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

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Abstract

Despite all the advances in diagnosis and management of Duchenne muscular dystrophy over the past 50 years, the average age at diagnosis in most countries in the world around is still around 4–5 years. This retrospective study investigates 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.

Keywords: DMD; Delayed diagnosis; Survey; DMD screening

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1. Introduction

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy of childhood and affects approximately one in every 5000 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.

2. 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 evidence 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.

3. 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 Fig. 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 were raised by parents.

Following a clinical suspect, the CK level was tested in all patients. In the whole cohort, EMG was performed in 34 patients (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%) 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 thephenotype (n = 31). The diagnosis of DMD was genetically confirmed in all but two cases and in 109 cases it preceded the