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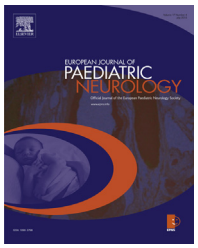

Original article

Growth and psychomotor development of patients with Duchenne muscular dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is one of the most common hereditary degenerative neuromuscular diseases and caused by mutations in the dystrophin gene. The objective of the retrospective study was to describe growth and psychomotor development of patients with DMD and to detect a possible genotype–phenotype correlation. Data from 263 patients with DMD (mean age 7.1 years) treated at the Departments of Pediatric Neurology in three German University Hospitals was assessed with respect to body measurements (length, weight, body mass index BMI, head circumference OFC), motor and cognitive development as well as genotype (site of mutation). Anthropometric measures and developmental data were compared to those of a reference population and deviations were analyzed for their frequency in the cohort as well as in relation to the genotypes. Corticosteroid therapy was implemented in 29 from 263 patients. Overall 30% of the patients exhibit a short statue (length < 3rd centile) with onset early in development at 2–5 years of age, and this is even more prevalent when steroid therapy is applied (45% of patients with steroid therapy). The BMI shows a rightwards shift (68% > 50th centile) and the OFC a leftwards shift (65% < 50th centile, 5% microcephaly). Gross motor development is delayed in a third of the patients (mean age at walking 18.3 months, 30% > 18 months, 8% > 24 months). Almost half of the patients show cognitive impairment (26% learning disability, 17% intellectual disability). Although there is no strict genotype–phenotype correlation, particularly mutations in the distal part of the dystrophin gene are frequently associated with short stature and a high rate of microcephaly as well as cognitive impairment.

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1. Introduction

Duchenne muscular dystrophy (DMD, MIM#310200) is a well-known X-linked hereditary neuromuscular disease which affects approximately 1 in 3500 live male births.[12] It is characterized by progressive muscle weakness with onset in early childhood and loss of ambulation usually early, by the second decade of life.[3] DMD has been associated with intellectual disability with a reduction of the mean intelligence quotient (IQ) by about 1 standard deviation (IQ 80–85) and mental retardation in about a third of all patients.[5] Obesity as well as underweight and short stature have also been reported.[39,21,29,9] Therapy is currently merely symptomatic.

DMD is caused by mutations in one of the largest genes of the human genome with a length of 2.3 million base pairs. The dystrophin gene encodes 7 protein isoforms: 3 full length isoforms (Dp427), which are regulated by different promotors and possess unique first exons, and 4 shorter isoforms (Dp260, Dp140, Dp116 and Dp71), which are derived from internal promotors.[28] Lack of dystrophin in muscle cells leads to progressive destabilization of the sarcolemma and deterioration of muscle fibers. Isoforms of dystrophin expressed in the CNS play a role in maturation of synapses and release of neurotransmitters,[31] a fact that can explain the CNS involvement in many patients. Especially isoforms Dp140 and Dp71 have been linked to cognitive function, while no clear correlation between genotype and motor function or anthropometric data has been reported.[23,14,24,10]

The effects of mutations on the phenotype depend mainly on whether or not they disrupt the open translational reading frame, a concept referred to as frame shift hypothesis.[25] The latter holds true for over 90% of cases.[2] Thereby, in-frame mutations result in partly functional proteins causing the milder phenotype of Becker Muscular Dystrophy (BMD), whereas out-of-frame mutations result in a truncated dysfunctional dystrophin causing DMD. There is a wide range of clinical presentations apart from the muscle phenotype in DMD patients. The objective of this retrospective data analysis was to compare anthropometric measures of DMD patients to those of a reference population and to determine the percentage presenting with psychomotor delay. The genotype was assessed and patients were subdivided according to site of mutation to determine if there is a genotype phenotype correlation and if genotype can be used as a prognostic factor for CNS involvement.

2. Patients and methods

2.1. *Patients and data acquisition*

Medical records of patients with DMD treated in the Departments of Pediatric Neurology at three German University Hospitals in Essen, Berlin, and Dresden from 1975 until 2011 were reviewed. Inclusion criteria were age over 2 years, clinical presentation suggestive of dystrophinopathy, diagnosis of DMD verified by molecular genetic testing and/or muscle biopsy analysis, and data for head circumference present in the records. Thereby, 263 boys with an age range of 2–17 years (mean 7 years 1.5 months) of largely (>90%) European origin could be included in the study.

Anthropometric measurements of the occipito-frontal head circumference (OFC), height, and weight were retrospectively collected from the medical records. Body mass index (BMI) was calculated for each patient. Additional parameters recorded were: anthropometric measurements at birth, genotype, corticosteroid therapy for 6 months or more prior to the follow up visit, age at walking as a milestone in motor development, and data depicting cognitive development. Since information on IQ was available only in a small subset of patients, the cognitive development of patients was categorized according to their schooling (normal school, special school for learning disabilities/mental retardation) in addition to their IQ values assessed through the Kaufman Assessment Battery for Children or Wechsler Intelligence Scale for Children. The number of patients for whom data was present for each variable is given in Supplemental Table 1. Steroid therapy was implemented in 29 of the 263 children at the time of data acquisition, the low percentage of treated boys being largely due to the retrospective nature of the study and in part due to the age of the children. In the steroid-treated cohort, 26 boys were treated with deflazacort 0.9 mg per kg bodyweight, whereas the remaining 3 received prednisolone 0.75 mg per kg bodyweight on a 10 days on and 10 days off scheme. Detailed data on the nutrition was not available in a representative number of DMD patients.

2.2. *Data analysis*

Growth percentile (P, percentile, e.g., P3, 3rd centile) was determined for each patient using age and sex matched reference populations: for head circumference and height,[34] for BMI,[19] and for anthropometric data at birth.[36] Genotypes were grouped according to site of mutation and subsequently according to affected isoforms of dystrophin. Motor development was rated, depending on the age when the patient learned to walk independently, as within the normal range (walking up to 18 months), delayed (walking at 18–24 months) and severely delayed (walking after 24 months of age). Patients were further categorized according to their cognitive development as within the normal range, presenting with learning disability, or presenting with intellectual disability. Frequency analyses were performed for distribution of percentiles for growth at birth and at follow up as well as for motor and cognitive development. All parameters were analyzed according to their frequency in the patient cohort and with respect to the genotype. The type of mutation and the frequency of deletions and deletion breakpoints were assessed.

3. Results

3.1. *Anthropometric measures*

Length, weight and OFC were normally distributed at birth (Fig. 1(A)) but became abnormal later in development (Fig. 1(B)). Overall almost 30% of patients with DMD exhibit a short stature (length < P3). The slowing of growth occurs early