Doctoral Thesis for the degree of Doctor of Medicine, the Sahlgrenska Academy,
University of Gothenburg, Sweden

Congenital and Childhood Myotonic Dystrophy type 1 -the impact on central nervous system, visual and motor function

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Göteborg 2009

Layout: Ann-Sofie Petersson, Fotografik,
Drottning Silvias Barn- och Ungdomssjukhus

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University of Gothenburg

ISBN: 978-91-628-7758-3
Printed by Geson Hylte Tryck, Gothenburg, Sweden 2009

To Karl-Johan
Carl-Marcus, Elisabeth, Gabriel, Ellenor and Sakarias
with love

"You, dear children, are from God and have overcome them, because the one who is in you is greater than the one who is in the world"

1 John 4:4

Abstract

Background and aims: Myotonic dystrophy type 1 (DM1) is an autosomal dominant multisystemic disorder, caused by an expanded CTG repeat on chromosome 19. The disorder can present both in children and adults. The overall purpose of this study was to gain further insight on neuropsychiatric and neurocognitive aspects, vision and motor function in individuals with congenital and childhood DM1. Further to correlate the size of the CTG repeat expansion, inheritance and the onset form with the clinical findings.

Methods: Fifty-nine children and adolescents with DM1 were included. Based on age at onset and presenting symptoms, the individuals were divided into four groups; severe and mild congenital, childhood and classical DM1. In study I and IV, the results were compared with healthy age and gender-matched controls. Measurement of muscle strength, motor function and contractures was performed. According to the DSM-IV criteria, neuropsychiatric diagnoses were assigned on the basis of all available information. The intellectual level was assessed using the Griffiths Mental Developmental Scale or the Wechsler Scales, and adaptive skills using the Vineland Adaptive Behaviour Scales. The ophthalmological examination included best corrected visual acuity, refraction, slit-lamp biomicroscopy, indirect ophthalmoscopy and flash visual evoked potentials (VEP).

Results: Motor function and muscle strength was significantly reduced in children with DM1 compared with healthy controls, but there was great variation regarding the degree of muscle weakness. Forty-nine percent had an autism spectrum condition (ASC) and autistic disorder was the most common diagnosis, present in 35% of the affected individuals. A large majority of the participants had learning disability, usually in the moderate to severe range. Almost all participants showed poor adaptive skills. The ophthalmological study shows a higher prevalence of low visual acuity and refractive errors compared with the controls. No true cataract was found. Subtle non-specific fundus changes were present in addition to VEP pathology. The frequency of ASC increased with increasing CTG repeat expansions. Motor function, intellectual level, visual acuity and adaptive skills presented lower values in individuals with larger CTG repeat expansion size. Maternal inheritance had a negative impact on intellectual and adaptive functioning. The more severe the form of DM1, the more reduced the motor function and visual acuity, and the higher the frequency of ASC and learning disability.

Conclusions: DM1 in childhood shows great variability regarding symptoms and age at onset. At the individual level, the size of the CTG repeat expansion cannot predict the DM1 form. No clear genotype-phenotype correlations were found, although the largest expansions were present in the severe congenital group. In everyday life, it appears that individuals with DM1 primarily suffer from their CNS-related symptoms, such as cognitive deficits, neuropsychiatric problems and visual dysfunctions, rather than their neuromuscular symptoms.

Key words: *myotonic dystrophy type 1, children, muscle strength, motor function, autism spectrum conditions, learning disability, adaptive skills, visual impairment, hyperopia*

ISBN: 978-91-628-7758-3 **Gothenburg 2009**

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Am J Med Genet B Neuropsychiatr Genet. 2008;147B:918-26

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Dev Med Child Neurol 2009; in press

IV. Ekström A-B, Sjöström A, Tulinius M, Aring E.Visual function in Congenital and Childhood Myotonic Dystrophy Type 1.
Submitted

Abbreviations

AD	Autistic Disorder
ADI-R	Autism Diagnostic Interview-Revised
ALC	Autistic-like Condition
APA	American Psychiatric Association
ADHD	Attention Deficit/Hyperactivity Disorder
AS	Asperger Syndrome
ASC	Autism Spectrum Conditions
BCVA	Best Corrrected Visual Acuity
CELF	CUG-BP- and ETR-3-like factors
CNS	Central Nervous System
COND	Childhood Onset Neuropsychiatric Disorders
CTG	Cytosine Thymidine Guanine
CUG	Cytosine Uracil Guanine
DM1	Myotonic Dystrophy type one
DMPK	Myotonic dystrophy protein kinase
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
FSIQ	Full-Scale Intelligence Quotient
FTF	The Five to Fifteen questionnaire
IQ	Intelligence Quotient
LD	Learning Disability
logMAR	logarithm of the Minimal Angle of Resolution
MBLN	Muscleblind-like protein
mRNA	messenger RNA
PDD-NOS	Pervasive Developmental Disorder, Not Otherwise Specified
PIQ	Performance Intelligence Quotient
RNA	Ribonucleic acid
SCQ	Social Communication Questionnaire
SE	Spherical Equivalent
TD	Tourette's Disorder
VA	Visual acuity
VABS	Vineland Adaptive Behaviour Scales
VEP	Visual Evoked Potential
VI	Visual Impairment
VIQ	Verbal Intelligence Quotient
WAIS-III	Wechsler Adult Intelligence Scale-Third Revision
WHO	World Health Organization
WISC-III	Wechsler Intelligence Scale for Children-Third Revision
WPPSI-R	Wechsler Primary and Preschool Scale of Intelligence-Revised

Introduction and background

During 1995-1997, the National Swedish Board of Health and Welfare funded a survey of children and adolescents with neuromuscular disorders in the western health care region of Sweden. The results of the survey showed that more knowledge on DM1 in childhood was needed. In parallel with this survey, the dentist Monica Engvall had performed studies on adults with DM1, showing impaired orofacial function and inadequate dental care. Her studies gave rise to the question of whether these problems could be inhibited or delayed during childhood. Our multidisciplinary research work was undertaken as an effort to improve the knowledge of childhood onset DM1.

To a neuropediatrician working with children with neurodevelopmental disorders, DM1 is a most challenging disorder due to the multiorgan involvement, the progressive course, the affection of various members of the same family and, last but not least, the complex pathogenetic mechanisms. The goal of rehabilitation is that children and adolescents with impairments should be able to live as independently as possible, with the same rights, opportunities, responsibilities and obligations as the rest of society. (The Swedish National Board of Health and Welfare. Art. No 2006-114-24). To optimise the rehabilitation efforts for children and adolescents with DM1, specific knowledge on the different aspects of the disorder and their consequences is needed. This thesis focuses on classification and the impact on motor, visual and cerebral function in patients with congenital and childhood DM1.

Historical background

DM1 can be traced back as far as the Egyptian pharaoh Akhenaton (1380-1362 BC), the predecessor of Tutankhamen and the husband of Nefertiti (Albretsen and Albretsen, 1999, Cattaino and Vicario, 1999). Statues and reliefs of Akhenaton show an unhealthy man with elongated face, ptosis, half-open mouth, gynecomastia, prominent abdomen and distal limb atrophy, all suggestive of DM1 (Figure 1). The similarity in the clinical appearance of the members of this royal family suggests a disease with autosomal dominant inheritance that may have caused the end of the royal bloodline.

Figure 1 *The Egyptian pharaoh Akhenaton (1380-1362 BC)*

Another famous historical person with DM1 (the diagnosis confirmed by DNA analysis in a late relative) is the impressionist painter Claude Monet (1840-1926). He was diagnosed with cataract in his 60s and had progressive deviant perception of colour, shape and perspective maybe as early as from 30 years of age, with wonderful consequences for his art (Lane et al., 1997, McLellan, 1996).

DM1 was first delineated as a distinct disorder in 1909 by the reports by Steinert (Steinert, 1909) and Batten and Gibb (Batten and Gibb, 1909), although several reports of cases classified as atypical Thomsen´s disease (atypical mytonia congenita), later recognised as DM1, had been published in the literature since the late 19th century. During the past 100 years, the knowledge of clinical features, inheritance and pathophysiology has increased, although there are still many puzzling issues left to be solved, especially in the field of pathophysiology. In addition, the knowledge of childhood forms of myotonic dystrophy type 1 (DM1) is more limited than of the adult forms. The congenital form was not recognised until 1960, when it was described in six individuals by Vanier (Vanier, 1960). Another study presented children with DM1 but without congenital presentation (O'Brien and Harper, 1984); however, the accepted classification of the childhood form was first stated by Koch and co-workers (Koch et al., 1991).

The autosomal dominant inheritance of the disorder was recognised early. There may be a variation in the clinical expression of the disease with exclusively cataracts, to the fully developed neurological disorder in the same family. This observation made the German ophthalmologist Fleischer introduce the concept of anticipation (Fleischer, 1918). The specific phenomenon of anticipation was finally confirmed by Höweler (Höweler et al., 1989) and is defined as progressively earlier onset of the disease with increasing severity in successive generations within the same family.

When the molecular basis for the disorder was identified in 1992, the phenomenon of anticipation was elucidated (Aslanidis et al., 1992, Brook et al., 1992, Buxton et al., 1992, Fu et al., 1992, Harley et al., 1992, Mahadevan et al., 1992). The mutation responsible for DM1 is caused by an expansion of a DNA sequence, the trinucleotide CTG, in the gene coding for the enzyme myotonic dystrophy protein kinase (DMPK) on chromosome 19. The situation was complicated by the identification in 1994 of a second multisystemic disorder similar to this classic form of myotonic dystrophy, but without a CTG expansion (Ricker et al., 1994, Thornton et al., 1994a). This syndrome was initially referred to as proximal myotonic myopathy (PROMM) or proximal myotonic dystrophy (PDM), but the nomenclature was changed to DM2 in 1999. The mutation responsible for DM2 is a CCTG repeat expansion in the first intron of zinc finger protein 9 (ZNF9) on chromosome 3q21 (Liquori et al., 2001, Ranum et al., 1998, Ricker et al., 1999). DM1 and DM2 show similarities with regard to the clinical phenotype with some exceptions; no congenital presentation or mental retardation has been described in DM2. How mutations in two unrelated genes in different parts of the genome could give similar multisystemic features

was a puzzling phenomenon until the "gain of function" RNA mechanism as the common denominator in both types of myotonic dystrophy was found (Liquori et al., 2001, Ranum and Day, 2004).

Pathogenesis

DM1 is caused by an expanded CTG trinucleotide repeat located in a 3′ intron,; i.e., in an untranslated region of the DMPK gene on chromosome 19 (19q13.3) No other mutations are found and DM1 was the first dominantly inherited disease found to be caused by an untranslated repeat expansion (Brook et al., 1992, Fu et al., 1992).

Unaffected individuals have approximately 5-35 CTG repeats and expansions greater than approximately 55 copies are associated with the disease. The CTG expansions are highly unstable in the germ-line and most intergenerational transmissions result in a progressive increase in the repeat length in successive generations (i.e., anticipation) (Harper et al., 1992). The repeat length varies from 50 in the mild form to several thousands in the congenital form, the latter inherited maternally in most cases (Zeesman et al., 2002). The number of CTG repeats is broadly correlated with age at onset and severity of the disorder, but caution is warranted in predicting disease severity on the basis of the CTG repeat number in separate individuals (Marchini et al., 2000, Salehi et al., 2007). In addition to the germ-line instability, the triplet repeat expansion shows somatic mosaicism, implying genetic instability with variable repeat size in different tissues of affected individuals, as well as increasing expansion length with increasing age (Jansen et al., 1994, Thornton et al., 1994b).

Three distinct models have been put forward to explain how a triplet repeat expansion in a non-coding region of a gene could cause DM1: 1) haploinsufficiency of DMPK, 2) altered expression of neighbouring genes and 3) RNA toxicity (Figure 2). The DM1 models reveal a complex picture where the three separate mechanisms appear to contribute simultaneously to the onset of each particular DM1 clinical feature (Kaliman and Llagostera, 2008).

1) Haploinsufficiency is defined as the occurrence of only a single functional copy of a gene with the other copy inactivated by mutation. The single functional copy of the gene does not produce enough of the gene product; a protein. In DM1, the CTG expansion is transcribed into mRNA containing CUG expansions and the level of DMPK mRNA is not decreased (Krahe et al., 1995), but the mRNAs are retained in nuclear foci inhibiting nucleocytoplasmatic transport (Davis et al., 1997, Taneja et al., 1995). Subsequently, there is a decrease in the translation to DMPK protein in the cytoplasm (Furling et al., 2003, Furling et al., 2001b). Haploinsufficiency may contribute to the DM1 phenotype especially in skeletal and cardiac muscles but does not account for all the clinical features of the disease (Jansen et al., 1996, Reddy et al., 1996).

2) The expanded CTG mutation may cause chromatin condensation and alter the transcription of either one of three genes in the DM1 locus: the DMPK itself, the

adjacent upstream **DMWD (**dystrophia myotonica-containing WD repeat motif) and the downstream **SIX5** (formerly DMAHP) genes (Frisch et al., 2001, Klesert et al., 1997, Otten and Tapscott, 1995, Thornton et al., 1997). SIX5 mRNAs are expressed in tissues such as skeletal muscle, the heart, eye and brain. The DMWD is expressed in the brain and testes. Like the first model, this second model explains some but not all the clinical features of the disease.

3) RNA toxicity is considered the main pathogenic process in DM1. The CTG expansion is transcribed into mRNA containing CUG expansions and retained in nuclear foci (Davis et al., 1997, Taneja et al., 1995). The longer the CUG repeat expansion, the more likely it is that formation of highly stable hairpins occurs (Napierala and Krzyzosiak, 1997). Shorter expansions form single strands of CUG repeats. The mutant RNA disrupts the regulation of alternate splicing of mRNA (Mankodi et al., 2000, Tapscott, 2000). RNA splicing is the process in which introns are removed from pre-mRNA, the primary transcript, and exons are joined together. Selection of which exons to include in the mature mRNA makes the process flexible and a single gene can produce multiple mRNA. The splicing process is firmly regulated by regulatory proteins. Changes in the concentration of these regulatory proteins influence the frequency of inclusion or skipping of a particular exon (Black, 2003). Essential to the pathogenesis of spliceopathy in DM1 is that developmentally regulated splicing events fail to switch from an embryonic to an adult splicing pattern, resulting in aberrant expression of embryonic isoforms that are unable to support the functional requirement of adult tissue. The splicing of the pre-mRNA is controlled by splicing of regulatory proteins from two antagonistic factor families, the muscle blind-like (MBNL) and the **C**UGBP1/**E**TR-3-**l**ike **f**actors (CELF) (Ho et al., 2004, Kanadia et al., 2003, Philips et al., 1998, Timchenko et al., 1996a, Timchenko et al., 1996b).

The muscle blind-like (MBNL) family binds to large CUG expansions (Kino et al., 2004, Miller et al., 2000) and are sequestered in DM1 skeletal muscle and neuronal ribonuclear foci (Jiang et al., 2004, Mankodi et al., 2003, Mankodi et al., 2001). The other splicing regulatory protein, the CUG-BP1, binds to the single-stranded CUG expansions which remain soluble in the nucleoplasm and, unlike MBLN, CUG-BP1 does not co-localise with nuclear foci (Fardaei et al., 2001, Jiang et al., 2004, Junghans, 2009, Mankodi et al., 2003). The binding of MBLN and CUG-BP1 to the CUG expansion causes a downregulation of the former and upregulation of the latter protein with improper splicing of pre-mRNA as a consequence (Timchenko et al., 2001).

Transcripts with less expanded repeat show less nuclear retention, indicating that the length of the CUG repeats determines nuclear foci formation (Davis et al., 1997). Mutant DMPK transcripts containing expanded CUG repeats are detected as large nuclear foci as well as multiple complexes of smaller sizes found throughout the cytoplasm and in nuclei. Two stages of DM1 development have been suggested (Mahadevan et al., 2006) (Dansithong et al., 2008, Junghans, 2009, Timchenko,

2006). In the first stage, MNBL binds to pathogenic CUG repeats and reduces their toxicity, representing a protective mechanism. When a significant portion of MBNL is recruited into foci, CUG repeats bind to CUG-BP1, leading to increased CUG-BP1 levels and development of DM1 symptoms.

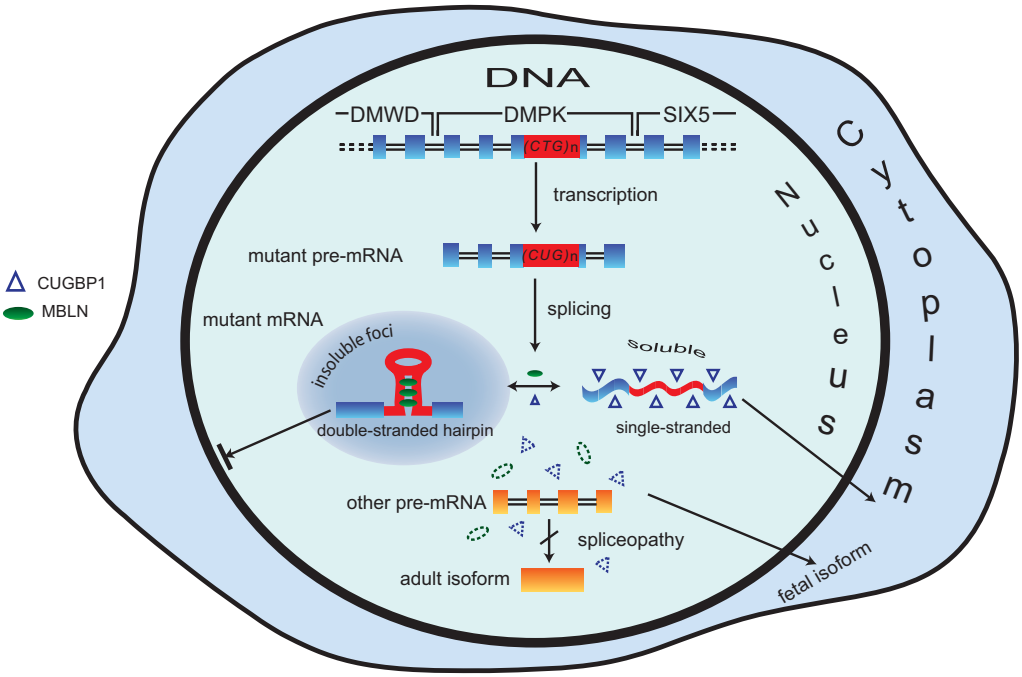

Figure 2 Model of RNA pathogenesis
The CTG expansion is transcribed into mutant mRNA which is retained in nuclear foci inhibiting nucleocytoplasmatic transport. Alternate splicing of other pre-mRNA's and the switch from an embryonic to an adult splicing pattern is disrupted. The splicing of the pre-mRNA is controlled by the regulatory proteins MBLN and CUGBP. CUGBP binds to the single-stranded CUG expansions which remain soluble throughout the cytoplasm and in the nuclei. MBLN binds to the double-stranded CUG expansions, forming "hairpins" in insoluble nuclear foci.

In DM1, more than 15 splicing alterations have been found but, most certainly, there are many more that have not yet been described (Jiang et al., 2004, Lin et al., 2006, Osborne and Thornton, 2006, Ranum and Cooper, 2006). The following genes have been found with altered splicing in skeletal and cardiac muscles: cardiac troponin T (TNNT2), insulin receptor (IR), muscle-specific chloride channel (ClC-1), myotubularin-related protein 1 (MTMR1), fast skeletal troponin T (TNNT3), ryanodine receptor (RyR), and sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2). Misregulated alternative splicing of the Tau, NMDAR1 (N-methyl-D-aspartate receptor 1) and APP (Amyloid Precursor Protein) has been described in the

brain. Additional molecular mechanisms influence the DM1 phenotype. Aberrant methylation at the DM1 locus, as well as increased levels of mutant transcripts in skeletal muscles, occurs only in congenital DM1 (Filippova et al., 2001, Steinbach et al., 1998).

Epidemiology

The DM1 mutation worldwide is supposed to originate from one or a few ancestors, as all disease chromosomes include the same insertion allele in intron 8 of the DMPK gene (Neville et al., 1994). The mutation occurred in human history recently after a population had moved out of Africa. The disorder is practically absent in southern and central Africa, less prevalent in Southeast Asia, and more common in western Europe, Japan, USA and Canada (Emery, 1991). Due to the founder effect; i.e., the loss of genetic variation when a new colony is formed by a very small number of individuals from a larger population, the prevalence reported varies between different populations with remarkably high numbers from specific regions, such as Norrbotten, Sweden, in the 1960s, where the prevalence was reported to be 36.5/100 000 (Rolander and Floderas, 1961) or Quebec, Canada, with a prevalence of 189/100 000 (Mathieu et al., 1990), in contrast to the worldwide prevalence of approximately 1-10/100 000. Few epidemiological studies have been carried out on childhood onset DM1, but a prevalence of 5/100 000 has been reported (Darin and Tulinius, 2000). In the same study, birth incidence of congenital DM1 was 5.2/100 000 and 6/100 000 has been reported in Great Britain (O'Brien and Harper, 1984). Individuals with congenital DM1 contribute more to incidence than prevalence, due to the increased mortality during the neonatal period. The frequency of childhood DM1 is most certainly underestimated. In families with DM1, the mutation will gradually be lost, as individuals with congenital DM1 do not give birth to children. Within the normal population, there will be individuals with slightly expanded CTG repeat sizes (20-35 repeats) and due to anticipation, the repeat expansion will gradually increase on transmission giving rise to new families with the disorder. The disorder may be discovered for the first time in a family when a previously undiagnosed mother gives birth to a child with congenital DM1.

Clinical features

The term myotonic dystrophy is in itself disputable. The myotonia in DM1, at least in the congenital and childhood forms, is not a prominent feature, compared with the other ion channelopathies such as myotonia congenita or Scwartz-Jampel syndrome. Furthermore, to classify DM1 as a muscular dystrophy is not warranted as dystrophic features are not the major finding in the phenotype. It would be more reasonable to describe and classify DM1 amongst the trinucleotide repeat disorders.

DM1 can be divided into four main categories, each presenting specific clinical features and management problems: (1) congenital; (2) childhood; (3) classical/ adult onset and (4) late onset/asymptomatic (Harper, 2001b, Koch et al., 1991). No absolute distinction exists between these categories, which rather form a continuum (De Die-Smulders, 2004).

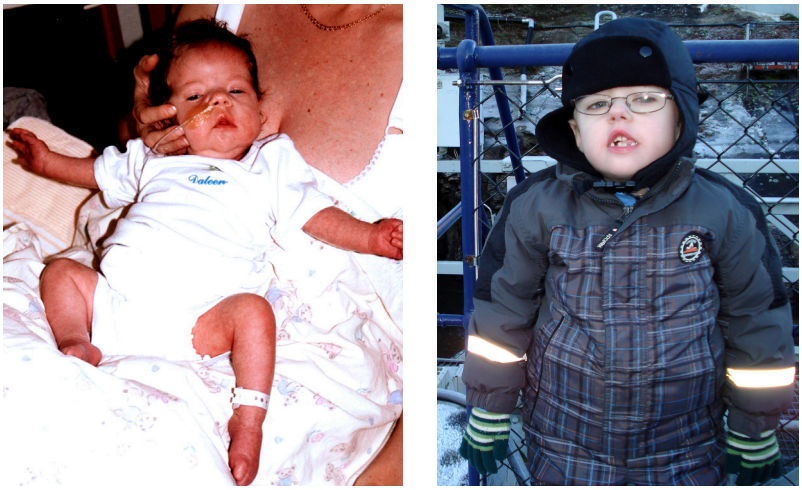

Figure 3 *Boy with severe congenital DM1 in the neonatal period and at 5 years of age*

Congenital DM1:
Patients with congenital DM1 present *in utero* with reduced foetal movements and polyhydramniosis reflecting reduced foetal respiratory movements and swallowing. Premature delivery is common. In the immediate postnatal period there is a variable degree of hypotonia. The most severely affected individuals exhibit severe hypotonia, immobility and hyporeflexia, and fail to establish spontaneous respiration. Sustained respiratory distress due to intercostal muscle weakness and/or pulmonary hypoplasia requires assisted ventilation. On X-ray there will be signs of thin ribs and raised right hemidiaphragm. Most children survive nowadays with modern neonatal care and, in most cases, the respiratory problems decrease as the child grows older (Campbell et al., 2004). The duration of mechanical ventilation has been regarded as guidance for the prognosis (see below).

Furthermore, the neonate demonstrates a characteristic facial weakness (facial diplegia) with tented upper lip and mild ptosis. Weakness is also present in the jaw and palate, resulting in poor sucking and swallowing. Due to slow gastrointestinal motility together with respiratory distress and risk of aspiration, nasogastric tube feeding is required in many children. Congenital hip luxation and flexion contractures may be present with talipes equinovarus or, with severe presentations, arthrogryposis multiplex congenita involving several large joints. Other features, such as atrial septal defect (ASD) and patent ductus arteriosus (PDA), hematomas of the skin, oedema, undescended testes, inguinal hernias, raised head circumference with ventriculomegaly and sometimes even obstructive hydrocephalus requiring shunt operation, have also been described. Perinatal

complications are most likely the cause of the obstructive hydrocephalus.
Most individuals survive the neonatal period and the hypotonia improves gradually. Subsequently, after achieving motor functions and muscle strength during childhood and early adolescence, motor function will deteriorate. Myotonia is seldom present before school age. Scoliosis and contractures may occur and eventually require orthopaedic surgery. Multisystemic features similar to the adult form such as cardiac and gastrointestinal abnormalities arise in late childhood or adolescence. In parallel with delayed motor development, learning disability (LD) becomes obvious and the vast majority requires special schools for pupils with LD.

Figure 4 *Boy with childhood DM1 and his mother with classical DM1*

Childhood DM1:
In contrast to the congenital form, childhood DM1 is characterised by an uneventful pre- and postnatal history and a normal development during the first year of life. Symptoms present between one and ten years of age with increasing problems such as failure to thrive accompanied by abdominal symptoms, variable degree of LDs and muscle hypotonia including clumsiness (de Die-Smulders, 2000, Koch et al., 1991). Weak facial expression is present, but without the characteristic tented upper-lip appearance of the congenital form. Indistinct speech is common and some have swallowing problems. School difficulties during the early years may be present, and language delay and/or school difficulties are sometimes the cause of the first medical consultation (Echenne et al., 2008).
Presentation with early cardiac involvement with conduction abnormalities from approximately 10 years of age may occur (Bassez et al., 2004). Annual electrocardiograms should therefore be included in the routine management. In adolescence, myotonia is frequently present and symptoms of distal muscular weakness may evolve. In the second decade of life, individuals with childhood onset DM1 show many of the symptoms seen in the adult onset form.

Classical/adult onset DM1:
Classical DM1 is the most common category of DM1 with début of symptoms in adolescence or early adult life. The core symptoms are characteristic muscle involvement with facial weakness, ptosis, distal weakness and myotonia. The initial presentation could relate to other organs rather than to muscle weakness or myotonia. Such atypical presentations include cardiac rhythm abnormalities, excessive daytime sleepiness, irritable bowel syndrome, premature balding in males and, for women, the birth of a congenitally affected child. There is an insidious progression of the muscle weakness and many become severely disabled by the fifth and sixth decades. Respiratory insufficiency due to weakness of the diaphragm and respiratory muscles, aggravated or precipitated by aspiration and chest infections, are common. Sudden death is probably attributable to cardiac rhythm disorders and is not entirely preventable by pacemaker insertion.

Late onset/asymptomatic DM1:
Late onset DM1 presents with cataract in middle or older age but only rarely with signs of muscle weakness or myotonia. Besides mild verbal memory dysfunction no major cognitive impairment is detected (Modoni et al., 2004). The main reason for identifying a transmitting grandparent, with respect to genetic counselling, is to identify other affected family members, as the individuals themselves will not likely develop any significant complications of DM1 other than cataract.

Muscle involvement in DM1
Skeletal myogenesis is a firmly regulated developmental programme that directs muscle precursor cells (myoblasts) to differentiate into muscle fibres. This process occurs in adults to replace lost muscles fibres as well in the embryo to produce muscles fibres in the first place. Fibres mature into several different types and exhibit plasticity as muscle fibers can adapt to changing demands by changing their size or fibre type composition (Scott et al., 2001). The satellite cells in muscles are the tissue-specific muscle stem cells. These cells are activated by muscle stress or damage to form new myotubes that are incorporated into the damaged myofibers (Seale and Rudnicki, 2000). The abnormal retention of mutant RNA in nuclear foci in myoblasts and myotubes in congenital DM1 muscle cells may modify the myogenic programme, as a reduction in the proliferative capacity of cultured congenital DM1 myoblasts is accompanied by a decrease in the number of satellite cells (Furling et al., 2001a). Modification on the myogenic programme could also be the consequence of altered splicing of Myotubularin-related 1 (MTMR1) mRNA as abnormal MTMR1 transcript in differentiated congenital DM1 muscle cells has been demonstrated (Buj-Bello et al., 2002). Foetal muscle development is affected in the congenital form of DM1 with severe hypotonia present from birth. The histopathological features in muscle biopsies from neonates with congenital DM1 have revealed small, immature muscle fibres and increased numbers of satellite cells (Farkas-Bargeton et al., 1988, Sarnat and Silbert, 1976). Normally, the number of satellite cells decreases during muscle development as the satellite cells are incorporated into myofibres.

The severe hypotonia in the newborns with congenital DM1 causes characteristic facial weakness with tented upper lip, ptosis and wasting of temporal muscles. Sucking difficulties due to facial weakness, respiratory distress and dysmotility often require initial nasogastric tube feeding. The severe oral motor impairment during the neonatal period improves gradually. The speech pathologist in our research team has assessed a cohort of individuals with congenital and childhood DM1. All had impaired facial expression, moderately or severely reduced intelligibility and, in a majority of individuals, moderate or severe impairment of lip motility, tongue motility and lip force. The families reported problems with chewing, swallowing and drooling. Oral motor dysfunction was most prominent in congenital DM1 (Sjogreen et al., 2007). Over a period of four years, progression of the orofacial muscle weakness was seen in many individuals and often began before puberty (Sjogreen et al., 2008). Swallowing problems as well as mild facial weakness were also reported in childhood DM1 by other researchers (De Die-Smulders, 2004).

As muscle strength gradually improves, most children achieve independent walking (Echenne et al., 2008, Roig et al., 1994). In the long run, children will gradually develop progressive muscle weakness, but it is still unclear at what age improvement in muscle strength turns to deterioration, although Hageman has proposed the age around puberty (Hageman et al., 1993).

The pattern of muscle weakness in adults includes facial weakness, ptosis and weakness of the sternocleidomastoid and distal limb muscles (Harper, 2001b). Weakness of ankle dorsiflexors causes foot drop. The facial weakness is typical and an early feature, but rarely noted by the patient. Weakness of neck flexion is also an early sign, often noticeable already in childhood (De Die-Smulders, 2004), and patients may notice problems with lifting their head from the pillow or a tendency for the head to fall backwards during acceleration of the vehicle in which they are travelling.

Myotonia; slow relaxation of the muscles after voluntary contraction, is another typical feature in patients with DM1. It is the clinical symptom of delayed relaxation of the muscle due to repetitive and inappropriate opening of the sodium channels. Clinical myotonia is never present in the first year of life, and even electrical myotonia is uncommon, but appears later in childhood.

Muscle pain may be present, but is not a major complaint in childhood, although some children may experience pain after excessive exercise.

Brain lesions in DM1

The normal developmental process of the brain includes formation of the neural tube, formation of prosencephalon, neuroepithelial cell proliferation and migration, neuroglial differentiation, organisation of the cortical circuit network and finally myelination. At what stage of brain development an insult occurs determines the outcome of the pathological process (Suzuki, 2007).

Histopathological studies on cerebral changes in DM1 include findings from only a few children, mainly with the congenital form. The data presented vary from a normal architecture (Young et al., 1981) to a wide range of abnormalities. Disturbed neuronal migration with neurons present in the subcortical white matter, abnormal cortical layering, polygyria and leptomeningeal neuroglional heterotopia have been described. Other abnormalities such as periventricular leukomalacia, ventriculomegaly, olivary dysplasia, small tegmentun, defects of the septum pellucidum, corpus callosum hypoplasia as well as hypoxic-ischaemic encephalopathy and basal ganglia abnormalities have been reported (Endo et al., 2000, Garcia-Alix et al., 1991, Hageman et al., 1993, Rosman and Kakulas, 1966, Sarnat and Silbert, 1976).

Brain imaging studies in children with DM1 have revealed a high prevalence of brain abnormalities, such as ventriculomegaly, mild atrophy of the frontal cerebral cortex, hypoplasia of the corpus callosum, brainstem hypoplasia, neuronal migrational disturbances and cerebellar abnormalities (Bergoffen et al., 1994, Di Costanzo et al., 2002, Garcia-Alix et al., 1991, Hashimoto et al., 1995, Kuo et al., 2005, Martinello et al., 1999, Nakagawa et al., 1994, Regev et al., 1987). With rare exceptions, all the studies present findings from congenital DM1 and neuroimaging studies on large numbers of patients with childhood DM1 are lacking. The ventriculomegaly already present at birth points to a prenatal developmental origin (Kuo et al., 2005). Obstructive hydrocephalus has been reported in rare cases (Rettwitz-Volk et al., 2001, Rutherford et al., 1989). Another recurring finding of hyperintensity of the white matter is shown in several studies (Di Costanzo et al., 2002, Hashimoto et al., 1995, Kuo et al., 2005, Tanabe et al., 1992). The origin of these often periventricular white matter lesions is unclear. One explanation may be delayed myelination, another perinatal asphyxia (Tanabe et al., 1992).

Although CNS abnormalities have been shown in childhood-onset DM1, the connection to the pathogenic mechanisms remains unclear. The early presence of mutant transcripts may alter the expression of genes regulating later stages of brain development (Modoni et al., 2004). This hypothesis is supported by the fact that the expression of the DMWD protein in mice increases during the early neonatal stages in neurons localised in central nervous system areas with a high density of synaptic connections (Westerlaken et al., 2003). If expression of the DMWD protein is decreased in DM1, the formation of neuronal networks will be compromised.

Splicing of tau is tissue and cell-specific and is highly regulated during development and cell differentiation. Splicing alterations of tau pre-mRNA with reduced expression of exons 2, 3, 6 and 10 in DM1 are known so far. Further evidence is needed to determine whether DM1 could be regarded as a so-called tauopathy (Leroy et al., 2006, Sergeant et al., 2001). Recently published data showed increased levels of T-tau in the cerebrospinal fluid in patients with classic DM1 but no correlation with CTG repeats was found (Winblad et al., 2008).

Learning disability

Learning disability (LD) is characterised by significant limitations in both intellectual functioning and adaptive behaviour. According to the DSM-IV, LD is defined as A: Significantly subaverage intellectual functioning: an IQ approximately 70 or below on an individually administered IQ test (for infants, a clinical judgement of significantly subaverage intellectual functioning); B: Concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected for his or her age by his or her cultural group) in at least two of the following areas of communication; self-care, home-living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety; and C: The onset is before 18 years of age (APA, 1994). In the thesis, the following definition of intelligence levels was used: Normal IQ $\geq$85; Borderline IQ: 70-84, Mild LD: 50-69, Moderate LD: 35-49, Severe LD: 20-34 (APA, 1994).

The prevalence of LD, defined as two standard deviations below the mean, is approximately 2.5% and 85% of the population with LD is in the mild range (APA, 1994).

In the US, the widely and long-used term mental retardation is increasingly being replaced by intellectual disability. The renaming of the American Association on Mental Retardation (AAMR) in 2006 to the American Association on Intellectual and Developmental Disabilities—AAIDD, reflects this terminology change (Schalock et al., 2007). In the UK, the term LD is used.

Neuropsychiatry

Childhood onset neuropsychiatric disorders (COND) with their onset in infancy or early childhood and with significant impairments in social, communicative, cognitive, emotional and behavioural functioning are severe neurodevelopmental disorders. CONDs largely result from complex interactions of genomic vulnerability and environmental factors occurring over the course of the development of the brain. CONDs include conditions such as autism spectrum conditions (ASC), attention deficit/hyperactivity disorder (ADHD) and tics spectrum disorders (APA, 1994).

Autism was first described by Kanner in 1943 (Kanner, 1943). The core features of the concept of autism were delineated in 1979 by Lorna Wing and are referred to as the symptom-triad. Impairment in three broad areas are present: reciprocal social interaction and communicative abilities and restricted behaviour and interests (Wing and Gould, 1979). These symptoms, which in most individuals persist throughout life lead to significant impairment. In recent years, awareness of autism as a broader spectrum of conditions has resulted in the introduction of the concept of ASC. Conditions included in the spectrum are autistic disorder (AD), Asperger syndrome (AS) and autistic-like condition (also known as pervasive developmental disorder not otherwise specified (PDD-NOS) and atypical autism). Autistic-like condition has no specific operationalised diagnostic criteria or algorithms in the DSM-IV. Efforts have been made by researchers to tighten up the definition. With this ap-

proach, the proposed criteria for autistic-like condition are defined as following: the social interaction criterion for AD met plus a total of at least four items, but not the full DSM-IV criteria for AD. The strict definition of the condition makes it possible to compare data across research groups. With respect to the diagnostic criteria for AS, delineated by Gillberg and Gillberg (Gillberg and Gillberg, 1989) and based on Asperger's own descriptions, these are more stricter than the ICD-10 and the DSM-IV (Leekam et al., 2000, Miller and Ozonoff, 1997) (Table 2).

The rate of ASC varies from 0.5% to 1.1% (Fombonne, 2005, Gillberg et al., 2006, Petersen et al., 2006). The prevalence of ASC in children with LD is reported to be higher than in the general population; 20.5% of children with severe LD and 5.3% of mild LD (Nordin and Gillberg, 1996). In a review of 32 studies on ASC in 2001, Fombonne (Fombonne, 2003) found that 30% of children with AD were in the normal intelligence range, 30% had mild to moderate LD and 40% had severe to profound LD.

Attention deficit hyperactivity disorder (ADHD) is defined according to the DSM-IV criteria as mainly inattentive, mainly hyperactive/impulsive, or of combined type (APA, 1994). ADHD is most typically identified in children with normal neurodevelopment. Children with LD may have reduced attention spans, impulse control, and activity levels. If these symptoms are inappropriate according to their developmental age, a diagnosis of ADHD can be assigned.

In this thesis, the diagnosis "ADHD" was made in individuals with LD in combination with clinically significant problems in the area of hyperactivity and/or attention combined. It should also be emphasised that attention problems may be present to some extent in ASC without justifying a diagnosis of ADHD. The diagnoses of ASC and ADHD are not mutually exclusive; both diagnoses may be present in one and the same individual at the same time.

Psychiatric disorders, cognition and adaptation in DM1

Children with DM1 and comorbid LD were first described as early as 1948 (Thomasen, 1948). In the sixties, Calderon pointed out that DM1 was a neglected cause of LD (Calderon, 1966). Several authors have reported LD to be the most important feature of congenital DM1 (Hageman et al., 1993, Harper, 2001b, Modoni et al., 2004, Nicholson et al., 1990, Roig et al., 1994). Johnson and co-workers (Johnson et al., 1995) reported on significant differences between congenital DM1 and DM1 with later onset with respect to intellectual and cognitive functioning, with individuals with the congenital form being more severely affected.

Studies on childhood DM1 have demonstrated significantly higher achievement regarding verbal IQ than performance IQ (Angeard et al., 2007, Cohen, 2006). In childhood DM1, FSIQ can be influenced by inheritance with the most prominent deficits in individuals with maternally transmitted disorder. Deficits in attention/executive functions, action planning and organization, visuo-spatial deficit and reading impairment have also been reported in childhood DM1 (Angeard et al.,

Table 1 Diagnostic criteria for autistic disorder according to the DSM-IV

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3)

1. qualitative impairment in social interaction:
    a. marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
    b. failure to develop peer relationships appropriate to developmental level
    c. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
    d. lack of social or emotional reciprocity
2. qualitative impairments in communication:
    a. delay in, or total lack of the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
    b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
    c. stereotyped and repetitive use of language or idiosyncratic language
    d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
3. restricted repetitive and stereotyped patterns of behavior, interests and activities:
    a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    b. apparently inflexible adherence to specific, nonfunctional routines or rituals
    c. stereotyped and repetitive motor mannerisms (e.g hand or finger flapping or twisting, or complex whole-body movements)
    d. persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication or (3) symbolic or imaginative play

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

Table 2 Diagnostic criteria for Gillberg and Gillberg's Asperger syndrome

1. Severe impairment in reciprocal social interaction (at least two of the following)
a. inability to interact with peers
b. lack of desire to interact with peers
c. lack of appreciation of social cues
d. socially and emotionally inappropriate behavior
2. All-absorbing narrow interest (at least one of the following)
a. exclusion of other activities
b. repetitive adherence
c. more rote than meaning
3. Imposition of routines and interests (at least one of the following)
a. on self, in aspects of life
b. on others
4. Speech and language problems (at least three of the following)
a. delayed development
b. superficially perfect expressive language
c. formal, pedantic language
d. odd prosody, peculiar voice characteristics
e. impairment of comprehension including misinterpretations of literal/implied meanings
5. Non-verbal communication problems (at least one of the following)
a. limited use of gestures clumsy/gauche body language
b. limited facial expression
c. inappropriate expression
d. peculiar, stiff gaze
6. Motor clumsiness: poor performance on neurodevelopmental examination

2007, Cohen, 2006). Homogeneously weak subtest results have been found in children with congenital DM1 (Echenne et al., 2008).
Decline on neuropsychological measures in childhood DM1, has been reported in some studies (Echenne et al., 2008, Steyaert et al., 1997) but not in others (Tuikka et al., 1993).

Psychiatric disorders, ADHD and anxiety disorders in particular, have been shown to be common in both congenital and childhood DM1 (Echenne et al., 2008, Goossens et al., 2000). Behavioural abnormalities, especially within the autism spectrum, in children and adolescents with DM1 have been described in sporadic cases (Blondis et al., 1996, Echenne et al., 2008, Paul and Allington-Smith, 1997, Saccomani et al., 1992, Steyaert et al., 1997, Yoshimura et al., 1989). Furthermore, the behavioural profile has been characterised by marked emotional lability and social withdrawal indicating underlying psychopathology (Roig et al., 1994, Thompson et al., 1995).

A high prevalence of day-time sleepiness, fatigue and reduced initiative has been reported in childhood DM1 (De Die-Smulders, 2004, Quera Salva et al., 2006). Fatigue has been defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion and is not explained by muscle weakness (Kalkman et al., 2005). Fatigue has been reported in 76% of children and adolescents with DM1, while somnolence has been found in 52%. Some patients with DM1 show sleep onset REM, similar to that observed in narcolepsy.

There are no studies with systematic assessments of adaptative behaviour in DM1 with childhood onset. However, as one researcher stated, "children and their parents experience great problems in coping with the combination of learning difficulties, chronic fatigue and the somatic complaints. Most children have little contact with their peer groups and live socially isolated lives" (De Die-Smulders, 2004). Another research group reported that all children with congenital DM1 in their study needed special education, and only a few individuals with childhood DM1 were able to continue to the college level (Echenne et al., 2008).

Vision
The visual pathways include the optic media, the receptors and ganglion cells of the retina, the optic nerve (formed by the axons of the ganglion cells) and the optic tract. Further, the axons from the ganglion cells synapse at the lateral geniculate nucleus of the thalamus and pass through the optic radiation along the lateral ventricle to the termination in the primary visual occipital cortex.

Several modalities compose the visual function, not all of which could be assessed, especially not in individuals of low developmental age. VA is the ability to distinguish details and shapes of objects and is correlated to the function of the fovea and the visual pathways. Proper development of visual acuity depends on normal visual input from an early age. Any visual deprivation, such as corneal or lens opacities,

uncorrected refractive error or strabismus will usually result in a severe and permanent decrease in visual acuity if not treated early in life. VA develops from birth to adolescence and VA of 1.0 is reached by 5-6 years of age (Fern and Manny, 1986, Gronlund et al., 2006). Depending on the child's developmental age and cooperative ability, different methods are used for assessing VA. Recognition of letters or symbols of decreasing size (optotypes) are used in school-aged children. For children with a chronological or developmental age below three years of age, pictures or gratings to gain the child's attention (Kay's pictures or Cardiff cards) are used.

The World Health Organisation (WHO) definition of visual impairment (VI) is VA < 0.3. VI could be due to processes in the eye alone (ocular visual impairment) and/or pathological processes in the visual pathways. Cerebral visual dysfunction or cerebral visual impairment include visual field defects, visual perceptual-cognitive impairment and subnormal VA (although some have normal VA). The prevalence of visual impairment in the Swedish pediatric population is 0.11 % (Blohme and Tornqvist, 1997).

The refraction of the eye depends on the curvature of the cornea, depth of the anterior chamber, lens power and axial length. The newborn infant is normally hyperopic and astigmatic, and the process towards emmetropia is most pronounced during the first years of life (Saunders, 1995). Emmetropia is defined as the state of vision where an object at infinity is in sharp focus with the eye lens in a neutral or relaxed state. Successive growth of axial length and flattening of the lens facilitate emmetropisation as the infant grows older. The process of emmetropisation is not fully understood but is at least monitored, in part, by central nervous processes as the emmetropisation is dependent on visual feedback (Troilo, 1992). Strabismus and impaired fixation are other factors that influence emmetropisation negatively (Ingram et al., 2003, Whatham and Judge, 2007).

Visual evoked potential (VEP) is an electrophysiologic measurement that provides information about afferent input to the visual cortex. Compound neuronal activity is evoked by a visual stimulus and can be measured electrophysiologically. VEP consists of specific and non-specific components representing activation of different afferent pathways to the visual cortex; the specific response mediated through the primary visual pathway and the non-specific via nuclei in the mesencephalon, brainstem and thalamus. An abnormal VEP response reflects abnormality in the primary geniculo-cortical pathway or the non-specific pathway. Disorders of the cerebral white matter may result in distorted VEP (Kristjansdottir et al., 2002). A VEP investigation could be performed either as pattern or flash VEP (Odom et al., 2004). The pattern VEP is considered to provide more specific information but requires stable fixation. Flash VEP, on the other hand, may be used in individuals unable to communicate or cooperate, which is the case in many individuals with LD and/or autism.

Ophthalmological findings in DM1

The prevalence of cataract is an important clinical feature of DM1 (Burian and Burns, 1966, Reardon et al., 1993a). The link between cataract alone in previous generations with later affected family members and obvious muscle disease was recognised early (Fleischer, 1918). Ophthalmologists are familiar with the typical findings of a multicoloured iridescence localised in the subcapsular regions of the lens and have sometimes been the first to make the diagnosis of DM1 on the basis of these typical findings (Burian and Burns, 1966). In childhood, lens opacities are infrequently described in the literature, and rarely in individuals below ten years of age (Echenne et al., 2008, Harper, 2001a).

Data on ophthalmological findings in children with DM1 are scarce. Strabismus is reported in congenital DM1, but not during the neonatal period (Harper, 1975). Short axial length has been reported in one study on children with DM1 (Weiss et al., 1989). Another publication presented occurrence of high hyperopia in 86% (on average +6.0 D), esotropia in 56% and amblyopia in 22% (Bollinger et al., 2008). According to the authors, an increased prevalence of hyperopia may be related to low intraocular pressure (IOP). This assumption was based on the knowledge of low IOP being present in adults with DM1 (Burian and Burns, 1966). The mechanism responsible for the development of low IOP is still unclear, but it could be due to increased uveoscleral outflow or aqueous secretion (Khan and Brubaker, 1993), but is not related to increased corneal thickness (Rosa et al., 2008). Low IOP may result in a mildly microphthalmic state and hyperopic refractive error (Bollinger et al., 2008). The degree of hyperopia may roughly be correlated with the CTG repeat expansion size, but other factors contribute as well (Bollinger et al., 2008).

Prognosis

The prognosis and progression of the disease is most likely associated with the disease type and age at onset. In patients with childhood onset, and especially congenital DM1, the prognosis with regard to work and normal family life is poor (O'Brien and Harper, 1984).

In congenital DM1, the mortality is higher, both during the neonatal period and in later life. The duration of initial ventilation assistance during the neonatal period is supportive in predicting the outcome. A 100% mortality rate before 15 months of age has been reported for children ventilated more than 30 days (Rutherford et al., 1989). A more recent study has shown a more optimistic picture, with 25% mortality in the first year in children ventilated > 30 days, but developmental delay and morbidity were more obvious in this group than in children ventilated less than 30 days, where no mortality was observed during the first year of life (Campbell et al., 2004). Adults with congenital DM1 have reduced survival by 50% beyond their mid-30s (Reardon et al., 1993b). Life expectancy is greatly reduced in DM1 patients compared with the healthy population. Patients with DM1, including adolescents, are at particular risk of sudden cardiac death (Bassez et al., 2004) In adulthood,

severe abnormality on ECG and a diagnosis of atrial tachyarrhythmia predict sudden death (Groh et al., 2008). In retrospective studies, the mortality was 5.3-7.3 times higher than expected (Mathieu et al., 1999, Mladenovic et al., 2006). Excessive mortality is mainly related to respiratory diseases, cardiovascular complications, and malignancies. Lower age at onset is a significant unfavourable prognostic factor (Mladenovic et al., 2006).

Therapy

Various supportive treatments are available. Modafinil is considered to improve excessive daytime somnolence and is widely used in DM1 (MacDonald et al., 2002, Talbot et al., 2003). According to a Cochrane report, more randomised trials are needed to evaluate the efficacy and safety of psychostimulants (Annane et al., 2002). Somnolence and fatigue are also reported in children and adolescents with DM1 (Quera Salva et al., 2006), but no trials with modafinil have been performed. Another putative pharmacological option for treating somnolence are stimulants such as metylphenidate (Peterson and Husain, 2008), well established in the treatment of ADHD. Increases in heart rate and systolic and diastolic blood pressure are possible cardiac side effects, but have been thought to be clinically insignificant for most children with ADHD. Children and adolescents with DM1 could be a special risk category, and thorough follow-up is required if treatment with stimulants is initiated.

So far, there is no cure for DM1. Current supportive treatment does not influence the disease progression. However, understanding the molecular pathogenesis makes it possible to develop molecularly based treatments that target the RNA disease mechanism directly, thereby making it possible to reverse the disease phenotype (Wheeler, 2008).

DM1 in the western and southern health care regions of Sweden

The study was performed as a part of a multidisciplinary study of children and adolescents with DM1 at the University of Gothenburg, Sweden (Aring et al., 2009, Engvall et al., 2008, Engvall et al., 2007, Sjogreen et al., 2007, Sjogreen et al., 2008). In addition, studies on adult onset DM1 have been performed in Gothenburg with the focus on cerebral involvement (Winblad et al., 2006a, Winblad et al., 2006b, Winblad et al., 2005, Winblad et al., 2008).

Aims of the present thesis

The overall purpose of the study was to gain further insight into congenital and childhood DM1 regarding neuropsychiatric and neurocognitive aspects, vision and motor function.

The specific aims were:
To classify a group of children and adolescents with DM1 into congenital and childhood onset forms and to estimate the size of the CTG repeat expansion;

To investigate range of motion, muscle strength and motor function in congenital and childhood DM1 and to compare muscle strength and motor function with a matched healthy control group;

To investigate the neuropsychiatric problems in congenital and childhood DM1;

To investigate cognition and adaptive skills in congenital and childhood DM1;

To investigate visual function in a group of individuals with congenital and childhood DM1, and to compare the results for visual acuity, significant refractive errors and electrophysiological findings with groups of matched controls;

To correlate the size of the CTG- repeat expansion, inheritance and onset form to motor function, neuropsychiatric findings, cognitive and adaptive skills and visual function.

Methods

Study population

The study population is described in Figure 5. Between January 1999 and December 2003, 64 children and adolescents with a DNA-confirmed diagnosis of DM1 before 18 years of age living in the western and southern health care regions of Sweden were through their pediatric rehabilitation centers invited to participate. Fifty-nine individuals accepted to participate in this study. All individuals were below 18 years of age when included in the study for the first time. As some of the individuals were almost 18 years of age when included in study I, they were older than 18 when participating in study II, III and IV.

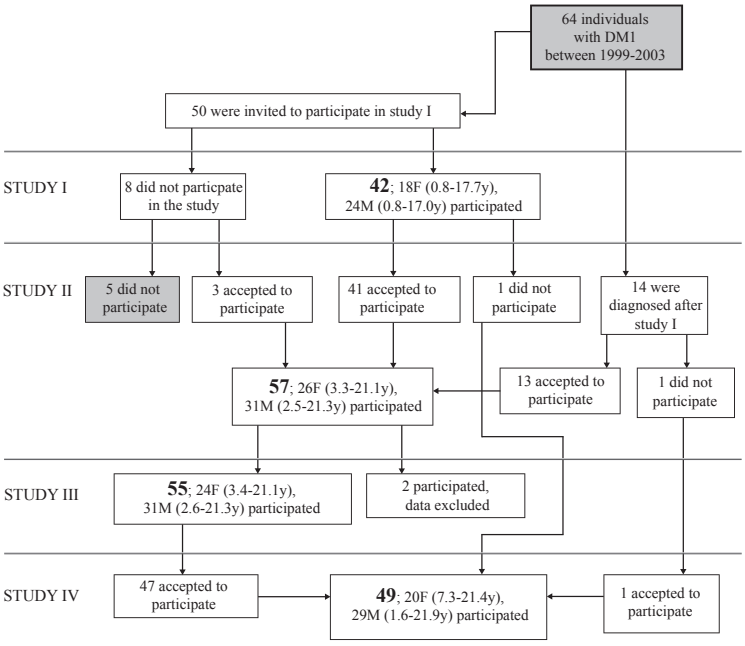

Figure 5 Recruitment of the study population
Abbreviation: M:Male, F:Female, y:years

Thirty-four individuals participated in all four studies, and an additional 20 patients took part in three of the four studies.

Procedure

A thorough medical history was taken for all the patients, according to a systematically applied protocol. A clinical neurological examination was performed, and all the medical records were reviewed. All children were videotaped during neurological and motor examinations.

Classification
A new classification for congenital DM1 was introduced: All children with congenital DM1 have symptoms present *in utero* (polyhydramniosis and reduced foetal movements) or from birth (respiratory insufficiency, sucking difficulties, facial diplegia, hypotonia and/or multiple congenital contractures). Congenital DM1 is divided into a severe and a mild form. The difference between the two groups is that the former is characterised by a life-threatening condition at birth with need for resuscitation and/or respiratory assistance.

According to age at onset and presenting clinical symptoms, the children were divided into four groups; severe congenital (n=20) and mild congenital DM1 (n=18), childhood DM1 (n=19) and classical DM1 (n=2).

Analysis of the CTG repeat expansion size in the DMPK gene
All patients had a confirmed diagnosis of DM1 with CTG repeats > 40. Except for the two adopted children, the CTG repeat expansion size was estimated in the transmitting parent. DNA was extracted from peripheral blood using a Puregene DNA Isolation Kit (Gentra Systems, Minnesota, Minneapolis, USA) and digested with restriction endonucleases *Eco*R1 and *Pst*1. Fragments were separated on a 0.8% agarose gel and subjected to Southern blotting using the pM10M-6 probe (Brook et al., 1992). Because of deletion/insertion polymorphism, *Eco*R1 blots show alleles of 9 or 10 kilobases (kb) in normal individuals, whereas *Pst*1 blots show fragments of approximately 1.2 kb. CTG expansions in patients were estimated relative to a size marker from the *Pst*1 blots. As most patients show a smear rather than a distinct band, because of somatic mosaicism, the approximate midpoint of the smear was reported.

Study I
Forty-two children and adolescents participated, 18 females (0.8 - 17.7 years) and 24 males (0.8 – 17.0 years); severe congenital DM1 (n=13), mild congenital DM1 (n=15) and childhood DM1 (n=14). A control group of 42 healthy children was matched by gender and age. Gross motor function was assessed by the same physiotherapist in all patients.

Measurement of isometric muscle strength
Isometric muscle strength was measured with a hand-held dynamometer (Penny and Giles, Chicester, Dorset, Hants, UK) by one and the same physiotherapist in all children. Ten muscle groups in the upper and lower extremities were measured in a standardised way, and the values obtained were compared with reference values from age and gender-matched controls. The best of three values obtained on the non-dominant side was compared with values obtained by a matched control subject. To enable a comparison between the groups of DM1, regardless of the age of the children, a quotient was calculated between the isometric muscle strength obtained by the child with DM1 and the matched control subject.

Measurement of myotonia
Myotonia was tested by percussion of the thenar muscle and the tongue, or revealed as a delayed ability to relax the grip after forceful contraction of the hand.

Measurement of range of motion (ROM) and skeletal deformities
ROM was measured with a goniometer and photographs of skeletal deformities were taken at the time of investigation. A review of medical records and interviews with the parents provided information on contractures and skeletal deformities at birth.

Measurement of motor function and walking ability
Motor function was assessed using the Hammersmith motor ability scale (HMA) (Scott et al., 1982) (Table 3). The performance is scored on a three-point scale: 0 (unable), 1 (needs self-reinforcement), and 2 (succeeds). The maximum score is 40. Children less than six years old were excluded, as performance on this motor assessment test has been shown to be age-related. The age when the children began to walk was noted as well as the children's walking ability at the time of investigation.

Table 3 *The Hammersmith motor ability scale*

1.	Lifts head in supine	11.	Standing on toes
2.	Supine to prone over right	12.	Standing on right leg
3.	Supine to prone over left	13.	Standing on left leg
4.	Prone to supine over right	14.	Jumps on right leg
5.	Prone to supine over left	15.	Jumps on left leg
6.	Gets to sitting	16.	Gets of chair
7.	Sitting	17.	Climbing step right leg
8.	Gets to standing	18.	Descending step right leg
9.	Standing	19.	Climbing step left leg
10.	Standing on heels	20.	Descending step left leg

Study II-III
Fifty-seven children and adolescents participated, 26 females (3.3 -21.1 years) and 31 males (2.5 – 21.3 years); severe congenital (n=19), mild congenital (n=18), childhood (n=18), and classical DM1 (n=2). The children and adolescents were primarily assessed by the author and a neuropsychological evaluation was then performed by a child psychologist, on average, 0.2 years later (range 0 - 0.8 years). In study II, the results from the two individuals with classical DM1 were not presented.

Neuropsychiatric evaluation
One or both parents of all 57 individuals were thoroughly interviewed using structured interviews regarding neuropsychiatric problems. A clinical neuropsychiatric assessment including medical examination and observation of all participants was performed.

Autism Diagnostic Interview-Revised (ADI-R)

Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994), a standardised, investigator-based semi-structured caregiver interview, was used by a clinical child psychologist to interview the parents. According to the ICD-10 (WHO, 1992) and the DSM-IV (APA, 1994) the diagnosis of autistic disorder (AD) requires specific types of abnormalities in three key areas of functioning: reciprocal social interaction, language and communication, and restricted, repetitive and stereotyped behavior, together with evidence of delayed or deviant development in at least one of these areas before 36 months of age. The interview contains 84 questions and provides separate scores in the distinct areas, as well as early history, with specific threshold scores; 10 for reciprocal social interaction, 8 for communication for verbal individuals and 7 for non-verbal, 3 for restricted, repetitive behavior, and 1 for deviation in early development. The cut-off scores provide an algorithm where four points indicate deficits in all areas and render a diagnosis of AD. The cognitive level was taken into account when evaluating the results on ADI-R. ADI-R was used for all 57 participants, but as four individuals were at a non-verbal age (younger than 18 months), results from only 53 individuals are presented.

Questionnaires

Social Communication Questionnaire (SCQ)

The SCQ (previously known as the Autism Screening Questionnaire) is a parent questionnaire regarding core diagnostic features of autism (Berument et al., 1999). The 40 items are based on the ADI-R, but they have been modified in order to be understood by parents without further explanation. There are two versions of the SCQ: current and lifetime. The current version is suitable for children younger than 4 years, while the lifetime version is used with older individuals. This study utilised the lifetime version translated into Swedish by Wentz, Råstam and Gillberg 2000.

The Five to Fifteen (FTF)

The FTF is a parent questionnaire for the age group 5-15 years and covers the core symptoms of ADHD and related neurodevelopmental disorders (Kadesjo et al., 2004). The FTF comprises 181 statements and cover eight domains (motor, executive functions, perception, memory, language, learning, social and emotional problems). Each statement may be endorsed as either "does not apply" (=0), "applies sometimes or to some extent" (=1) or "definitely applies" (=2). In addition, there are a number of open-ended questions regarding the child's strengths and weaknesses.

In most cases, the parents had difficulties completing the questionnaires (SCQ and FTF) on their own. For this reason, the author used the questionnaires in the interviews with the parents.

Neuropsychiatric diagnostic procedure

The diagnostic procedure of COND involves clinical evaluation, systematic interviews and instruments. The videotapes recorded during motor and neurological ex-

amination were analysed retrospectively by the author and two co-authors; a child psychologist and a child psychiatrist. On the basis of all the available information, neuropsychiatric diagnoses were assigned conjointly by the author and co-authors using specific symptom checklists regarding COND (ASC, ADHD and TD), according to the operationalised diagnostic criteria of the DSM-IV (APA, 1994). With respect to other psychiatric disorders, diagnoses were also assigned according to the DSM-IV.

Regarding autistic-like condition (ALC), we used the criteria presented in the introduction. As motor clumsiness and limited facial expressions are both symptoms of Asperger syndrome and DM1, both the Gillberg and Gillberg (Gillberg and Gillberg, 1989) and the DSM-IV (APA, 1994) criteria had to be met.

Global cognitive assessment

Psychometric assessment of general intellectual ability was performed, and the methods used were based on developmental age and functioning rather than chronological age. The three Wechsler scales (WPPSI-R, WISC-III and WAIS-III) provide measures of global intellectual ability – the full scale IQ (FSIQ) and the subscores of verbal and performance IQ (VIQ; PIQ). Furthermore, the WISC-III and the WAIS-III provide subtests and the results are given as raw scores which are transformed into scale scores (1-19, mean 10 [SD 3]) for comparison with age-related normative data.

Behavioral observation of all participants was performed during the neuropsychological examination. The observation covered aspects of attention, activity level, impulse control, social interaction, cooperation, emotional state, speech and language.

The following definition of intelligence levels was used: Normal IQ $\geq$85; Borderline IQ: 70-84, Mild LD: 50-69, Moderate LD: 35-49, Severe LD: 20-34 (APA, 1994).

Forty-six of the 55 individuals were assessed by the child psychologist in our research team. In four cases, other neuropsychologists had recently assessed the individuals and those results were collected (in one case, only four subtests of the WAIS-III were assessed). Five children did not complete any tests (three individuals exhibited a very low level of functioning; one individual was too tired, and one individual had recently had a concussion of the brain). Two individuals were left-handed.

For the assessment of children at a developmental age below 3 years, the *Griffiths Developmental Scale* (Griffiths, 1970) was used (n=8), and the developmental quotients (DQ) obtained were converted to IQ equivalents. The results were compared with mean scores on the Vineland Adaptive Behaviour Scales (VABS) (Sparrow et al., 1984). When the developmental age was between 3 and 7 years, the Wechsler Primary and Preschool Scale of Intelligence *(WPPSI-R)* (Wechsler, 1999) was ap-

plied (n=15). In school-age children (n=23), the Wechsler Intelligence Scale for children (*WISC-III*) (Wechsler, 1992) was used. At age 16 years and older, the Wechsler Adult Intelligence Scale (*WAIS-III*) (Wechsler, 2002) was administered (n=2).

Adaptive assessment
Adaptive functioning was assessed by interviewing caregivers of all 55 children using the Vineland Adaptive Behaviour Scales (VABS) (Survey Form). The VABS are an informant-based measure of adaptive behaviour with four domains and several subdomains (within brackets) assessed: Communication (Receptive, Expressive and Written), Daily living skills (Personal, Domestic and Community), Socialisation (Interpersonal Relationships, Play and Leisure Time, and Coping Skills), and Motor skills (Gross and Fine). The motor domain was excluded, as that scale is not applicable to individuals older than 6 years. Age-equivalent scores for each domain were examined (mean 100; SD 15). Each subdomain consists of five descriptive levels: high, moderately high, adequate, moderately low and low. No Swedish normative data exist; therefore, American norms were used.

Study IV
Forty-nine individuals participated, 20 females (7.3 – 21.4 years) and 29 males (1.6 – 21.9 years); severe congenital (n=17), mild congenital (n=13) and childhood DM1 (n=19). Three age and sex-matched control groups of Swedish preschool and school children living in Gothenburg were selected from a larger cohort. The results in each DM1 subgroup were compared with the results in the control groups matched for age and gender (Gronlund et al., 2006). For the VEP results, a group of 51 healthy children aged 1-15 years was used (Kristjansdottir et al., 2002).

Visual acuity
The method of assessment was based on cognitive level and/or ability to participate rather than chronological age. Distance visual acuity (VA) was tested binocularly in all children with own (if any) correction. If possible, assessment with optotypes, the KM-Boks chart, HVOT chart or Kay's pictures, were made.

The KM-Boks chart, a linear arithmetically based letter-matching chart with seven equal readability different letters (C D E F K N V) was used (n=36) (Moutakis et al., 2004). The KM chart is designed for a testing distance of 3 m. If an individual could not manage to read the KM-Boks chart, the HVOT chart was used instead (n=2) (Hedin and Olsson, 1984). For illiterate children measurement of VA with the Kay Picture test (n=5) (Kay, 1983), the Cardiff test (n=2) (Adoh et al., 1992), or "hundreds and thousands" was performed (n=2) (Richman and Garzia, 1983). Two individuals (one with severe congenital, aged 5.8 years, and one with mild congenital DM1, aged 14.2 years) could not take part in any VA test but could fixate and follow a penlight.

Visual impairment (VI) was defined as VA≤0.3 (logMAR ≥0.5) (WHO), subnormal VA as VA >0.3 to <0.8 (logMAR 0.5 to >0.1) and normal VA as ≥0.8 (logMAR ≤0.1).

Cycloplegic refraction
After a single instillation of a mixture of cyclopentolate (85 %) and phenylephrine (1.5 %), autorefraction was performed with Topcon A6300 (Topcon Corporation, Tokyo, Japan) or Nikon Retinomax (Nikon Corporation, Tokyo, Japan). Significant refractive errors in children ≥ four years of age were defined as a spherical equivalent (SE) of hyperopia ≥ 2.0 diopters (D) (Mayer et al., 2001), myopia ≥ 0.5 D and astigmatism ≥ 1.0 D in one or both eyes (Gronlund et al., 2006). In children ≤ four years of age, significant refractive errors were defined as hyperopia ≥ 4.5 D, myopia ≥ 5.0 D and astigmatism ≥ 3.0 D (Ophthalmology, 1993).

Lens and fundus examination
Slit-lamp biomicroscopy and indirect ophthalmoscopy were used for lens evaluation and fundus examination.

Visual Evoked Potentials (VEP)
Measurement of VEP was performed in 38 individuals by using Grass equipment with a short supramaximal light flash stimulus (<50μs, ~ 0.5J). Equipment of our own construction, based on a National Instrumental amplifier, was used, with Lab View software and a Macintosh G3 or later version. Recordings were performed from three positions in a horizontal row at the occipital level (O_1, O_z, O_2, according to the international 10-20 EEG system). The VEP single sweep activity was averaged (*n*=20-40) with a 0.3-250 Hz band pass filter. A 50/60 Hz filter setting was sometimes used when a high background noise was impossible to extinguish by electrode, wire and skin manipulation (Sjodell et al., 1996).

VEP was considered pathological if N_1 differed >2 SD from that of the control group i.e. < 39 ms and > 70 ms, P'/P_1 complex > 2 SD i.e. < 62 ms and > 104 ms, or otherwise altered in the wave form.

For the electro-ophthalmologic assessment, both the methods and the investigator were the same in the study and the control group (Kristjansdottir et al., 2002).

Statistical methods
The statistical analyses were performed using Statview 4.02 for Macintosh (I), SPSS for Windows 15.0 and SAS 8.2 (II-IV). As normal distribution could not be assumed in combination with small sample sizes, non-parametric tests were used. For comparison between two groups, the Mantel-Haenszel Chi2 test was used for ordered categorical variables (all studies), Fisher's exact tests for dichotomous variables (II, III, IV), the Mann-Whitney U-test for continuous variables (all studies) and the Wilcoxon Signed Ranked Test for paired comparisons (I, III). The Spearman correlation coefficient was calculated for analysis of relationships between two continuous variables (all studies). To adjust for gender in the comparison between two groups, van Elteren's test was used for continuous variables ((II, III, IV). The Spearman partial correlation coefficient was calculated to adjust for gender in correlation analysis (II, III, IV). All tests were two-tailed and conducted at a 5% significance level. Due

to the many significance tests the significance level has been set to 1% for the correlations between verbal and performance subtests and CTG (III).

Ethics

According to the Declaration of Helsinki, the individuals participated voluntarily after verbal and written information and written informed consent was obtained from the caregivers. The Human Ethics Committees of the Medical Faculties at Göteborg University and Lund University, Sweden, approved the studies.

Results

Classification and baseline characteristics

Baseline characteristics are given in Table 4. On the basis of the disease classification, the children and the adolescents were divided into four subgroups: severe congenital (n=20); mild congenital (n=18); childhood (n=19) and classical (n=2). A male preponderance (16 out of 20 individuals) was found in the severe congenital group, in contrast to an almost even distribution of males and females in the other two childhood onset groups.

Some individuals with childhood DM1, some showed mild symptoms during the gestational and neonatal period; two children had had mild excess of amniotic fluid, five children had been floppier than healthy children and four children had been slow suckers but did not require nasogastric feeding. These children had been diagnosed as having the childhood type, as the symptoms could be regarded as mild and their overall development during the first year was normal. Unilateral subluxation of the hip was found in one patient with childhood DM1 and one of the girls with classical DM1 was born with unilateral *pes equino varus adductus*, but presented no other characteristics of congenital or childhood DM1. Six individuals with severe and five with mild congenital DM1 were assessed during the neonatal period with either ultrasonography or computer tomography of the brain. One individual had obstructive hydrocephalus requiring a shunt operation. Three had ventriculomegaly and one had both periventricular leukomalacia and ventriculomegaly. Spasticity was found in two children with severe congenital DM1, one of whom had the shunt-requiring hydrocephalus. Brain imaging was not performed in the other individual with spasticity.

Table 4 *Diagnostic criteria for severe and mild congenital, and childhood DM1*

	Severe congenital	Mild congenital	Childhood
Pre-/perinatal period	Symptoms present	Symptoms present	Uneventful
Resp. assistance and/ or asphyxia	Respiratory assistance required and/or asphyxia	No respiratory assistance required, no asphyxia	Not present
Hypotonia	Severe	Mild	Not present
Sucking difficulties	Severe, require nasogastric tube feeding	Moderate, may require nasogastric tube feeding	Not present
Talipes and/or other contractures	Frequently present	Frequently present	Not present
Developmental delay	Present before 1 year of age	Present before 1 year of age	Present between 1-10 years of age

Table 5 *Baseline characteristics in the 59 individuals with DM1*

	Severe cong.DM1 (n=20)	Mild cong. DM1 (n=18)	Childhood DM1 (n=19)	Classical DM1 (n=2)[a]
Male	16 (80%)	8 (44%)	9 (47%)	0
Female	4 (20%)	10 (56%)	10 (53%)	2 (100%)
Age at time of study inclusion				
Mean (SD)	7.6 (5.3)	7.8 (4.4)	11.1 (4.4)	16.7;17.2
Median (range)	6.5 (0.8-17.0)	8.8 (0.8-15.3)	10.9 (5.1-17.7)	
No. of CTG repeats				
Mean (SD)	1580(420)	980 (450)	910 (320)	475;625
Median (range)	1590 (730-2100)	1000 (130-2100)	930 (260-1500)	
Inheritance[b]: Maternal/Paternal	20/0	13/3	14/5	0/2
CTG repeats in aff. mothers				
Mean (SD)	770 (420)	540 (430)	620 (350)	
Median (range)	650 (100-1700)	500 (100-1250)	600 (70-1250)	
affected fathers				
Mean (SD)		710 (700)	500 (410)	50; 525
Median (range)		625 (65-1450)	525 (65-900)	
Myotonia	11	10	12	2
Median (age)	8.6 (1.3-17.0)	8.5 (3.6-15.3)	10.6 (5.2-17.5)	16.2;17.2
Walking ability unsupported	12	17[c]	19	2
Age of walking: Mean (range)	28 mo. (13-54)	21 mo. (12-43)	15 mo. (11-18)	12 mo.
Cognitive level NIQ/BIQ/MLD/ModLD/SLD	0/1/2/8/8[d]	1/2/3/9/3	1/1/7/9/0[e]	1/1/0/0/0
Somatic compl./symptoms				
Abdominal symptoms				
Constipation/soiling	9/5	8/6	5/3	No abdom. symptoms
Abd.pain/diarrhoea/lact.intol.	3/1/0	4/3/1	2/3/2	
Inguinal hernia	2	1	1	
UVI/bladder dysfunction	2/1	2/1	0/1	
Undescended testis	10 (62%)	4 (50%)	1 (11%)	
Body weight and length				
Body weight/length < 2SD	6/5	0/1	0/0	Normal body composition
Body weight/length > 2SD	0/0	0/0	2/0	

	Severe cong.DM1 (n=20)	Mild cong. DM1 (n=18)	Childhood DM1 (n=19)	Classical DM1 (n=2)[a]
ENT-problems				
Recurrent otitis	12	2	4	
Otosalpingitis/hearing loss	5	5	3	1
Transmyringeal drenage	6	5	3	
Adenectomi/tonsillectomi	0/0	4/1	4/0	
Gestational/neonatal period				
Polyhydramniosis	14	5	2	0
Preterm delivery (GA)	11 (34-37)	3 (33-36)	0	0
C.section/ vacuum extraction	14/2	4/3	3/4	0/0
Low Apgar score[f]	9	0	0	0
Individuals req. assisted vent.	13 (65%)	0	0	0
Days with assisted ventilation Mean (SD)	26 (43)			
Median (range)	3.5 (0-150)	-	-	-
Sucking diff./req. nasog. tube	20/20	13/7	5/0	0/0
Neonatal hypotonia	19	17	5	0
Birth weight (g) Mean (SD)	2790 (610)	3170 (690)	3470 (580)	3500; 3640
Median (range)	2800 (1735- 4000)	3050 (2090-4400)	3400 (2040-4250)	
SGA: BW ≤ 2SD	3 (15%)	1 (6%)	2 (10%)	0
Neonatal cardiac involv. pulm.hyper./PDA	3/5	1/1	0/1	No cardiac abnormal.
rhythm./conduct./contractility	0/1/1	0/0/0	1/1/0	
ASD/VSD/cardiac valve abnorm.	1/1/2	1/0/1	0/0/1	
Cong. contract. /skel. def.	15	16	1	1

[a] the individual values are given regarding CTG repeat expansion size, age and birth weight;
[b] 2 children with mild congenital DM1 were adopted, parental transmission unknown;
[c] no information on cognitive level in 1 individual with childhood DM1;
[d] 5 individuals had not yet acchived independent walking (age range 0.8-4.4 years). Three individuals could walk with aids indoors at age of 10, 10 and 17 years.
[e] one male had not achieved indiepndent walking at 0.8 years of age.
[f] Low Apgar score was defined as < 5 at five minutes of age; mo.: months; cong.: congenital; no: number of; NIQ: normal IQ; BIQ : borderline IQ; MLD: mild LD; ModLD: moderate LD; SLD: severe LD; GA: gestational age; SGA: small for gestational age; BW: birth weight; pulm.hyper.: pulmonal hypertension; PDA: persistent ductus arteriosus; rhythm.: cardiac rhythm abnormalities; conduct.: cardiac conduct abnormalities; ASD: atrial septal defect;VSD: ventricular septal defect ;abnorm.:abnormalities; congenital contract.: congenital contractures.

Inheritance and molecular data

The participants represented 49 families. In ten children from seven families, the disease was paternally transmitted. Six out of these ten children represented three sibling pairs with two siblings in each pair. The disease was maternally inherited in 47 children from 40 families. Fourteen of the children constituted six affected sibling pairs; four siblings in one family, two siblings in each of the others. Two children were adopted from other countries and we had no information about the biological parents. Both the children had mild congenital DM1.

All individuals in the severe congenital group inherited the disorder from the mother. For paternal inheritance in the different DM1 types, see Table 4. The approximate CTG repeat expansions in the patients are shown in Figure 4. In 44 out of 57 children in whom information about the affected biological parent was available, the disease was not diagnosed in the parent until after the child was born.

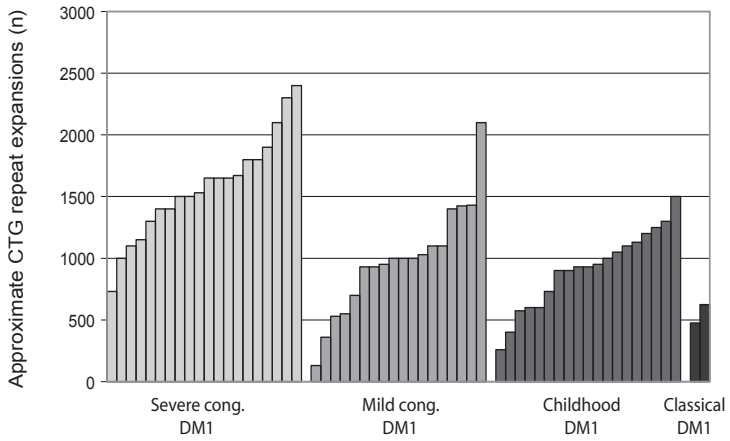

Figure 6 *The size of the CTG repeat expansions in the different DM1 forms*

Study I

Isometric muscle strength

Due to the high frequency of neuropsychiatric problems and the low cognitive level in the group of children with severe congenital DM1, participation in the assessment of muscle strength was difficult and sufficient data were not obtained. In addition, some of the children with mild congenital and childhood DM1 could not cooperate due to low developmental age. The children with mild congenital DM1 were significantly weaker than healthy control subjects in all assessed muscle groups. The children with childhood DM1 were significantly weaker in the wrist and ankle dorsiflexors, abductors and flexors of the hip, and flexors and extensors of the knee. There was, however, great variation regarding the degree of muscle weakness, where some of the children with childhood DM1 had normal muscle strength.

Motor function

Figure 7 shows the motor function score, with a maximum of 40, against age in children with DM1 and controls. The maximum score of 40 was not reached before 6 years of age in the control children. Motor function score is significantly reduced in children with DM1 compared to healthy controls.

Jumping, heel-standing and head-lifting in supine were the most difficult items to perform for the children with DM1.

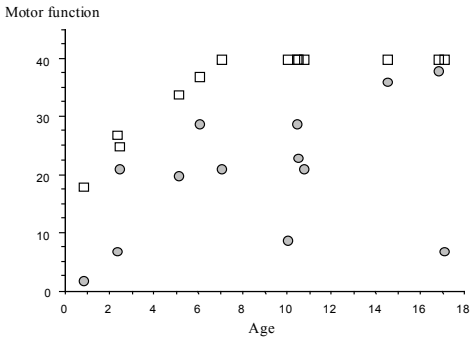

Figure 7a
Severe congenital DM1

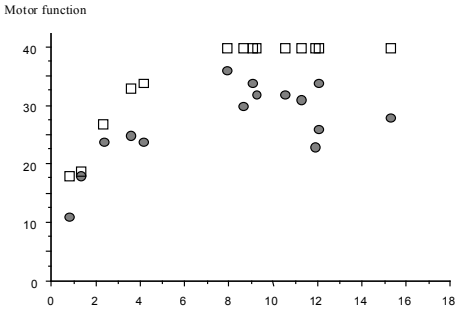

Figure 7B
Mild congenital DM1

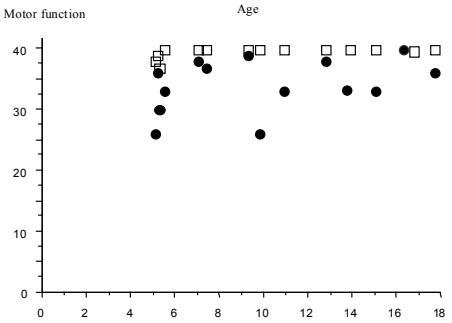

Figure 7C
Childhood DM1

***Figure 7 Motor function score**, with a maximum of 40, versus age in healthy control subjects (□) and children with: a) severe congenital DM1 (●) (n=13), b) mild congenital DM1 (●) (n=15) and c) childhood DM1 (●) (n=14). Significant difference was found between healthy control subjects and children with severe congenital DM (p=0,0015), mild congenital DM1 (p=0,0006) and childhood DM1 (p=0,0014).*

Contractures and skeletal deformities

Contractures and skeletal deformities were more frequent at the time of investigation than at birth, which suggests that especially foot and spine deformities increase over time. Foot deformities present at birth did not affect age at independent walking in any of the congenital subgroups.

Study II-III

Neuropsychiatric disorders

Fifty-four percent (n=31) of the children and adolescents with DM1 fulfilled at least one neuropsychiatric diagnosis as presented in Figure 6. ASC were present in 49% and the single most common diagnosis among the ASC was AD, present in 35% (n=20) of the study group. The individuals with ASC mainly had impairment in social interaction and communication, according to the DSM-IV criteria, and, to a lesser degree, problems in the areas of restricted repetitive and stereotyped patterns of behaviour, interests and activities, but enough to fulfill the criteria for ASC. One female had Asperger syndrome both according to the Gillberg & Gillberg and the DSM-IV criteria. Twelve individuals (22 %) fulfilled the criteria for AD according to the ADI-R algorithm. The mean scores of the different subdomains of the ADI-R were high in the whole DM1 group. Regarding the "repetitive" behaviour subdomain, none of the individuals with ASC exhibited self-injurious behaviour.
Individuals with ASC did not have significantly lower mean VIQ, PIQ or FSIQ, except for the individuals with mild congenital DM1 and ASC, where PIQ was significantly lower compared to those without ASC in the same subgroup. ASC was not correlated to gender or motor function.
Individuals with ASC and childhood DM1 scored significantly lower on the subdomain of Daily living

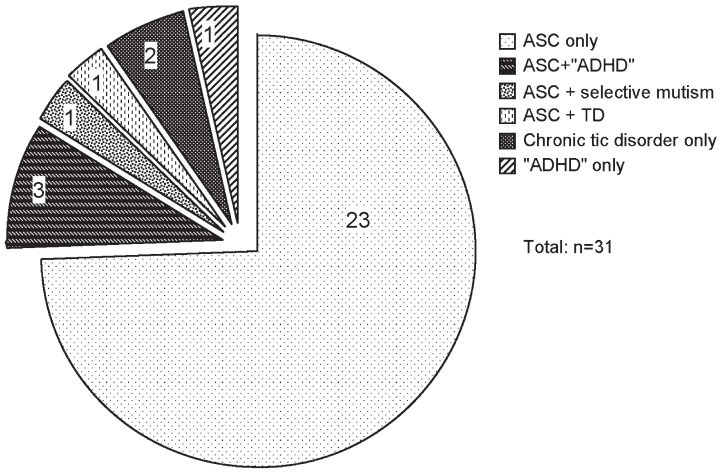

Figure 8 The childhood onset neuropsychiatric disorders in the study population
Abbreviation: ASC: autism spectrum condition, "ADHD": attention and hyperactivity disorder combined with LD, TD: Tourette´s disorder

Qualitative behavioural data

Most of the participants were kind, passive and had a low level of activity; more individuals tended to be passive, tired and calm rather than active and quick. The individuals talked fairly well even though they were withdrawn. They did not use language in a socially spontaneous way and they were not good at taking social initiatives. The symptoms of fatigue and excessive day-time sleepiness were frequently reported by the parents, although we lacked instruments to quantify the extent of these symptoms. There was no attrition from assessment caused by day-time sleepiness.

The clinical impression, according to the test results, indicate that their focusing skills were poor and they overlooked details, but they were not easily distracted by external impulses. In spite of the fact that many of the individuals had ASC, and although the Wechsler scales were a challenge to most of the participants, they cooperated and adjusted well to the examiner and the environment. All individuals who participated in the evaluations completed the assessments.

Global cognitive abilities

LD was found in 95% of individuals with severe congenital, 83% with mild congenital and 89% of those with childhood DM1. For the six individuals who could not complete any psychometric assessment, the level of LD was based on the mean VABS. No significant differences regarding mean FSIQ were found between males and females in the different DM1 subgroups. No significant correlations were found between FSIQ and gross motor function.

Verbal IQ (VIQ) and Performance IQ (PIQ) were assessed in 37 individuals using the Wechsler scales. VIQ was significantly higher than PIQ in severe congenital and childhood DM1. There were no gender differences with respect to VIQ and PIQ in any subgroup.

Adaptive behaviour

On the VABS scores, almost all the participants scored below the standard scores and adequate level matching their age. Where a psychometric assessment was performed, a significant correlation was found between the mean VABS score and FSIQ in mild congenital and childhood DM1. In general, the individuals performed better in the Socialisation domain, compared with the other domains. Mean VABS scores did not relate to gender or motor function in any DM1 subgroup.

Study IV

Visual acuity

Six individuals from the total cohort had VI (12 %) and 19 individuals had subnormal VA.

Only 48% of the individuals with DM1 > 4 years of age had BCVA ≥ 0.8 (including two individuals assessed with Cardiff cards), compared with 100% of the controls. Best corrected visual acuity (BCVA) in the different subgroups and the controls are presented in Figure 9.

Neither significant refractive error, nor fundus pathology affected visual acuity. Of the six individuals with VI, five were males with severe congenital DM1 and one a girl with mild congenital DM1. All but two with VI had a significant refractive error, three with hyperopia ≥ 4 D SE, one with hyperopia ≥ 2 D SE alone and two with astigmatism in combination with hyperopia ≥ 4 D SE. Four individuals had ASC, and all had LD.

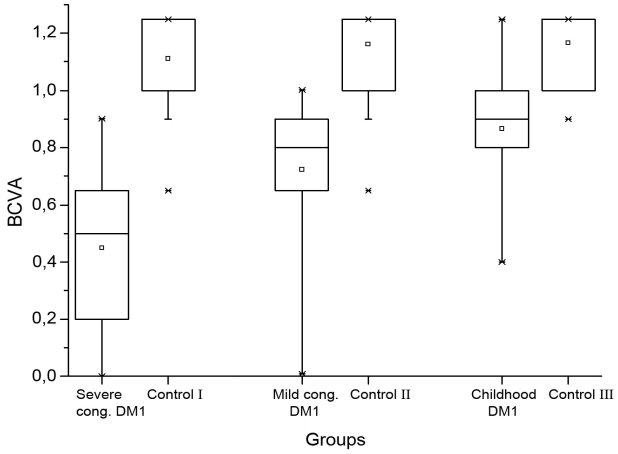

Figure 9 BCVA in the different subgroups of DM1 and the control groups
Box-plot values for best corrected visual acuity (BCVA) in the DM1 subgroups and the control groups. The boxes show the median (line), mean (small white squares) and 25th and 75th percentiles. The whiskers show the 5th and 95th percentiles and x the 1th and 99th percentiles.

Refractive error
Thirty-three (67%) of the individuals with DM1 had significant refractive errors. The individuals in the three DM1 subgroups had significantly more refractive errors than the controls.

Hyperopia ≥2 D SE was found in 27 (55%) of all individuals with DM1 and 19 (39%) of these individuals had hyperopia ≥4 D SE. Both hyperopia ≥2 and ≥4 D SE was significantly more prevalent in all the DM1 subgroups than in the control group. Hyperopia ≥4 D SE was significantly more prevalent in those with VI compared with those without. The individuals in the three DM1 subgroups were significantly more astigmatic than their controls.

Lens and fundus abnormalities
No true cataract was found in the whole study group; however, the most common finding was bilateral subtle haze or condensation in the posterior lens pole, found in 39% of the individuals.

Various scattered changes, such as tortuous vessels, indistinct foveal reflex and minor changes of the optic disc were found on fundus examination, but no pathological pigmentation.

VEP abnormalities

Nine individuals had abnormal VEPs; i.e., late P_1 latencies or side difference to monocular stimulation.

One adolescent with severe congenital DM1 presented with late N_1 (90 ms) in combination with late P_1 and subnormal vision. Four children in the congenital subgroups had normal N_1 but late P_1. 10.5 % of the study assessed with VEP had side difference to monocular stimulation.

Correlation visual and cognitive function

There were correlations between BCVA and FSIQ; the lower the BCVA, the lower the FSIQ (in severe congenital: $r_s = 0.54$, $p=0.029$; mild congenital $r_s = 0.62$, $p=0.025$; childhood DM1: $r_s = 0.48$, $p=0.041$). However, there was no correlation between BCVA and PIQ.

Discussion

Validity and reliability aspects

Isometric muscle strength

The dynomometer is a reliable method assessing muscle strength in children shown by several studies (Scott et al., 1982, Stuberg and Metcalf, 1988, Wadsworth et al., 1987). The method has previously been shown to be reliable also for investigating individuals with LD (Surburg et al., 1992). In the present study several individuals had LD, and assessment of individuals with a developmental age younger than four years of age was difficult. The individuals with severe congenital DM1 had the greatest reduction in motor function, which may reflect most severe muscle strength impairment in this group. However, due to the high frequency of neuropsychiatric problems and the low cognitive level of the participants, few assessments of musle strength were obtained and comparison with the other subgroups was not possible.

Motor function

The HMA scale is a method for evaluation of muscle function in children with muscle disease based on typical development. However, motor function in healthy children has never been assessed using the scale and at what age the total score is achieved is unknown. Motor function in the individuals with DM1 was therefore compared with the results of a control group. Some items require a normal motor developmental age of approximately six years of age, confirmed by the performance of the healthy individuals in the control group. The HMA scale is primarily valid for detecting reduction in motor function in individuals with mild motor impairment, but less valid in individuals with severe reduction as they do not manage more than the first items in the test.

ADI-R

This instrument has been shown to be valid and reliable in diagnosing autism and and in discriminating individuals with autism from individuals with LD when the non-verbal age is above 18 months (Hill et al., 2001, Lecavalier et al., 2006, Lord et al., 1997). By many, ADI-R is regarded as "the golden standard" in the diagnostic procedure of autism. ADI-R has not been validated for autism in co-occurence with DM1, cranial nerve dysfunction or sensory impairments. In younger children, the instrument is less valid as poor agreement was found between the ADI-R and clinical judgment in children aged 14–25 months (Chawarska et al., 2007) and 16–31 months (Ventola et al., 2006). These results suggest that caution is warranted in interpreting the results of the ADI-R in very young children. In our study population, twelve out of 20 diagnosed individuals with AD fulfilled the ADI-R logarithm for the disorder. All of these individuals had a developmental age above 18 months. The ADI-R interviews were all performed by the same clinical child psychologist. ADI-R was only one of the instruments used to collect information on autistic symptoms. ADI-R does not include an observation of the child. Aberrant personality traits and deficits in emotional recognition are described in adults

with DM1 (Delaporte, 1998, Winblad et al., 2005). Our impression was that the interviewed parents with DM1 tended to recognise and report too few symptoms and problems, which may contribute to explain the ADI-R results. For this reason, the diagnosis of ASC in children and adolescents with DM1 should not merely be based on the results of the ADI-R.

Neuropsychiatric diagnostic procedure

The ASC diagnoses were made conjointly and based on all available information; personal examination (pediatric neurologist and clinical psychologist), joint analysis of the videotapes, interviews, questionnaires and checklists according to specific diagnostic criteria (DSM-IV, Gillberg and Gillberg criteria for AS).

Global cognitive assessment

Psychometric assessment was performed by the same child psychologist in the majority of the study population (84%). The Wechsler scales were a challenge to most of the participants. They cooperated and adjusted well to the examiner and the environment in spite of the fact that many of the individuals had ASC. All individuals who participated in the evaluations completed the assessments.

The Griffiths Developmental Scale II is widely used in individuals with low developmental age, too young to be assessed with the Wechsler scales. Swedish normative data exist. According to one study, low scores on the language related scales at age 4 are correlated with moderate LD and behavioural problems at school (Conn, 1993). Children with AD have been found to perform better on the performance subscales as opposed to verbal subscales on the Griffiths test (Sandberg et al., 1993). The Wechsler scales are widely used instruments for providing measures of global intellectual ability (FSIQ). Swedish normative data were used. The Wechsler scales are widely used instruments for providing measures of global intellectual ability (FSIQ). Swedish normative data were used.

VABS

The VABS have been reported to be a valid instrument in assessing the cognitive level in individuals with profound and severe LD (de Bildt et al., 2005). To date, there is no consensus on how to combine the social quotient (the social developmental level in relation to age obtained by the VABS) and intellectual quotient (IQ obtained by psychometric assessment). Where a psychometric assessment was performed, a significant correlation was found between the mean VABS score and FSIQ in mild congenital and childhood DM1. The individuals with DM1 scored lower regarding adaptive level as opposed to intellectual level on all DM1 forms. We therefore believe that the poor results on the Griffiths and Wechsler scales represent the true cognitive level of the individuals with DM1 in our study population.

Visual function

Visual acuity testing requires intact recognition, visual memory as well as good cooperation. The mode of assessment was adapted to developmental age and testability.

All ophthalmological and orthoptic assessments were performed by an experienced orthoptist and a paediatric ophthalmologist, the latter performing all the VEP examinations.

The VEP testing was performed as flash testing as assessment with pattern VEP requires co-operation and stable fixation and many children were unable to participate properly.

Representativeness of study groups

Our cohort of individuals with DM1 was recruited from paediatric rehabilitation centres in the western and southern health care regions of Sweden. Sweden has a well-developed health care system for children with motor disabilities with virtually no privat alternatives to the public health care system. As individuals with the congenital forms of DM1 have motor impairment, they are most likely detected and known by the rehabilitation centres. A large group of the identified individuals with the congenital forms were included in this study. The findings and conclusions regarding congenital DM1 are therefore regarded as representative and generalisable.

Individuals with childhood DM1 are, however, an underrecognised group. As motor impairment is not a major problem, the individuals are often not known by the rehabilitation centres except for some individuals with LDs and speech problems. The individuals with childhood DM1 in our study could represent a more selected population with more pronounced impairment of motor and/or cognitive function, as opposed to the patients in other studies on childhood DM1 where the ndividuals were recruited from patient organisations or from paediatric genetic consultation clinics (Angeard et al., 2007, Steyaert et al., 1997). Most certainly there are undiagnosed individuals with childhood DM1 in the population in these two health care regions. The true frequency of childhood DM1 could only be ascertained by DNA analysis of all family members of known individuals with DM1, a procedure neither recommended nor ethical.

General discussion on major findings

Classification and correlations between CTG repeat expansion size and clinical findings

This study describes a group of children and adolescents with congenital and childhood onset forms of DM1. Within the group of children with congenital DM1 there was great heterogeneity regarding clinical features and a decision was made to split the group. All individuals presented with symptoms in utero or from birth, but in addition the children with severe congenital DM1 had had a life-threatening condition at birth with need for resuscitation and/or respiratory assistance.

The severe congenital form seemed to be a distinct group with clear differences compared to the children with mild congenital DM1. There was a male preponderance and in all individuals the disorder was transmitted maternally. There was less dif-

ference between the congenital groups with regard to the occurrence of ASC and age at independent walking. The phenotypic presentation regarding other variables varied less between the mild congenital and childhood DM1. Until recently, the presented classification had not been used in any previous study (Echenne et al., 2008). Classifying DM1 into four different forms (congenital, childhood, classical and late onset) is not a clearcut distribution; rather, there is a continuum between the different forms. Even if I agree with the conclusion by Echenne that there is an overlap between the different subgroups, there are major clinical differences between the severe and mild congenital groups during the neonatal period and between the mild congenital and childhood DM1 during early infancy. The more severe the form of DM1, the lower the FSIQ, motor function and BCVA, and the higher the occurrence of ASC and VI. Further research is warranted regarding the prognostic value of these subgroups.

The clinical picture showed great variability from one individual to another with the same CTG repeat expansion size. As an exemple, presence of expansion size by approximately 1000 expansions could be found in both the congenital as well as in the childhood DM1 subgroups. No clear phenotype-genotype correlations were found, even though the largest expansions were present in the severe congenital group. The CTG amplification had an impact on several parameters. The larger the amplification, the more reduced the motor function, FSIQ, VIQ, PIQ, BCVA and VI. Due to somatic instability, the CTG expansion size increases with time in all categories of DM1, affecting several organ systems, and it would be reasonable to expect an impact on cognition related to the duration of the disorder.

Paternal inheritance was found in one fifth of the study population and this small group calls for caution when interpreting the results. It seems, however, that maternal inheritance influences FSIQ, VIQ, PIQ and adaptation negatively. In the current study, the lower results on cognitive measurements found in individuals with maternal inheritance in the childhood subgroup corroborates another study, and may be a reliable finding (Angeard et al., 2007)

Motor function

The individuals with severe congenital DM1 had the most severely reduced motor function and the largest repeat expansions. The typical pattern of muscle weakness in DM1, with distal weakness being greater than proximal weakness was seen in most individuals in our study. However, the investigation revealed that the proximal muscles were also affected in many of the children, especially in those with the congenital onset form.

We have no information on the age at optimum motor function and time for deterioration and muscle wasting in the study population, as the children have only been assessed once regarding muscle strength. To achieve such data, a prospective follow-up study will have to be performed. However, few of the children had problems with walking, running or climbing stairs, although many were clumsy. Characteristic

compensatory manoeuvres due to muscle weakness were almost absent, but the children moved slowly which could be compensate for the muscle weakness.

Postural stability is the ability to maintain the body in equilibrium and requires information from the somatosensory, vestibular and visual systems. Activation of these systems induces postural reactions for the purpose of returning the body to equilibrium. To recover postural stability, the ankle joint movements are one of the essential strategies in sustained balance control and require intact range of movements and strength in the ankles (Shumway-Cook and Woollacott, 1985). Many of the children with DM1 had problems with postural stability and control. The foot deformities, limited range of movements and weak ankle flexors present in many of the individuals with DM1 contributed to the effect on postural control and stability. However, postural stability is well developed in other conditions with muscular weakness, such as spinal muscular atrophy (SMA), amyoplasia and Duchenne muscular dystrophy (Kroksmark, 2006). It seems that delayed psychomotor development and LD, frequently present in our population, may have a great impact on the automatic postural control system, similar to that in children with Down syndrome (Shumway-Cook 1985). Affection of the central motor control system has been shown in one study on adults with DM1 where movement-related cortical potentials preceding voluntary movements were investigated and subclinical abnormalities in CNS functioning were found independently of muscle weakness (Mitsuoka et al., 2003).

Motor function was affected by impaired postural stability, delayed motor development and, most certainly, by muscle weakness as well. The presence of contractures further aggravates motor function as contractures both have an impact on postural stability and muscle weakness. A muscle that is already weak may be further compromised if held in a shortened position (Eagle, 2002). Although delayed walking ability in children with congenital DM1 and talipes by 14 months have been shown earlier (Roig et al., 1994), this finding was not confirmed in the present study as presence of foot deformities during the neonatal period in individuals in the congenital subgroups did not affect age at walking.

The excessive fatigue and day-time sleepiness seen in children and adolescents with DM1 is a prominent feature and most likely primarily due to affection of the CNS, although muscle weakness may aggravate the symptoms.The knowledge oo the high frequency of fatigue and day-time somnolence in our study was gained by reports from caregivers. No instrument measuring these problems was included in the study; hence, there was no information on muscle weakness being responsible for the presence of fatigue or somnolence.

Neuropsychiatry with special reference to ASC

ASC and/or other neuropsychiatric disorders, such as ADHD and Tourette's disorder, were found in 54% of the total DM1 group. Forty-nine per cent had ASC and AD was the most common diagnosis, present in 35% of the individuals. The indi-

viduals with DM1 and ASC mainly had impairment in social interaction and communication and, to a lesser degree, problems in the area of restricted repetitive and stereotyped patterns of behaviour, interests and activities, but enough to fulfil the criteria for ASC. In the current study, most of the individuals with DM1 and ASC fit the description of the passive type of ASC delineated by Wing (Wing, 1997), with reduced spontaneous social interaction but passive acceptance of approaches from others. This phenotype may be less recognisable as a part of the ASC by parents and clinicians and could be the reason why there are few reports on ASC in DM1 in the literature. There may be a risk of interpreting the passiveness as inattention and not as a part of the ASC symptomatology.

In ASC, repetitive behaviour and stereotypies are common in addition to self-injurious behavior (Billstedt et al., 2005, Nordin and Gillberg, 1998). In our group, however, none of the individuals exhibited self-destructive behaviour. The behavioural phenotype of the individuals in our study population is further characterised by reduced initiative and slow pace, due, in part, both to fatigue and excessive day-time sleepiness. Day-time somnolence has been reported in childhood DM1 (Quera Salva et al., 2006), but not previously, to our knowledge, in individuals with congenital DM1. Day-time sleepiness has been found to be correlated with reduced size of the corpus callosum in adults with DM1 (Giubilei et al., 1999). In congenital DM1, MRI studies have shown corpus callosum hypoplasia (Hashimoto et al., 1995, Martinello et al., 1999), but whether such a correlation also exists between hypoplasia and excessive day-time sleepiness in our patients is unknown.

In several studies, children with ASC have been found to have reduced ability to recognise facial expressions of emotions (Celani et al., 1999, Hobson, 1986a, Hobson, 1986b), which, at least in part, accounts for the social disability in children with ASC (Frith, 1989). It has been argued that autistic symptoms in DM1 may be caused by difficulties in interpreting facial expressions secondary to poor non-verbal communication in parents with DM1. In that case, the predominant autistic feature in children with DM1 would be difficulties with reciprocal communication. However, according to the results on the ADI-R, the problems pertaining to reciprocal communication did not specifically exceed symptoms in other areas.

The high rate of ADHD in childhood DM1 reported in another study (Goossens et al., 2000) could not be confirmed in the present study. Factors contributing to the discrepancy could be a referral bias or different assessment tools. In the present study, we used the DSM-IV checklist as well as the FTF to assign ADHD diagnoses. In adult DM1, attention deficits are also present (Modoni et al., 2004, Winblad et al., 2006b).

Behaviour abnormalities seem to be a constant feature in childhood and adult variants of DM1 with many symptoms in common. Studies on adult DM1 regarding personality have shown an avoidant personality profile in approximately 20%. Reduced empathy and cooperativeness have also been observed (Delaporte, 1998,

Winblad et al., 2005). Furthermore, lack of social cognitive ability with failure in the ability to recognise facial emotions such as anger, fear and disgust has been found in a study on individuals with adult DM1 (Winblad et al., 2006a). The extent of inability was associated with the CTG repeat expansions size. Other studies on adult individuals with DM1 have used the Temperament and Character Inventory (TCI) pertaining to personality traits. High scores on Harm Avoidance (HA) and low scores on Persistence (PE) and Cooperativeness (CO) were identified (Meola et al., 2003, Winblad et al., 2005). A similar TCI profile with high scores on HA and low scores on CO have also been reported in adult patients with ASC (Anckarsater et al., 2006). Since one of the diagnostic criteria for AD is evidence of delayed or deviant development before 36 months of age, individuals with adult onset DM1 cannot fulfill the criteria for AD.

Emerging evidence of autism as a disorder affecting synaptic connections has recently been presented (Garber, 2007). Inefficiently organised synaptic connections influence the formation of functional connectivity between different cortical regions. Synapse-specific local protein synthesis is thought to be crucial for neurodevelopment and plasticity and involves neuronal RNA-binding proteins. As described earlier, it would be reasonable to assume that both sliceopathy of Tau, NMDAR1 and APP, as well as impaired transcription of DMWD, will have an impact on synaptogenesis and accordingly development of autistic symtoms in DM1.

Cognitive and adaptive skills

LD was found in 95% per cent of those with severe congenital, 83% of those with mild congenital and 89% of those with childhood DM1. These results are in accordance with the only other study using the same classification of the congenital groups as our study (Echenne et al., 2008). The individuals with childhood DM1, however, presented lower results than two other studies with a reasonably large sample of childhood DM1 patients (Angeard et al., 2007, Steyaert et al., 1997). Interestingly, in the childhood and mild congenital subgroups, individuals with paternal inheritance had higher scores than individuals with maternal inheritance on the Wechsler subscales.

The significant difference of a stronger VIQ than PIQ in childhood DM1 group corroborates another study on childhood DM1 (Angeard et al., 2007). Visuoperceptual deficits are also present in adults (Winblad et al., 2006b). Low results on PIQ compared to VIQ are observed in several other syndromes and neurological disorders involving the central nervous system, including hydrocephalus (Lindquist et al., 2005), 22q11 deletion syndrome (Niklasson et al., 2005), and cerebral palsy (Carlsson et al., 1994). The relative strength in verbal compared to performance tasks in individuals with childhood DM1 group is due to better verbal understanding (Vocabulary and Similarities). The relatively high scores on the performance subtest Picture arrangement in childhood DM1 is probably explained by the verbal element in this task. According to the VABS, impressive language exceeded expressive language ability in all DM1 subgroups.

The poor results on the WISC-III/WAIS-III subtests in the congenital groups made it impossible to perform in-depth analyses of cognitive profiles in these groups. However, all groups seemed to show poor results on Arithmetic. In AD, selective impairment is seen in certain subtests (Picture Arrangement and Comprehension) and good performance in others (Block Design and Digit Span) (Happe, 1994). In childhood DM1, with better subtest results, the typical peaks and troughs described in AD were not found. On the other hand, the occurrence of AD was not as prevalent in this group.

Almost all participants showed poor results on the VABS. Individuals with AD usually have higher scores on Communication and Daily Living than on Social skills on the VABS (Kraijer, 2000). Even though the individuals in our study achieved the comparatively highest scores in the Socialisation domain, the results were generally low, as 94-100% of individuals with congenital and childhood DM1 scored less than adequate in the socialisation subdomain, indicating problems with social interaction. No difference regarding the VABS profile was detected between the individuals with and without ASC, respectively.

Visual function

The size of the CTG repeat expansion had an impact on BCVA in all subgroups with lower values in individuals with larger expansion size. The CTG repeat expansion size affected the occurrence of high hyperopia and astigmatism negatively only in the childhood subgroup**.** VI was found in 12% of the total study population and all but one of these individuals were in the severe congenital DM1 group. Subnormal VA was found in 39% of the individuals, mainly in the congenital groups. Only 18% of the individuals with severe congenital DM1 had normal VA. Hyperopia was found in 55% of all individuals with DM1 and 39% of them had high hyperopia (≥4 D SE). Hyperopia was significantly more prevalent in all the DM1 subgroups than in the control group and high hyperopia was significantly more prevalent in individuals with VI than in those without.

The majority of infants are normally born with hyperopia. The process of emmetropisation is partly due to visual feedback. Blurring of the retinal image due to strabismus, short axial length, corneal abnormalities and accommodative failure will all influence the process. Short axial length has been reported in children with DM1 (Weiss et al., 1989) and increased thickness of the cornea in adults (Rosa et al., 2008). Furthermore, if the afferent visual pathways are affected due to brain damage, the emmetropisation will be affected as well, with persistent hyperopia. Our findings of high hyperopia, astigmatism and VI in individuals with childhood DM1 may be suggestive not only of eye pathology but of CNS involvement also in this group.

This study included individuals with severe hyperopia without reduced BCVA, as well as individuals with severely reduced BCVA without refractive errors. Normal visual feedback could be assumed in individuals achieving normal VA with correc-

tion, but in those individuals with reduced BCVA, abnormalities of the eye alone or in combination with CNS affection is present.

Affection of the lens would also affect visual feedback. In our population, however, manifest cataract was not present, although lens pathology suggestive of early stages of cataract was present in 41% of individuals. Preliminary data from our own multidisciplinary study show an increased prevalence of strabismus, especially esotropia, mainly of a partially accommodative type (Aring, forthcoming data).

The VEP assessment indicated normal primary visual pathways, i.e. normal N_1 potential and short latency activation of the primary visual cortex. However, impaired extrageniculate non-specific pathways or impaired central nervous impulse processing was present in 10 % similar to that found in children with progressive white matter abnormalities albeit to a lesser extent (Kristjansdottir et al., 2002). Just over 10% showed VEP findings with cortical side differences to monocular stimulation, indicating abnormalities in the chiasma, as those found in albinism (Apkarian, 1992) suggestive of a developmental anomaly.

Evaluation using evoked potentials seems to be one way to elucidate the CNS involvement in DM1. In adults with DM1, evidence of central involvement has also come from studies of brainstem auditory, somatosensory and visual evoked potentials (Sandrini et al., 1986, Shaunak et al., 1999, Verhagen et al., 1992). Furthermore, electrophysiological alterations were not correlated either with subject age or disease duration (Cosi et al., 1992)

Regarding pathogenic mechanisms, mouse models have shown that enlarged CTG repeat expansions cause loss of function in the adjacent SIX5 gene due to epigenetic effects including methylation and chromatin condensation and result in progressive destruction of lens tissue and occurrence of cataract in mice (Klesert et al., 2000). However, decreased SIX5 transcription did not affect either corneal or retinal structures and/or function.

Relation between visual impairment, cognition, ASC and motor function

A wide range of brain pathologies cause VI. Periventricular white matter lesions are the most common cause of cognitive visual dysfunction, mainly visual perceptual problems (Dutton 2001). Cognitive visual dysfunction includes other modalities as well, such as visuospatial and constructive abilities. Cognitive visual dysfunction in children have been described in several neurodevelopmental disorders and syndromes such as CP (Stiers et al., 2002), hydrocephalus (Andersson et al., 2006), Williams syndrome (Farran and Jarrold, 2003), 22q11 (Zinkstok and van Amelsvoort, 2005), and cerebral white matter disorders (Kristjansdottir et al., 2002).

VI affects the quality of eye contact and also impacts on several aspects of development of communication and social skills. Occurrence of visual perceptual problems is known to render difficulties in recognition of facial expressions. In individuals

with ASC, presence of visuospatial difficulties further aggravates their impairment.

Afferent visual information is processed in the occipital cortex. The information is then transferred to associative areas of the brain along the dorsal and the ventral streams (Dutton, 2003). The dorsal stream transfers information from the occipital cortex to the parietal and frontal cortex. The parietal lobe chooses which visual information to pay attention to and the information is passed on to the frontal lobes, which direct the head and eyes to look at the specific object. The motor cortex receives visual information and on basis of this information, movements are initiated. The ventral stream, on the other hand, carries information to the temporal lobes. The temporal lobes are responsible for visual recognition, orientation and visual memory, among other functions (Dutton and Jacobson, 2001). Damage in the temporal area can result in impaired face recognition.

In the current study, PIQ was lower than VIQ, but specific assessment of visual perception was not performed. It has been postulated that early brain damage may give rise to specific visual perceptual deficits, independently of - although occurring in association with - selective impairment of non-verbal intelligence (Stiers et al., 1999). As several brain abnormalities of developmental origin are known in at least congenital DM1, it would be more surprising if no cognitive visual dysfunction would be present. However, the low developmental age in many of the children with DM1 makes assessment of visuoperceptual abilities a challenge. Visuoperceptual problems have been demonstrated in individuals with childhood DM1 with the poorest performance on tests measuring visuospatial construction ability (Object assembly and Block design) (Angeard et al., 2007). The same study demonstrated a negative correlation between CTG repeat expansion size and IQ measures but also a negative correlation between repeat size and measures of working memory and visuospatial skills, also in a context of normal or subnormal intelligence. The subtest profile in our population was in accordance with this study, with maternal inheritance resulting in lower values than those obtained in individuals with paternally inherited disorder. Although the test results were poorer in our population compared to the French study.

Eye motility problems are common in children with VI due to CNS affection such as strabismus, nystagmus, unstable fixation, inaccurate fast eye movements (dysmetric saccades), and deficient smooth pursuit movements (Jacobson et al., 2002). Abnormal saccadic and smooth pursuit (SP) eye movements have an impact on visuoperceptual ability. Abnormalities of saccadic eye movements have been described in adults with DM1 (Bollen et al., 1992, Verhagen et al., 1992, Versino et al., 1998), as well as altered smooth pursuit (SP) eye movements (Anastasopoulos et al., 1996, Bollen et al., 1992, Verhagen et al., 1992, Versino et al., 1998). No correlation of saccadic eye movement defects and severity of muscular affection or disease duration has been shown. Affection of saccadic eye movement may be attributable to CNS dysfunction (Di Costanzo et al., 1997). This statement is supported by the finding that low gain SP eye movement was unlikely to be related to extra-ocular

myopathy, but could rather be explained by periventricular white matter abnormalities (Bollen et al., 1992). Furthermore, impairment of SP performance is related to both parieto-occipital and frontal white matter, the latter leading to the most severe SP impairment (Kimmig et al., 2002). Preliminary data from our own multidisciplinary study show abnormal horizontal SP, saccade abnormalities and nystagmus (Aring, forthcoming data).

Visual feedback is essential to remain postural stability. The refraction errors and low visual acuity as well as strabismus and altered eye-movements present in the study population will most certainly affect motor function, which may account for the reduced postural stability found in the individuals with DM1. Additionally, impaired processing of visual information will aggravate motor dysfunction further.

Gender aspects

A preponderance of males in congenital DM1 was reported in 1984, but has not been mentioned or discussed since then (O'Brien and Harper, 1984). Evidence suggests that females have an advantage over males, with a better outcome during the perinatal period, particularly after preterm birth (Di Renzo et al., 2007), and that male neonates are at greater risk of developing periventricular leukomalacia (PVL) than females (Hatzidaki et al., 2009). On the other hand, in Down syndrome mortality is greater in females (Leonard et al., 2000).

Our finding of a male preponderance in the severe congenital group may reflect the vulnerability of males. On the other hand, there is a possibility that females with severe congenital DM1 are overrepresented as stillbirths in early pregnancy. Maternal inheritance was found in all individuals in the severe congenital group. In the mild congenital form, paternal inheritance was present in only three individuals, who had smaller CTG repeat expansions than the 13 individuals with maternal transmission. In childhood DM1, there was no significant difference in CTG repeat expansion size between individuals with maternal and paternal inheritance.

The reported higher rate of ASC reported in males as opposed to females (Fombonne, 2003) was not confirmed in our study, as no gender difference regarding ASC was present; nor were there any gender differences regarding FSIQ, VIQ or PIQ results.

Strengths and limitations

Strengths

The current study provides data from a comparatively large group of young patients with congenital and childhood DM1. To our knowledge, this is the first study on childhood onset DM1 where motor function and isometric muscle strength, neuropsychiatric disorders, adaptation and several visual parameters have been assessed systematically, and correlated with the size of the CTG repeat expansion. By combining assessments of both global cognition and adaptation, the level of functioning

was more adequately described. The subgroups have been extensively examined including complete molecular data on all individuals as well as their affected parent.

Limitations:
The lack of more suitable instruments for assessing the low levels of intellectual functioning is one limitation, but adding the VABS to the test battery and the strong correlation between the VABS and the intellectual level strengthen the results. No appropriate scales to quantify the degree of sleepiness were included in the test battery.

The conjoint diagnostic procedure carries a potential risk of bias, and separate diagnostic assignment would have provided the possibility of analysing inter-rater reability, which was not the case in our study.

No instrument based on interaction with and observation of the individuals in order to assess ASC was included. A valuable instrument would have been the Autism Diagnostic Observation Scale-Generic (ADOS-G) (Lord et al., 2000). In toddlers, good agreement has been found between the results on ADOS and the clinical diagnosis based on the DSM-IV criteria (Ventola et al., 2006). A recently published study has also shown that a combination of ADI-R and ADOS provides important information in the diagnostic procedure of ASC in toddlers (Gray et al., 2008).

Research implications
The results presented in this thesis are based on a cross-sectional study. Further studies are warranted to improve our understanding of several parameters. Prospective longitudinal follow-up studies will provide further knowledge on how age and the severity of the disorder influence the progress.

A decline in intellectual functioning over time has been reported in individuals with childhood DM1 (Echenne et al., 2008, Steyaert et al., 1997). Due to somatic instability, the CTG expansion size will increase with time affecting different organs. To show a possible degenerative impact on several organ systems, including the brain and muscles, further research is needed.
In-depth analyses of visuoperceptual deficits, as well as trials to examine whether the social deficits exhibited by children with DM1 include impairment of face recognition and emotion perception similar to the findings in adults with DM1, would be of great interest.

As almost no ophthalmological studies on children with DM1 have been carried out, there is a need for further studies. Assessment of accommodation and saccadic eye movement are some parameters to be investigated, as the parents in our study reported a high prevalence of photosensitivity but no systematic investigation was performed. Investigation with electroretinography would also be of interest, as photosensitivity could be a symptom of retinal abnormalities. Retinal changes have not yet been described in children but are well known in adults with DM1 and may be

due, either to peripheral pigmentary degeneration similar to retinitis pigmentosa, or to a central macular lesion (Kimizuka et al., 1993).

The impact of day-time sleepiness on cognitive abilities is still unclear, but has an influence on activities of daily life. Structured trials on different treatment modalities are warranted.

So far, no studies have been performed in children and adolescents with DM1 regarding the effect of muscle training. In adults, aerobic training has been shown to be safe and can improve fitness effectively and increase the muscle fibre diameter significantly without any creatine kinase increase (Orngreen et al., 2005). Whether any kind of systematic training of motor activity can postpone the noticed and expected deterioration of motor function is still unknown. It is possible to investigate both muscle strength and motor function in most of the children with DM1, which is a prerequisite for prospective longitudinal studies.

To elucidate what molecular events cause neuronal impairment in children with congenital and childhood forms of DM1, exploration of the correlation between brain imaging and molecular data with symptoms of ASC, LD and VI would be of great interest. Hopefully, further advances in the research into DM1 in children will shed light on the pathophysiology of ASC.

Further studies including MRI, PET and SPECT studies are warranted to elucidate what molecular events cause neuronal impairment with symptoms of ASC, LD and VI in children with congenital and childhood forms of DM1. Hopefully, further advances in the research concerning DM1 in children, will shed light on the pathophysiology of ASC.

Finally, as molecularly based treatments targeting the RNA disease mechanism directly are being developed, further and closer collaboration between clinical and molecular-based research is required to evaluate the desirable reversal of the clinical features. Further research is required, hopefully making DM1 a treatable disorder in the future.

Clinical implications

Although no trials on the effect of muscle training have been performed in children and adolescents with DM1, development of normal motor control and prophylactic chest care should be encouraged. Due to the risk of increasing contractures and skeletal deformities, regular follow-ups are recommended.

Once muscle strength improves, LD and behavioural disturbances become the main clinical problems. LD and behavioural disturbances are the factors that have the greatest influence on the long-term management and prognosis of this cohort of individuals.

The occurrence of ASC in almost half of the patients in our sample indicates that ASC is common in children and adolescents with DM1. Awareness of this comorbidity is crucial and may contribute to understand why patients with DM1 may not function as well as expected in their activities of daily life. Furthermore, knowledge of ASC is essential when planning the educational support and rehabilitation care for these patients. Occurrence of VI and limited facial expressions necessitate a variety of autism diagnostic instruments in an effort to diagnose ASC in individuals with DM1; both interviews and observational instruments are needed. I believe that individuals with DM1, especially with the childhood onset form, will be discovered within the group of patients with unexplained ASC, LD and mild hypotonia. Early identification of ASC is of great clinical importance in order to instigate ameliorative multimodal support and interventions.

It seems that the ASC in DM1 represent a unique phenotype and that the individuals are not as socially impaired as in "classic" autism. It should be emphasised that ASC represent a spectrum, and include a variety of conditions with different aetiology; DM1 being one of these disorders with a complicated pathogenesis. There is no doubt, however, that cerebral involvement is a direct consequence of the genetic disorder.

It is important to make an accurate neuropsychological assessment in children with DM1 to obtain information on the individual's cognitive level and overall functioning, in order to improve school and everyday life functions. Awareness of ASC and LD comorbidity in DM1 is essential when planning the educational support and rehabilitation care provided to these patients.

An increased incidence of refractive errors, strabismus and visual impairment has a significant impact on visual function, which also influences neurodevelopmental and educational issues.
Visual impairment in individuals with congenital and childhood DM1 may be due to a combination of CNS abnormalities and focal changes in the eye. In clinical practice, individuals with DM1 are referred to ophthalmological assessment due to expected cataract, but this is true only for adult patients. Instead, the children and adolescents need early ophthalmological assessment and follow-up because of the variety of their visual function pathology, such as hyperopia, astigmatism and low VA.

Early and careful assessment, taking into account both neurophthalmological and ophthalmological aspects, is essential for a correct diagnosis and the development of individualised rehabilitation programmes.

Conclusions

DM1 in childhood shows a great variability with regard to symptoms and age at onset. Based on age at onset and presenting symptoms, the individuals were divided into severe and mild congenital, childhood and classical DM1. At the individual level, the size of CTG repeat expansions cannot predict the DM1 form. No clear phenotype-genotype correlations were found even though the largest expansions were present in the severe congenital group.

Children with DM1 were significantly weaker than healthy controls in most of the assessed muscle groups but there was great variation regarding the degree of muscle weakness. Motor function was significantly reduced in children with DM1 compared to healthy controls.

Almost half the study population had ASC and AD was the frequent ASC diagnosis. ASC did not predict the level of LD. Both conditions should be regarded as a consequence of the disorder.

In the present study, most of the children and adolescents with congenital and childhood DM1 had LD, usually in the moderate to severe range. Almost all the participants showed poor adaptive skills.

Compared with the controls, the children and adolescents showed a high prevalence of visual dysfunction with impact on the developing visual system, such as low visual acuity and refractive errors. No true cataract was found. Subtle non-specific fundus changes were present in addition to VEP pathology. In DM1, a variety of visual function pathologies are present with impact on the developing visual system.

The size of the CTG repeat expansion had an impact on several variables. The frequency of ASC increased with increasing CTG repeat expansions. Motor function, FSIQ and BCVA and VABS presented lower values in individuals with larger expansion size. Maternal inheritance had a negative impact on intellectual and adaptive functioning. The more severe the form of DM1, the more reduced the motor function and BCVA and the higher the frequency of ASC and LD.

In everyday life, it appears that individuals with DM1 primarily suffer from their CNS-related symptoms, such as cognitive deficits, day-time sleepiness, neuropsychiatric problems and visual dysfunctions, rather than their neuromuscular symptoms.

Sammanfattning på svenska

Dystrofia myotonika typ 1 (DM1) ***orsakas av en instabil mutation*** (förstorad CTG repetition) på den långa armen av kromosom 19 (19q13). Sjukdomen är autosomalt dominant ärftlig vilket innebär att upprepningsrisken vid varje graviditet är 50 %. Sjukdomen karakteriseras av att den tenderar att förvärras från generation till generation, vilket kallas anticipation. DM1 drabbar många olika organ och uppvisar varierande svårighetsgrad och ålder vid sjukdomsdebut. DM1 förekommer i fyra former: medfödd - (svår och mild), barndoms-, klassisk vuxen- och mild vuxenform. Vid den medfödda formen ärvs sjukdomen i de allra flesta fall från mamman. Den medfödda formen av DM1 ***förekommer*** hos ca 5:100 000 barn, men förekomsten varierar mellan olika geografiska områden. ***Den medfödda formen*** debuterar under fosterlivet eller vid födelsen. Minskade fosterrörelser och överskott av fostervatten är symptomen under fosterlivet. Vid födelsen uppvisar barnet en uttalad generell muskelslapphet inklusive ansiktssvaghet. Till följd av denna slapphet har barnet andnings- och sugsvårigheter samt leddeformiteter (tex klumpfot). Vid både ***svår och mild medfödd form*** har barnet symptom från födelsen men ***skillnaden*** består i att den svåra formen innebär ett livshotande tillstånd vid födelsen med tecken på syrebrist och behov av andningsunderstöd. Hos barn med ***barndomsformen*** debuterar symptomen mellan 1 och 10 års ålder efter en okomplicerad graviditet och nyföddhetsperiod. Utvecklingen är normal under första levnadsåret, men under småbarnsåren förekommer tal- och inlärningssvårigheter, viss grad av nedsatt muskelspänning, men muskelsymptomen är oftast diskreta. Myotoni (”muskelspasm”) debuterar oftast i skolåldern. Buksmärtor är ett vanligt förekommande symptom.

Denna avhandling presenterar resultaten från några av de delstudier som ingår i en multidisciplinär deskriptiv tvärsnittsstudie, ett samarbetsprojekt mellan Drottning Silvias barn- och ungdomssjukhus, Göteborg, NU-sjukvården NÄL, Trollhättan, Odontologen och Mun-H-Center, Göteborg, Barn- och ungdomshabiliteringar i Västra Götaland, Skåne och Halland, samt Barn- och ungdomsklinikerna i Skåne och Halland.
Projektets målsättning har varit att undersöka problem och svårigheter hos barn med DM1. Resultaten skall untgöra ett underlag för att optimera vården och omhändertagandet av barnen.

Syftet med studien har varit att 1) beskriva den kliniska bilden under barn- och ungdomsåren, 2) att undersöka eventuell genotyp/fenotypkorrelation, d v s ta reda på om det fanns ett samband mellan antal repetitioner av CTG och symtombild, 4) beskriva motorisk förmåga och muskelfunktion, 5) undersöka kognitiva, adaptiva och neuropsykiatriska svårigheter samt 6) beskriva de syn- och ögonmässiga avvikelser som finns i gruppen.

I de tre regionerna Skåne, Halland och Västra Götaland inbjöds 64 barn och ung-

domar med känd DM1 diagnos att delta i studien varav ***59*** tackade ja och ***ingick i studien***, 20 hade svår medfödd-, 19 mild medfödd -, 19
barndoms- och 2 hade klassisk form.

I de ***metoder*** som användes ingick insamling av medicinsk information från journaler. Sjukgymnast undersökte muskelstyrka, motorisk funktion och ledrörlighet. Muskelstyrka och motorisk förmåga jämfördes med värden hos barn i en kontrollgrupp. Föräldrarna genomgick strukturerad intervju om svårigheter beträffande beteende, utveckling, och anpassning i vardagslivet ingick. Alla barn och ungdomar bedömdes av psykolog avseende begåvningsnivå. Neuropsykiatriska diagnoser ställdes utifrån DSM-IV:s diagnoskriterier. Ögonläkare och ortoptist undersökte barnen med avseende på synskärpa, ögats brytningsförmåga, ögonbotten och linsens utseende. Slutligen ingick en elektrofysiologisk undersökning av synbanorna. Resultaten jämfördes med värden hos barn i en kontrollgrupp.

DM1 hos barn och ungdomar uppvisar stor variabilitet i symptom och debutålder. Antal CTG repetitioner kan ej på individnivå förutsäga sjukdomsformen, men de största repetitionerna återfinns i den svåra medfödda formen. I denna form var det en övervikt av pojkar och alla hade ärvt sjukdomen från sin mor.

Barn med den milda medfödda formen och barndomsformen är svagare än barn i kontrollgruppen i samtliga undersökta muskelgrupper. Barn med mild medfödd DM1 är svagare än barn med barndomsformen men det är stor variation vad gäller muskelstyrka. Kontrakturerna är vanligare vid undersökningstillfället än vid födelsen. Särskilt fot- och ryggdeformiteter ökar med stigande ålder.

Knappt hälften av gruppen barn och ungdomar med DM1 har autismspektrumstörning (ASC), men även andra neuropsykiatriska tillstånd förekommer. Det finns ingen koppling mellan förekomst av ASC och kön eller motorisk förmåga. Inte heller fanns det någon relation mellan begåvningsnivån och förekomsten av ASC, utan båda tillståndet är en konsekvens av sjukdomen.

En övervägande majoritet av barnen och ungdomarna med dom medfödda formerna och barndomsformen har utvecklingsstörning, oftast av måttlig eller svår grad. Nästan alla uppvisar dålig adaptiva förmåga, dvs nedsatt anpassningsförmåga gällande dagliga aktiviteter.

Jämfört med friska kontroller har barn och ungdomar med DM1 en hög förekomst av ögon- och synförändringar till följd av bristande utveckling såsom låg synskärpa och brytningsfel. Många barn och ungdomar har linsförändringar. Därutöver finns varierande och ospecifika ögonbotten- och elektrofysiologiska förändringar. Vid DM1 förekommer varierande avvikelser i synförmågan som i sin tur påverkar synens vidare utveckling.

Mutationens storlek påverkar sjukdomsbilden. Motorisk förmåga, begåvningsnivå, synskärpa och adaptiv förmåga är mer påverkade vid större mutation. Begåvning och adaptiv förmåga är lägre hos individer som har ärvt sjukdomen från modern jämfört med de som ärft sjukdomen från fadern. Ju svårare sjukdomsform desto sämre är motorisk förmåga och synskärpa. ASC och utvecklingsstörning är vanligast vid den svåraste sjukdomsformen.

I första hand påverkas vardagslivet hos individer med DM1 av de hjärnrelaterade symptomen såsom nedsatt begåvning, ne,ropsykiatriska svårigheter och synproblem. De neuromuskulära symptomen har inte lika stor betydelse för individens funktion i vardagen.

Acknowledgements

This research is the result of true teamwork in many ways and I wish to express my sincere gratitude, first and foremost to all children, adolescents and parents for participating in all the time-consuming examinations. Without your willingness and patience, this work would not have been possible.

I especially wish to thank:
Professor Már Tulinius, my scientific supervisor, for your never ending enthusiasm, inspiration, encouragement and humble attitude. You have guided my research, step by step and were always available when necessary. I'm looking forward to our future cooperation, both with work and further research.

Elisabet Wentz, my associate supervisor, an excellent researcher who has also become a dear friend. Your systematic approach to scientific work, especially in the field of COND, has been of great inspiration and invaluable help. You willingly read and commented my manuscripts with great thoroughness.

Many people have supported the completion of this work most generously and I would further wish to thank:

Anna-Karin Kroksmark, my co-writer and friend, for all the hours we have spent together examining and travelling back and forth to the different habilitation centres. Thank you for all our stimulating discussions and the research work we have had together so far.

Louise Hakenäs-Plate, my co-author and friend, for the hours we have spent together preparing papers and lectures, and for being a great travel companion on our trips to the conferences in Milan and Istanbul. Where do we go next?

Eva Aring, my co-author and friend, for your enthusiasm, encouragement and stimulating discussions on research, but also on many other important issues. Thank you also for reading and answering my e-mails very quickly and for improving my knowledge of Excel.

Anders Sjöström, my co-writer, for your valuable and constructive criticism, for your awareness, interest and care for children with CNS-related impairments.

Lena Samuelsson, for collaboration and genetic analyses.

Lotta Sjögreen and Monica Engvall, for the enjoyable multidisciplinary teamwork we have had over the past ten years; may it continue!

Carl-Marcus Ekström, my oldest son, for invaluable and never ending computer assistance and graphic designs.

Nils-Gunnar Pehrsson, for expert statistical assistance, and Ann-Sofie Petersson for your excellent assistance with the lay-out.

Yvonne Tizard, for revision of the English text. Thanks for working so fast.

Gösta Blennow, for your devotion to DM1 and assistance in including the individuals from the southern health care region.

Mårten Kyllerman, for introducing me to the field of neuropaediatrics in the first place, reviewing my papers and generously sharing your experience.

Niklas Darin, Ingrid Emanuelsson, Peder Rasmussen and Gerd Viggedal for taking an interest in my research and for constructively reviewing different parts of my manuscripts.

Stefan Winblad, for valuable discussions and comments and for co-authorship on congnition and behaviour in DM1.

Per Lundgren, my superior, all colleagues and all in the staff at the Departmemt of Paediatrics, especially Marie Romell and Jan Schrevelius for all your encouragement, support and for always believing in me.

Anna Kågeson, my superior at the habilitation unit Mariedal; Alena Novak, my former supervisor and everyone in the staff, for creating such a friendly atmosphere, for all the years of good collaboration, warm support and encouragement.

Professor Christopher Gillberg for teaching and introducing me to the field of neuropsychiatry in the first place.

My dear friends and relatives for never giving up on me, for all the joy and laughter we have shared.

Kirsten Holmberg, my sister, for sharing the joys and sorrows in life, and the hardship of being a PhD student.

My parents Anne and Trygve Kristoffersen, for always being there, loving, supporting and believing in me, no matter what! A special thanks to you, father, for encouraging me to go into medicine and not choose your own research field; horticulture.

Finally, but most of all, my beloved husband Karl-Johan and our children Carl-Marcus, Elisabeth, Gabriel, Ellenor and Sakarias, for all your love and support and for reminding me of what is most important in life. What would life be without you…

This research work has been financially supported by grants from the Health and Medical Care Executive Board of the Region of Västra Götaland, the Linnéa and Josef Carlsson Foundation, the Western Sweden Muscle Foundation, the Research and Development Department of the Northern Älvsborg/Bohus County Council, the Wilhelm and Martina Lundgren Foundation, the Per and Mandis Molin Foundation, the Göteborg Medical Society, the Häggquist Family Foundation, the Folke Bernadotte Foundation, the Mayflower Charity Foundation for Children, the W&M Lundgren's Science Foundation, and the Petter Silfverskiöld Foundation.

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