INTRODUCTION

Neuromuscular disorders have always been an area of particular interest in general pediatrics. The primary care pediatrician, in particular, is required to **evaluate the neuromotor system** of a child during the **longitudinal observation** of the broader field of neurodevelopment, which is part of the clinical activities foreseen by **well-baby assessments**. According to the modern dimensional approach, early recognition of neurodevelopmental disorders is achieved through longitudinal monitoring, identifying the most sensitive and specific signs/symptoms starting from the detection of expected signs of normality as well as the presence of abnormalities within three basic neuro-functional areas: the neuromotor area, the regulatory area and the area of social communication and relations.

The recognition of a neuromuscular disorder emerges from the evaluation of signs/symptoms attributable to the neuromotor area in particular. Within the neuromuscular disorders, **Duchenne muscular dystrophy** (DMD) has recently attracted particular attention because studies of new drugs seem to offer the promise of treatment strategies already in the initial stages of the disease. This new scientific evidence and the availability of novel therapeutic strategies should encourage the family pediatrician to take more responsibility for formulating the suspicion of a diagnosis and for orienting the family.

NEUROMUSCULAR DISORDERS

Neuromuscular disorders are characterized by structural and functional alterations of the motor unit. Each motor unit comprises four functional components: the cell body of the motor neuron, its axon, which extends as a peripheral nerve, the neuromuscular junction and the muscle. The distinctive characteristics of neuromuscular disorders depend on which of these four components is particularly affected: there are forms that mainly affect cell bodies (motor neuron diseases), nerve fibers (peripheral neuropathies), neuromuscular junctions (myasthenic syndromes) and muscles (myopathies).

The classification of these diseases is constantly evolving in relation to continuous discoveries in molecular genetics which have recently revolutionized understanding of the etiology and pathophysiology of numerous hereditary degenerative disorders and, in many cases, have enabled isolation of the gene, identification of the protein coded by the gene and, consequently, the search for mutations of the former and/or quantitative or functional deficits of the latter.

DMD is the most widespread neuromuscular genetic disease in childhood and is characterized by progressive atrophy and weakness of skeletal muscles and myocardium [1,2]. The **dystrophinopathies** are due to mutations in the dystrophin gene, located on the short arm of chromosome X, which lead to a lack of dystrophin in the muscle (in DMD) or to a partial reduction of this protein (in Becker muscular dystrophy, BMD) [1,2].

DMD occurs in 1 of 3600/6000 newborn males and, in about one third of patients, develops as a consequence of new spontaneous mutations in the dystrophin gene [3-5]. DMD is manifested, on average, at the age of **3-5 years** with symptoms of slowly evolving muscle weakness leading to loss of motor skills, in the absence of treatment, at around 10-12 years of age. BMD presents later and the clinical course is variable, with the ability to walk being lost in adulthood [6]. Most patients with muscular dystrophy have serious orthopedic, respiratory, and cardiac complications as the disease progresses. Cardiomyopathy and respiratory failure are the most frequent causes of death of patients in adulthood [3,7]. The first signs and symptoms of motor difficulties potentially associated with muscular dystrophy generally appear between 2.5 and 3 years of age [12,13]. However, children with DMD may have a delay in acquiring motor skills that can already be detected by **18 months**, including a delay in autonomous walking, difficulty in acquiring a fast gait, as well as problems in getting up from the ground and climbing stairs [8-11]. Furthermore, one third of children with DMD have mental retardation and a warning sign in young children may be a language delay in addition to motor delay [29].

A prompt diagnosis is the key to ensuring integrated and effective care for the child with muscular dystrophy [20-22]. Early diagnosis allows initiation of the therapeutic and rehabilitative process, which has a recognized impact on the progression of the disease, substantially improving the quality of life not only of patients but also of members of the family. In fact, it has been reported that prophylactic physiotherapy, combined with long-term treatment with corticosteroids, can substantially modify the outcome of patients with DMD, slowing down the deterioration of muscle tone, prolonging the ability to walk, reducing the risk of scoliosis and stabilizing respiratory and cardiac function [14-17]. Moreover, recent studies suggest that an early onset of corticosteroid therapy (before the age of 4) could prolong the period of autonomous walking [18-19].

Prompt diagnosis is important not only for establishing appropriate steroid therapy at an early stage but also because it provides access, in those 10-15% of children aged 5 years or more with DMD who are walking and have "nonsense" mutations in the DMD gene, to therapy with new drugs such as Ataluren which has shown clinical efficacy, in terms of muscle performance, and a safe tolerability profile [18,19]. Extension of this treatment, to start from 2 years of age, is currently undergoing the approval process in Italy, after having been approved at a European level (by the European Medicines Agency) in August 2018 [28]. The initial evaluation is, therefore, a decisive phase in the care of the child with DMD.

STRATEGIES TO FACILITATE EARLY RECOGNITION

Taking into account the recent scientific literature and the new international guidelines developed by the US Centers for Disease Control and Prevention in collaboration with the "TREAT-NMD" network and patients' associations ("Muscular Dystrophy Asso-

ciation" and "Muscular Dystrophy Parent Project"), we analyzed the main recommendations useful for recognizing the early clinical signs of neuromuscular disorders and the timing of the longitudinal process of observation [20-22].

In the context of the Italian healthcare system, characterized by the widespread presence of **Family Pediatricians**, the most useful approach for facilitating early recognition of neuromuscular disorders is **longitudinal detection** (process evaluation) of the most sensitive and specific signs/symptoms for the identification of these disorders starting from monitoring expected signs of normality, integrated by assessment of any anomalies detected.

In this regard, the activities envisaged by the institution of **well-baby assessments** represent the most natural area for implementation of new longitudinal observational interventions to be extended to the entire target population as they constitute the privileged care setting in which it is possible to identify, in a **shared, codified** and **uniform** way, the main characteristics of a child's neurodevelopment.

In addition to the clinical evaluations carried out directly by the pediatrician, an analysis of the family and social environment in which the child lives is of paramount importance and is achieved through targeted questioning of the parents to uncover other possible anomalies in the progress of neuropsychomotor development.

It is important to appreciate that although the scientific evidence shows that the onset of the main symptoms of DMD occurs during childhood, usually around 2.5 years of age, some early signs of impairment in motor skills may be found **already in the first months of life** [12].

However, the great variability in both the times and the modalities of motor development in the first years of life complicates the early identification of real delays. On this background, as an integrative support to the existing guidelines on the early identification and management of muscular dystrophy [20-22], some of the main motor skills that are generally acquired at an early age and whose absence can be an indicator of possible delays in motor development have been highlighted [12].

Children with neuromuscular disorders generally have deficits in gross motor skills, but delays in fine motor and cognitive skills may also be present [24]. The most common defects in the development of gross and fine motor skills in relation to the age of the child are presented in Table I [13,20,23,24].

Besides the defects in motor development listed above, it has been shown that children aged < 18 months, who do not have a family history of neuromuscular diseases, may have signs of muscle weakness, hypotonia, muscle pain, stunted growth and/or poor weight gain [13].

Neuromotor development and the acquisition of the related skills expected in the various stages of growth of the child must be detected through a broader neurodevelopmental assessment that comprises Psycho-relational and Regulatory areas, in addition to the motor area.

It is worth noting that, based on currently available guidelines, the finding of signs and symptoms of muscular weakness (hyposthenia), reduced muscle contraction and hypotonia should make the primary care pediatrician suspect the diagnosis of a neuromuscular disorder and possibly also muscular dystrophy. The pediatrician should direct the family to local specialists in childhood neuropsychiatry [20,23].

FIRST-LEVEL DIAGNOSTIC WORK-UP

Assaying the level of serum creatine kinase (CK) in a child is indicated in the presence of:

- delays in normal motor development (as listed above) associated or not with other neurodevelopmental disorders;
- unexplained increases in the levels of transaminases not attributable to hepatic disorders [20];
- a family history of muscle disorders.

CK is considered one of the key biochemical markers in the diagnostic algorithm for muscular dystrophies [25,26]. The levels of CK, an enzyme released in conditions of muscle damage, are raised in patients with DMD [27]. Depending on the concentration of CK [27], it may or may not be necessary to send the patient to a specialized center (see following sections) [20], as indicated in the Table II.

The definitive diagnosis of DMD requires genetic studies [30], which are carried out by the network of Rare Diseases Centers distributed throughout the country [20,28,29].

TABLE I.

Main neurodevelopmental disorders in the neuromotor area of the child between 1 and 48 months of life.

Age (Months)	Neuromotor Area	Present	Not Present	Not Evaluable
1	Valid muscle tone? (valid axial tone, raises the head slightly in a prone position)			
	Spontaneous harmonious movements? (rich-fluid, not poor-stereotyped)			
3	Can raise and hold head in a prone position			
	Aligns head and trunk during forward traction			
6	Can lie on side and/or roll			
	Holds things and brings them to the mouth using both left and right hands			
9	Moves autonomously when put on the ground			
	Can sit alone and pass an object between hands			
12	Can stand upright with the help of a support (chair, low table, etc.)			
	Grasps with the first two digits of both hands (pinches with both the right and the left)			
18	Walks well			
	Climbs stairs either by crawling or on foot, using a support			
	Gets up easily from the ground			
36	Goes up and down stairs with alternate feet			
	Draws, cuts and/or pastes and/or inserts an object into another			
48	Walks and runs well			
	Absence of muscle pseudohypertrophy (calf muscles)			

THE PRIMARY CARE PEDIATRICIAN: ROLE AND PLACE IN THE CHAIN OF PUBLIC HEALTHCARE FOR CHILDREN WITH RARE DISEASES

The family pediatrician is responsible for the management of two important phases in the life of the child with a rare disease: the phase of **suspicion** (so many times the diagnosis remains unknown) and the phase of **returning home**. In both phases the pediatrician must interact with the public healthcare networks. In the former phase, the primary care pediatrician interacts above all with the network of specialists. As soon as there is a suspicion, even generic, that a disorder/group of possible disorders could be the cause of a child's problems. The pediatrician must link up (learning how to do so) with the networks of hospitals that have been identified and accredited by the Region in which they are located to be referral centers for rare diseases/groups of rare diseases.

When the child returns home, the pediatrician must become the **channel for all the services** involved in the management of the disorder. The therapeutic plan produced by the referral hospital within the Region or in another Region must be translated into concrete care.

WHO ARE THE EXPERTS IN RARE DISEASES AND HOW CAN THEY BE REACHED?

Through their respective regional coordinators, the Regions have surveyed and identified hospitals with the necessary competences for the management of rare diseases; they have also established regional Rare Diseases Registries that, in addition to collecting data on affected individuals, have enabled the care capacity of accredited hospitals to be monitored. In accordance with European recommendations, Rare Diseases Centers are identified in those hospitals in

TABLE II.

CK values, adapted from the National Task Force for Early Identification of Childhood Neuromuscular Disorders [27].

High CK (3 x normal, ≥ 750* U/L)	Refer to specialized center
Mildly increased CK (1-2 x normal, < 500* U/L)	Follow-up indicated, with repeat CK assay after 2-3 weeks
Normal CK (up to 250* U/L)	Does not exclude other neuromuscular disorders

* Absolute values may differ among laboratories.

which the diagnosis and treatment of the disorders are concentrated. Competence comes from seeing more patients and the centers with experience of treating the largest number of patients are those considered competent.

It was a very demanding survey, but it allowed orientation in what is now a highly complex world. This is partly due to the fact that the Regions have overcome their geographical and political boundaries and have shared programs and actions.

The regional registries have provided and continue to provide information to the National Register of Rare Diseases. The National Center for Rare Diseases (CNMR), at the Italian National Institute of Health, has become a repository of homogeneous information deriving from the entire country, a process which is only possible in a universalistic health system such as the Italian one. The CNMR website provides a list of centers, region by region, which manage rare diseases in a given territorial area, divided by disorder or group of disorders

The Regions have set up their own help lines. In just a few years, after the initial planning phase, Italy established the definitive organization of this field of public healthcare, with the institution of Regional and National Networks.

The hospital center for the management of rare diseases is called a national network Rare Diseases Center (RDC) ***(Presidio di Rete Nazionale Malattie Rare, PRN)***. Each center is a referral center for a specific group of disorders and produces the certificate of diagnosis that generates, within the respective Healthcare District, the rare diseases exemption certificate and the associated rights.

Only a RDC, anywhere in the whole country, can produce the individualized diagnostic-therapeutic care plan which is valid in the Region in which the patient lives. The new "Essential Levels of Care" aim to overcome differences between Regions caused by the fact that only Regions that have an essentially stable financial balance can use their own funds to guarantee all healthcare services beyond the basic, unlike the Regions that are subject to programmed restitution of budget resources to restore their financial balance.

The organization defined by Italian legislation is not a bureaucratic imposition, but stems from the desire to protect patients with rare diseases by guaranteeing that the diagnostic and prescriptive care setting is appropriate. Patients must be treated by those who have greatest scientific experience and who treat more patients. Thanks to a UNIAMO project, the "rare diseases community" brought together experts from the Ministry of Health, the National Institute of Health, the Regions, scientific societies, pediatricians and general practitioners and defined the "quality" of RDC.

HOW TO OBTAIN INFORMATION?

Despite numerous sources of information (the *Orphanet* website, whose users increased from 4.4 to 5.4 million between 2012 and 2014, the National Institute of Health's Rare Diseases Green Phone, which has about 2,000 contacts a year, the free telephone number of the Veneto Registry and others) finding useful information remains a critical issue for people with rare diseases; medical training also has ample room for improvement, considering that there were only 42 CME courses on rare diseases in 2016 in the whole of Italy, and that the delay in diagnosing such diseases is estimated to be 6.5 years. Rare diseases have not yet been included as a subject in a structured manner in basic and specialized training courses, which is part of the reason for the consistent difficulties of family pediatricians and general practitioners, in particular, who are the first point of contact of the patient with the regional or national healthcare system.

FROM SUSPICION TO DIAGNOSIS

As soon as the family pediatrician suspects a neuromuscular disorder, he or she must begin to interact with specialists to convalidate the diagnostic suspicion. **The diagnosis will be made in a specific RDC**, in which the clinical suspicion will be confirmed following the procedures set out in international recommendations.

GUIDING THE FAMILY DURING THE DIAGNOSTIC PROCESS: THE RESPONSIBILITY OF THE PRIMARY CARE PEDIATRICIAN

Muscular dystrophies were already included in the old list of rare diseases defined by Ministerial Decree n. 279 of 2001 and are still present in the updated list published in the annex to the Prime Ministerial Decree "New Essential Levels of Care" * of January 2017 within the macro-group of neuromuscular disorders in the macro-area/dimension "Diseases of the Central and Peripheral Nervous System".

Children and people with muscular dystrophy in Italy do, therefore, have the rights set out in Ministerial Decree n. 279 of 2001 and the National Plan for Rare Diseases 2013-2016. With these documents Italy defines the responsibilities and roles of the components of the public healthcare system involved in the management of "rare" patients and gives meaning to the specific Diagnostic-Therapeutic Care Pathways for these patients. Because of the low prevalence of these diseases (an estimated rate in Europe of fewer than 5 people affected in 10,000 individuals), patients are very frequently forced to undertake long journeys to the centers of expertise for their care (RDC) which are not always in the Region in which they live.

The patient will have confirmation of the diagnosis or the correct diagnosis and the rare diseases certificate in the specific RDC. It is this certificate that generates the rights that are due when the patient returns home.

The patient's Healthcare District gives the patient an exemption code for the specific disease. This code always starts with an "R" (R … ..). The primary care pediatrician will be able to use it when prescribing the contents of the Individualized Therapeutic Diagnostic Plans, drawn up by the RDC, and anything else the child may need according to science and conscience.

CONCLUSIONS

The delay with which neuromuscular disorders and muscular dystrophy are recognized has a significant impact, today even more than in the past, on the natural history of the diseases. In particular for the muscular dystrophy because of the gradual worsening of irreversible damage to the skeletal and cardiac muscles attenuates not only the efficacy of standard, corticosteroid-based treatments, but also that of the new-generation molecular ones (currently in approval in Italy with the extension, already approved by the EMA, of this treatment from 2 years of age) available for some forms of dystrophy (e.g., Ataluren).

It is now evident that the longitudinal assessment in the first 36-48 months of life is a fundamental part of the early recognition and care of the child with muscular dystrophy. The presence of suspicious signs/symptoms in the development of a child's motor skills must spur the pediatrician to assay CK levels in the blood as a first diagnostic approach; subsequent collaboration in the care process between the pediatrician, neuromuscular disease specialists and parents will be crucial for providing meaningful support in the clinical management of the child with muscular dystrophy.

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* Essential Levels of Care are the uniform set of services that the National Health Service is committed to provide to all patients, free of charge or upon payment of a fee (the so-called ticket).

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