International Journal of BioMedicine 3(4) (2013) 266-268

INTERNATIONAL JOURNAL OF BIOMEDICINE

PROBLEMS OF PEDIATRICS

Clinical-Diagnostic Features of Duchenne Muscular Dystrophy in Children

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Abstract

Duchenne Muscular Dystrophy (DMD) is a severe, progressive disease that affects about 1 out of every 5,000 male infants; this is the most destructive of all muscular dystrophies, which worsens rapidly. In this study, we performed a clinical analysis of 37 children with DMD. They ranged in age from 3 to 15 years, mean age being 7.8±0.48 years. The mean age at onset was 4.3±0.36 years and ranged from birth to 8 years. The biochemical examination included the determination of the serum levels of the following enzymes, AST, ALT, CPK-MM, and LDH. A genealogical analysis was conducted among 240 first-degree relatives of children with DMD. Electroneuromyography examination included registration of the biopotentials of the hand and foot muscles, measurement of the muscle response (M-wave) and the late-evoked responses. The clinical-diagnostic features of DMD in children were characterized.

Keywords: *Duchenne muscular dystrophy; children; muscle atrophy; electroneuromyography.*

Introduction

Among the different types of Muscular Dystrophies (MDs), Duchenne MD, Emery-Dreifuss MD and limb-girdle muscular dystrophy or Erb's MD are diagnosed most often in children [1,2]. Duchenne Muscular Dystrophy (DMD) is a severe, progressive disease that affects about 1 out of every 5,000 male infants[3,4]; this is the most destructive of all muscular dystrophies, which worsens rapidly [5].

DMD is caused by mutations in the dystrophin gene, which is located on the X chromosome. Due to the pattern of inheritance of the disease, only boys are affected, not girls. Therefore, the sons of females who are carriers of the disease (women with a defective gene but who express no symptoms themselves) each have a 50% chance of having the disease. The daughters each have a 50% chance of being carriers [6,7].

Despite the description of DMD being known almost a century ago, the pathogenesis, diagnosis and treatment of this disease are still unresolved [3,8]. DMD is a progressive disease, which eventually affects all the voluntary muscles and involves the heart and breathing muscles in the later stages. While the life expectancy is currently estimated to be around 25 years, this age span varies from patient to patient [6]. Recent advancements in medicine are extending the lifespan of those afflicted. Early planning of the supports required for later-life care has resulted in greater longevity in patients living with DMD.

The aim of this study was to investigate the clinical-diagnostic features of DMD in children.

Material and Methods

We performed a clinical analysis of 37 children with DMD. They ranged in age from 3 to 15 years, mean age being 7.8±0.48 years. The mean age at onset was 4.3±0.36 years and ranged from birth to 8 years. Control group included 30 healthy children of the same age range.

The biochemical examination included the determination of the serum levels of the following enzymes, AST, ALT, CPK-MM, and LDH.

A genealogical analysis was conducted among 240 first-degree relatives (parents, siblings) of children with DMD. It included all the information related to the disease in three generations. Genealogical data were collected for both parent lines through the cross-examination of both parents, and sometimes the grandparents.

Electroneuromyography examination included registration of the biopotentials of the hand and foot muscles,

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measurement of the muscle response (M-wave) and the late-evoked responses. ***Statistical analysis*** was performed using the statistical software «Statistica».

Results and Discussion

The obstetric history showed that pregnancy with anemia occurred in 32.4% of cases, with the presence of toxemia in 10.8% of cases. Also, 10.8% of the women suffered from acute *respiratory infections* during pregnancy. The exacerbation of chronic diseases during pregnancy was recorded in 2.7% of the mothers of the sick children. The average age of mothers at the time of the birth of the children with DMD was 26.0±0.85 years.

The number of the family members with DMD was 13.5%. According to our results, DMD was identified in siblings in 10.8% of the cases and in maternal uncles in 2.7% of the cases. Analysis of the medical history detected the occurrence of consanguineous marriages in 13.5% of the cases. It also was noted that, in most cases, the children were born from 2nd or 3rd (2.2±0.19) pregnancy or 2nd or 3rd (2.15±0.17) childbirth. Two children were twins, of which one twin was healthy.

Childbirth was normal in 89.2% of the cases; a speedy delivery was noted in 5.4% of the cases, a prolonged dry period in 2.7% of the cases, and an operational delivery in 2.7% of the cases. The average birth weight was 3,130±107.3g. Cord entanglement was recorded in 5.4% of the children, while 8 children were born in asphyxia.

The analysis of the development of psychomotor skills showed that the children, in most cases, revealed a delay in learning to hold up their heads and to sit up (after 9 months and more, in 51.3% of the cases). The psychomotor development was inconsistent with the age norm before the onset of the manifestations of DMD in 35.1% of the cases.

Interestingly, MD was the preliminary diagnosis in 78.4% of the cases. Only one of the 37 patients was under medical supervision, whereas the other patients were examined in the first visit.

According to the literature, DMD symptoms usually appeared between 2 and 5 years of age. The muscles of the hips, pelvic area, thighs, shoulders, and calf muscles were affected first. According to our data, the first symptoms of the disease appeared at 4.6±0.35 years.

The main clinical symptoms of DMD included, awkward manner of walking, stepping or running, toe walking; frequent falls; difficulty with motor skills (running, hopping, jumping); increased lumbar lordosis leading to a shortening of the hip-flexor muscles that affected the overall posture and manner of walking, stepping, or running; also, deformities of the chest and back (including scoliosis).

We noted symmetric pseudohypertrophy of the calf muscles. The pseudohypertrophy, was usually observed in children over 6 years. The pseudohypertrophy, however, tended to decrease with further progression of the disease. Tendo Achilles contracture occurred in 21.6% of the children.

The typical skeletal deformities included lumbar lordosis (100%), kyphoscoliosis (94.6%), scoliosis (5.4%), keeled chest or funnel chest (32.4%), and high-arched feet (100%) (Fig. 1). With the progression of DMD, an equinovarus deformity and contractures of the large joints were observed to develop. Dental problems characterized by the expansion of the jaw and a widening of the gap between the teeth were observed in 67.6% of the children.

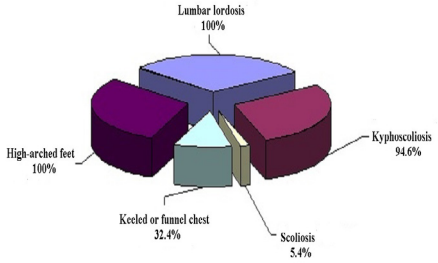

Figure 1.
Skeletal deformities among children with DMD

Initially muscle atrophy was localized in the pelvic girdle muscles, with maximum expression in the proximal lower extremity muscles. With age, a tendency for the process to spread in an upward direction towards the muscles of the shoulder girdle, back and proximal upper extremity muscles was seen.

A neurological exam revealed the characteristic "duck walk" in 97.3% of the cases, while restriction of active movements with progressive difficulty in walking was observed in 72.9% of the cases. The decline and loss of the knee reflexes and long-term preservation of the Achilles reflexes were noted. Reduced reflexes in the biceps and triceps were observed in older children. Total muscle hypotonia and reduced muscle strength, more pronounced in the legs, were observed in all the cases. The average foot muscle strength was 1.5±0.03; the average hand muscle strength was 2.2±0.07. Spastic syndrome was observed in two children and tremors in one patient.

Another distinctive feature of DMD is the combination of muscle atrophy with associated abnormalities in the cardiovascular and neuroendocrine systems as well as respiratory disorders. Cardiovascular disorders include lability of heart rate and blood pressure, deaf heart sounds, arrhythmias and the development of congestive heart failure. The ECG of patients with DMD was characterized by abnormal ventricular repolarization, bundle-branch block, and deep Q waves in the leads II, III, aVF, V6, as well as tall T waves in lead V6. The advanced stage of DMD was often associated with hypertrophic cardiomyopathy (in 51.4% of the cases) and dilated cardiomyopathy (in 27% of the cases); however, mitral valve prolapse and left ventricular myxoma occurred in 21.6% of the cases.

Neuro-endocrine disorders were found in 40.5% of the patients, including Cushing's syndrome in 53.3% of the cases and adiposogenital dystrophy in 46.7% of the cases.

Psychomotor impairments and mental retardation were observed in 35.1% of the children.

Electroneuromyography was performed in all the 25 children surveyed. In all the children, the M-response in the left and right tibialis anterior muscles was lower when

compared with the control group by almost in 3.5 times ($p<0.001$). The rate of excitation propagation along a nerve was also significantly lower than in the control group on both sides (30.6±1.9 and 31.2±2.1 *vs.* 44.8±1.4 and 45.4±1.3; $p<0.001$).

Thus, in all of the children surveyed, a primary muscle lesion of the proximal lower extremity muscles with a tendency to progression and poor reinnervation was found.

The high serum enzyme activity, particularly creatine phosphokinase (CPK), reflected the rate of myofibril degradation in the muscle fibers. Parallel with the elevated serum CPK levels, an increase in the serum concentration of the other cytolytic enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH), was noted. Thus, the CPK levels had increased by 71 times; the ALT by 15.2 times, AST by 8.4 times and LDH by 4.4 times compared with the control (n=20) (Fig. 2).

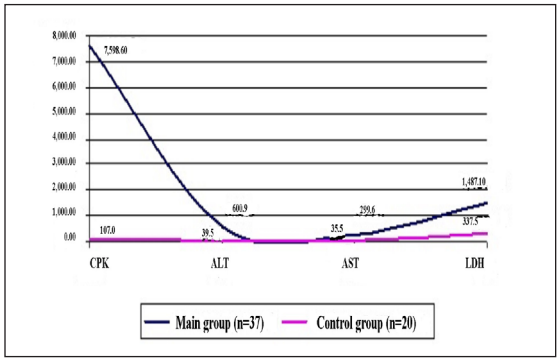

Figure 2.
Parameters of serum enzyme activity

The increased LDH level reflected the presence of hypoxia and impaired tissue respiration, which was clinically accompanied by the development of a feeling of muscle fatigue.

Conclusion

Thus, the diagnosis of DMD is a significant challenge that requires the use of special algorithms. Currently, the diagnosis of DMD is based on the data of clinical-genealogical anamnesis, clinical symptoms, as well as the results of electromyography, genetic tests, muscle biopsy and serum CPK-MM. Genetic counseling is advised if there is a family history of the disorder. DMD can be detected with about 95% accuracy by genetic studies performed during pregnancy.

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