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Long-term follow-up of motor function and muscle strength in the congenital and childhood forms of myotonic dystrophy type 1

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Abstract

The aims of this study were to explore how motor function and muscle strength change over time in the congenital and childhood forms of myotonic dystrophy type 1, further to investigate whether sex, age, disease severity or size of the mutation could explain these changes. Motor function and isometric muscle strength were evaluated at three occasions during 1999–2013 in 57 patients aged 0.7–28.9 years. Median time between first and last assessment was 11.5 years ranging from 9.6 to 13.3 years. The study shows that motor function improves during the first decade, is most pronounced during the first six years, reaches a plateau during adolescence and starts to deteriorate in the beginning of the second decade. The most predictive variables for change are age ($p < 0.0001$) and number of CTG-repeat expansions ($p = 0.0018$). Sex or disease severity grade do not predict changes in motor function. Deterioration of muscle strength is most pronounced in ankle dorsiflexors. Knowledge of development and deterioration of motor function is important for clinical decision making and for planning of interventions. This knowledge can also be of interest for patient recruitment in drug trials, since treatment effect might be easier to evaluate in the stable phases of this progressive disorder.

Keywords: Motor performance; Muscle function; Muscle weakness; Motor skills; Motor development

1. Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder caused by an unstable CTG-repeat expansion in the DM1 protein kinase gene (DMPK gene) on chromosome 19q13.3 [1]. The disorder is multi-systemic with symptoms from the muscles, eyes, heart, brain, gastrointestinal tract and endocrine system [2,3].

DM1 is classically divided into four subgroups based on age at onset and clinical symptoms: mild, classical or adult, childhood and congenital type [3]. The mild type includes the development of cataracts in middle or older age with minimum or no signs of neuromuscular symptoms. The classical or adult type features myotonia and progressive muscle weakness starting in adolescence or early adult life. The childhood type is characterised by symptoms presenting before the age of 10 and with normal development during the first year of life. Prominent features are learning disabilities, abdominal symptoms and/or muscle hypotonia. The congenital type is the most severe type with symptoms present *in utero* with polyhydramnios and decreased foetal movements, or from birth with respiratory insufficiency, sucking difficulties, facial diplegia, hypotonia and/or multiple congenital contractures [2].

DM1 is the most common neuromuscular disorder, but its prevalence is extremely variable in different regions; from 1/530 [4] to 1/50,000 [5]. Few epidemiological studies have been carried out on childhood-onset DM1, but a prevalence of 5/100,000 has been reported in western Sweden [6]. In the same study, the birth incidence of the congenital form was 5.2/100,000 compared with 6/100,000 reported by O'Brien and Harper [7].

Muscle involvement is a common feature of DM1, with muscle weakness and wasting, myotonia and, in affected newborns, severe hypotonia [8]. The muscle weakness is slowly progressive, but in children there is an increase in muscle strength during their first year of life [9]. Echenne et al. [10] showed, in a long-term evaluation of patients with DM1 in childhood, that the progression of muscle weakness varies markedly from one patient to another. In some patients, muscle function remained stable, while in others a rapid worsening occurred.

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In 1999–2001, a group of 42 children in western and southern Sweden, with congenital and childhood DM1, were investigated by a multidisciplinary team representing paediatric neurology, physiotherapy, odontology and speech pathology [11]. The results show that DM1 in children is a heterogeneous disorder with a wide spectrum of muscle involvement. The study also shows that it is possible to investigate both muscle strength and motor function in these children, but to increase our knowledge relating to the progression of the disorder, longitudinal data are needed. To our knowledge, no such prospective longitudinal study has been performed on the congenital and childhood forms of DM1. The aims of this study were therefore to explore how motor function and muscle strength change over time in the congenital and childhood forms of DM1 and further to investigate whether age, sex, disease severity or the size of the mutation could explain these changes.

2. Methods

2.1. Study population

All known children and adolescents with a confirmed diagnosis of congenital and childhood DM1, living in western and southern Sweden, were invited to participate in multidisciplinary studies on three different occasions (T_1, T_2 and T_3) during the period 1999–2013. At T_1 all invited participants were ≤18 years of age. At T_2 and T_3 all participants from previous investigations were invited together with children and adolescents ≤18 years of age who had obtained the diagnosis of congenital and childhood DM1 after previous study (T_1 and T_2).

The patients were classified into three subgroups: severe congenital, mild congenital and childhood form of DM1. The classification is based on age at onset and presenting clinical symptoms [2,11]. The children with congenital DM1 had symptoms presenting *in utero* (polyhydramnios and reduced foetal movements) or from birth (respiratory insufficiency, sucking difficulties, facial diplegia, hypotonia and/or multiple congenital contractures). The difference between severe and mild congenital DM1 was that all the children with severe congenital DM1 had a life-threatening disease at birth, requiring resuscitation and/or respiratory assistance. Children with the childhood form of DM1 had symptoms presenting before the age of 10 years, uneventful pre- and neonatal histories and normal psychomotor development during the first year of life.

All the participants had a confirmed diagnosis of DM1 with CTG-repeat expansions greater than 40 in the myotonic dystrophy protein kinase gene (DMPK) located on chromosome 19 (19q13). The mean size of CTG-repeat expansion was 1167, ranging from 130 to 2400. For the size of the CTG-repeat expansions in different DM1 forms, see Fig. 1. The size of the CTG-repeat expansion was investigated at the Department of Clinical Genetics, Sahlgrenska University Hospital, Sweden, according to a method described earlier [11].

Two cohorts were used for the analysis of motor function; Cohort 1 with measurements from all three occasions (T_1, T_2 and T_3) and Cohort 2 with measurements from two occasions (T_2 and T_3); see Fig. 2.

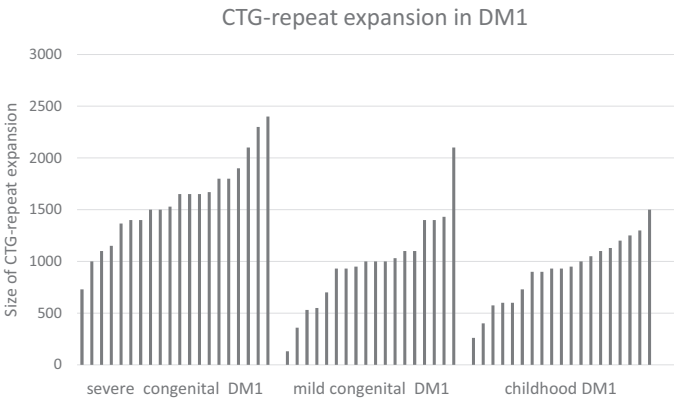

Fig. 1. Number of CTG-repeat expansions in severe congenital myotonic dystrophy type 1 (DM1) (n = 20), mild congenital DM1 (n = 18) and childhood DM1 (n = 19).

Ethical approval was granted by the Ethics Committees at the Medical Faculties at Gothenburg University and Lund University, Sweden. Informed consent to participate was obtained from caregivers and patients.

2.2. Assessment of motor function

Motor function was assessed using a scale, the Hammersmith Motor Ability Scale, designed by Scott et al. [12]. Twenty movements were assessed, including head-lifting, rolling, sitting up, long-sitting, getting up from a chair, standing up from lying, standing, heel-standing, standing on toes, one-leg standing, hopping and ascending/descending stairs. Performance is scored according to a three-point scale: 0 (unable); 1 (needs self-reinforcement); and 2 (succeeds) and with a maximum motor function score (MFS) of 40. The performance was videotaped and all the assessments were made by the same physiotherapist (AKK). The scale was previously used at T_1 and was found to be successful in monitoring motor function in children and adolescents with congenital and childhood DM1, and the method was therefore used for the follow-ups [11].

2.3. Measurement of isometric muscle strength

Isometric muscle strength was measured in the ankle dorsiflexors, the wrist dorsiflexors and the knee extensors with an electronic handheld myometer (adapted Chatillon, Axel Ericson Medical AB, Göteborg Sweden). A standardised method was used for the position of the patient, the application of the myometer and the instructions to the patient [13]. An isometric contraction of at least two to three seconds was required and the value of the peak force (in newton) was recorded. The best of three values obtained on the non-dominant side was compared with reference values [13,14]. All measurements were made by the same physiotherapist (AKK). The method was previously used at T_1 and was found to be successful in monitoring muscle strength in children and adolescents with congenital and childhood DM1 and the method was therefore used for the follow-ups [11].

2.4. Statistical analysis

Predictive variables of change over time in MFS were calculated from measurements collected at T_1, T_2 and T_3