Diagnosis of Duchenne Muscular Dystrophy in Italy in the last decade: Critical issues and areas for improvements

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Adele D'Amico[1], MichelaCatteruccia[1], Giovanni Baranello[2], Luisa Politano[3],Alessandra Govoni[4], Stefano Carlo Previtali[5], Marika Pane[6], Maria Grazia D'Angelo[7] ,Claudio Bruno[8], Sonia Messina[9], Federica Ricci[10], Elena Pegoraro[11], Antonella Pini[12],, Angela Berardinelli[13], Ksenjia Gorni[14],Roberta Battini[15], Gianluca Vita [9], Federica Trucco[8], Marianna Scutifero[3], Roberta Petillo[3], Paola D'Ambrosio[3], Anna Ardissone[2], Barbara Pasanisi[2], Giuseppe Vita[9], Tiziana Mongini[10], Maurizio Moggio[4], Giacomo Pietro Comi[4], Eugenio Mercuri[6], Enrico Bertini[1].

[1]Unit of Neuromuscular and Neurodegenerative Diseases, Department of Neurosciences, Bambino Gesù Children's Hospital, Rome; [2] Developmental Neurology, Child Neurology, and Neuromuscular Diseases and Neuroimmunology Units, Istituto Neurologico "Besta" Milan; [3]Cardiomiologia e Genetica Medica, Dipartimento di Medicina Sperimentale, Seconda Università di Napoli; [4]Neuromuscular and Rare Diseases Unit, Department of Neuroscience, and Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Neurology Unit, I.R.C.C.S. Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan; [5]INSPE and Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan; [6] Department of Pediatric Neurology, Catholic University, Rome; [7]Neuromuscular Disorders Unit, Scientific Institute IRCCS E. Medea, Bosisio Parini, Lecco;[8]Neuromuscular Disease Unit, G. Gaslini Institute, Genoa, [9] Department of Clinical and Experimental Medicine and Nemo Sud Clinical Centre, University of Messina, [10]Department of Neurosciences "Rita Levi Montalcini", University of Turin,[11]Department of Neurosciences, University of Padua, [12]Child Neurology and Psychiatry Unit, IRCCS Istituto delle Scienze Neurologiche, Bologna, [13]Child Neurology and Psychiatry Unit, "C. Mondino" Foundation, Pavia;[14]NEuroMuscular Omnicentre (NEMO), Fondazione Serena Onlus, Ospedale Niguarda

Cà Granda, Milan; [15]Department of Developmental Neuroscience, I.R.C.S.S. Stella Maris Foundation, Pisa.

Corresponding author: Adele D'Amico, Unit of Neuromuscular and Neurodegenerative Diseases, Department of Neurosciences, Bambino Gesù Children's Hospital, Viale San Paolo 15, 00146 Rome, Italy, Phone: +390668592105; fax +390668592024;
adele2.damico@opbg.net

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Highlights

- The mean age at diagnosis of Duchenne Muscular Dystrophy is around 4.2 -5 years all over the world.
- A delayed diagnosis of DMD has several clinical and therapeutic implication
- The mean age at diagnosis of DMD in Italy in the last decade was around 3.5 years.
- All male children should be screened in early infancy for DMD to avoid a delay in diagnosis

ABSTRACT

Despite all the advances in diagnosis and management of Duchenne muscular dystrophy over the past 50 years, the average age at diagnosis at most countries in the world around is still around 4-5 years. This retrospective study investigate the age at diagnosis in Italy in the past 10 years. We report findings from 384 boys who were diagnosed with DMD from 2005 to 2014. The mean age at first medical contact, which raised the suspicion of DMD, was 31 months. The mean age at diagnosis was 41 months. The finding that more frequently brought to suspect a DMD was the incidental finding of consistent elevated creatine kinase serum level detected during routine assessments in children undergoing general anesthesia or with intercurrent illness. This was followed by motor delay and signs of muscle weakness. Initial concerns were raised by general pediatricians (29%), specialists at tertiary centers (35%) or first level hospitals (23%). In children presenting incidental elevated creatine kinase values the diagnosis was achieved earlier than in children presenting a developmental delay. The mean age at diagnosis in our cohort was about 10-12 months lower than that reported in other countries.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy of childhood and affects approximately one in every 5,000 male newborns [1].

The onset of muscle weakness is typically in early childhood. Boys generally lose the ability to walk before the age of 13 years and death occurs in late teens or early 20s due to respiratory or cardiac failure [2]. Non-progressive cognitive dysfunction can also be present [3].

The mean age at diagnosis of DMD has been reported to be around the age of 4.2-5 years in several countries with a delay of about 2 years between the first symptoms are noted, and the diagnosis [4-10]. In order to evaluate the age at diagnosis of DMD in Italy and to compare our results to other studies performed in other countries [4-9], we retrospectively explored the age of DMD diagnosis, performed in the 15 tertiary Centers for muscular dystrophies in Italy, in the past 10 years. The aims of this study were to define the age at diagnosis of DMD in Italy, the most frequent signs that raised the suspicion of DMD and to assess the diagnostic pathway to reach the diagnosis, in Italy, highlighting its strengths and weaknesses.

Methods

This study includes 15 tertiary Italian Neuromuscular Center involved in the diagnosis and follow-up of DMD boys. The study was approved by the Ethic Committee of the coordinator center (Bambino Gesù Hospital).

Clinical charts of the children, who received a diagnosis of DMD from January 2005 to December 2014, were reviewed by a clinician in each center.

A dedicated excel file for data collection was provided by the coordinator (A.D.) and used in all centers after a training session.

For each boy the following information were collected: region of origin of patient, family history of DMD, age at first medical concerns, person who suspected the diagnosis, presenting sign or symptom, age at diagnosis, interval between the first suspicion of DMD and diagnosis, type of investigation that was performed to reach the diagnosis. (biopsy and/or genetic test). We considered as presenting sign or symptom the first sign or symptom revealed by a physician that raised the suspect of DMD. Only one sign or symptom, among the following, could be filled into our survey and was considered as the predominant sign: incidental finding of elevated creatine kinase (hyperCKemia) or transaminases serum levels, motor delay (a delay of motor milestones without

evidences of muscle weakness), tip-toe walking, muscle weakness, intellectual disability and speech delay. We considered as the age at diagnosis either the date of the muscle biopsy or the genetic test. All patients missing some information were excluded from the study.

A general descriptive statistics was generated to analyze the data.

The familial cases were analyzed separately.

RESULTS

Nine of the 15 tertiary centers involved in this study were in the northern part of Italy, 4 in the center and 2 in the south.

We identified 384 Italian boys diagnosed with DMD in the last 10-years. The patients, classified according to their region of origin, were equally distributed from North (n= 134), Center (n= 115) and South (n= 135) of Italy. Thirty boys (7,8%) had a positive family history of DMD. Forty-two patients were excluded by the study because not all the appropriate information were available.

The mean age at first medical contact, which raised the suspicion of DMD, was 31 months (range 0-95 months). The mean age at diagnosis was 41 months (range 0.3- 135 months). The reasons that led the child to medical attention were: incidental finding of consistent hyperCKemia (n=170, 44,3 %), motor delay (n=61, 15.9%), muscle weakness (n=54, 14,0%), increased levels of transaminases in serum (n=36, 9%), family history (n=30; 7,8%), tip-toe walking (n=20, 5,2%), intellectual disability (n=10, 2.6 %), speech delay, (n=4, 1%), other symptoms (0.4%).

In the group of children who presented hyperCKemia as an incidental finding, the mean age at suspicion was 25 months. In the two groups of patients with intellectual disability and motor delay, the first suspect of DMD was formulated at the mean age of 30 months, whereas in patients showing tip-toe walking or muscle weakness DMD was suspected later (45 and 49 months respectively) (see figure 1).

Initial concerns of DMD were more often raised by specialist at first level hospital (35%), followed by general pediatricians (29%) and specialists at tertiary level hospitals (23 %). In the remaining 13% initial concerns was raised by parents.

Following a clinical suspect, the CK level was tested in all patients. In the whole cohort, EMG was performed in 34patients (9%), and muscle ultrasound in 5 (1,3%).

Only a small percentage (18%) underwent further clinical and instrumental investigations before prompting a test for DMD. Seventeen out of the 36 patients (9.3%) who were initially examined for incidental high transaminases serum level, underwent liver ultrasound and serologic tests for hepatitis and in two cases a liver biopsy was performed. Ten of the 61 patients (2,6%) with 'pure' motor delay as the presenting symptom, underwent orthopedic or physiatrist examination before the CK assessment. Four of the 10 patients with intellectual disability had brain MRI and electroencephalography.

The mean interval between the first suspicion and the diagnosis of DMD was 12 months (range 10 days to 80 months). The interval was shorter in patients with the incidental finding of consistent hyperCKemia and longer in the group of patients with intellectual disability and tip-toe walking (see table 1).

In 275 of the 384 boys (%) muscle biopsy confirmed absence or near absence of dystrophin in the muscle. In 215 boys (55%) muscle biopsy was performed before the genetic test, whereas in 60 boys it was performed after a negative genetic test for deletions or duplications (n=29) or to better define the phenotype (n=31). The diagnosis of DMD was genetically confirmed in all but two cases and in 109 cases it preceded the muscle biopsy. The percentage of patients who underwent a diagnostic muscle biopsy decreased over the years, passing from 69%, in the period 2005-2009, to 44 %, in the quinquennial 2009-2014.

No significant differences in the diagnostic pathway and age at diagnosis in the three different areas of Italy were found. The mean age of clinical suspect was shorter in the North of Italy (6 months less than in the South), while the time for diagnosis was longer (5 months more than in the South).

The mean age at diagnosis of familial cases was 33 months (ranging between 10 day to 98 months).

Discussion

Despite advances in technology and increased availability of genetic testing, diagnosis in DMD is still often delayed, even when the first signs or symptoms are recognized early. Audit data and published papers, from different countries, show that the mean age at the diagnosis is still averaging between 4.2 and 5 years and is almost identical from the reports in the early 1980s[4-10].

In this study, we reviewed the mean age at diagnosis of a large cohort of Italian DMD patients, that were referred to tertiary care centers over the past 10 years and we analyzed different factors leading to the final diagnosis. Undoubtedly, we were not able to identify and include all DMD patients diagnosed in Italy in the last decade, thus this work is not intended as an epidemiological study on the incidence of DMD in Italy but rather it would describe the diagnostic approach to the disease. Over the last decade in Italy the mean age at diagnosis, was 41 months (3.5 ys), about 10-12 months less than the age reported in other studies [4-10]. The most frequent finding that brought to suspect DMD was the incidental finding of elevated CK or of transaminases serum levels (53% of cases). This was followed by delay in motor milestones (16% of cases). Unexpectedly, at variance with other studies, intellectual disability or speech delay were the first sign in only 3.6 % of cases.

The difference between our findings and previously published data is probably related to the fact that in Italy blood tests, including transaminases, and often CK, are often routinely requested by general pediatricians in children with vomiting, diarrhea or prolonged fever and, when needed, before general anesthesia. Once the elevated CK level is detected, the boys are often referred directly to a tertiary care center and this probably explains the shorter duration to reach the diagnosis in these cases.

Even when the presenting sign was different, such as delayed milestones, CK levels were the first and often the only investigation performed by physicians, including general pediatricians, and this

promptly led to the appropriate investigation for DMD. These data are different from other countries where the CK test was almost always performed in secondary care and the time to obtain the result significantly contributed to the diagnostic delay [5,9].The earlier age at diagnosis in Italy, confirm that, as reported by other authors [5], assessing CK levels in primary care can reduce the time of diagnosis.

Some aspects of neurodevelopmental delay in the first years, including intellectual disability and speech difficulties were the presenting symptoms in about 20% of patients, confirming the suggestion of other authors that CK levels should be tested in young children with walking delay (>18 months) [5],delayed speech or global developmental delay [5,10]. It is of interest that in our cohort the most delayed diagnosis (up to 135 months) occurred in patients not manifesting global developmental delay but having signs of muscle weakness, such as difficulties in running or in getting up from the floor, or showing tip-toe walking (14 and 5,2%, respectively) as these were probably thought to be a mild motor delay or clumsiness that would improve with age.

Another interesting finding in our study was that the mean age at diagnosis of a familial case was lower than in the sporadic cases but was still at31 months (versus 41 months in sporadic cases). This was not systematically assessed but it is probably due to the fact that if the children were close in age, by the time the first child had a diagnosis, the second was already older than 2 years. Another interpretation of this finding could reflect the choice of the family not to receive an early diagnosis in their second younger son.

In the diagnostic pathway in Italy we found that muscle biopsy is still performed -before the genetic test- in 55 % of cases, in contrast with the recent International Guidelines [10] that recommend to perform muscle biopsy only in cases of negative MLPA test for deletion/duplication. However, as shown in the results, this approach has progressively changed over the years because of the increasing availability of the MLPA test in tertiary neuromuscular centers.

One of the strengths of our survey is that it includes all the tertiary care centers in Italy and therefore provides an overall picture of all the patients who are followed by specialists. This is

however also a possible limitation as the large number of centers potentially increase the possibility that data may have interpreted differently by the different investigators. In order to reduce this bias, we had a preliminary survey and, after reviewing the first results, we had a training session discussing inconsistencies and agreeing on how to code different signs and symptoms.

Our results confirm that CK levels could be an accurate method to suspect DMD and contribute to the ongoing discussion supporting early screening in DMD. Keeping in mind the risk of recurrence in a family we believe that a CK test screening should be performed in early infancy. We recognize the practical challenges to make this screening feasible. However, we believe that it would be proposed and discussed with the family concurrently to routine obligatory vaccinations planned at the age of 1 year.

Early diagnosis would not only allow a prompt genetic counseling to identify carriers and to offer prenatal diagnosis, reducing the number of affected siblings [8,9] but also allow to start early intervention. This would include intervention for early neurodevelopmental difficulties that are often present in very young boys [12,13],as well as the use of nighttime splints that are often needed to prevent the development of severe ankle contractures [2] and steroid treatment [14,15].Their use is recommended by the 'plateau phase' of the disease (between the ages of 4 and 6 years) but recent advances suggest that, early treatment might be associated with slower functional decline and a better long term outcomes [14,15]. Early diagnosis will become even more important as several therapeutical approaches are currently being investigated in phase III clinical trials and, should these become available [16,17], ought be started as early as possible before muscle tissues lose the ability to self-regenerate [18] .

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Figure 1: in the graph are reported the mean ages at which the suspicion of a DMD was reached, in relation to the presenting symptom.

Table 1: in table are summarized the data analysis of ages at suspicion and diagnosis and the interval between presenting symptoms and diagnosis in the different groups of patients.

Regions of origin	**Age at first suspect**	**Age at diagnosis**	**Time for diagnosis**
Norther n=134	30 mo (0.2-84)	42 mo (1.1-101)	12 mo
Central n=115	32 mo (2-86)	39 mo (2-102)	7 mo
Souther n=135	36 mo (0.2-92)	45 mo (0.3-135)	9 mo
Presenting sign or symptom			
Whole cohort	31 mo (0.2-95 mo)	41 mo (0.3-135 mo)	10 mo
High CK/transaminases	25 mo (0-60 mo)	28.7 mo (1-81 mo)	3.7 mo
Motor delay	30 mo (10-84 mo)	48 mo (11-107 mo)	18 mo
Intellectual disability	30 mo (12-72 mo)	52 mo (13-102 mo)	22 mo
Muscle weakness	45 mo (18-92 mo)	62 mo (25-103 mo)	17 mo
Tip-toe walking	49 mo (12-95 mo)	70 mo (26-135 mo)	21 mo
Family history	27 mo (0-52 mo)	33 mo (1-69 mo)	6 mo