Myotonic dystrophy type 1: clinical manifestations in children and adolescents

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ABSTRACT

Objective Myotonic dystrophy type 1 (DM1) is an autosomal-dominant neuromuscular disease with variable severity affecting all ages; however, current care guidelines are adult-focused. The objective of the present study was to profile DM1 in childhood and propose a framework to guide paediatric-focused management.

Design, setting and patients 40 children with DM1 (mean age 12.8 years; range 2–19) were studied retrospectively for a total of 513 follow-up years at Sydney Children's Hospital. 143 clinical parameters were recorded.

Results The clinical spectrum of disease in childhood differs from adults, with congenital myotonic dystrophy (CDM1) having more severe health issues than childhood-onset/juvenile patients (JDM1). Substantial difficulties with intellectual (CDM1 25/26 96.2%; JDM1 9/10, 90.0%), fine motor (CDM1 23/30, 76.6%; JDM1 6/10, 60.0%), gastrointestinal (CDM1 17/30, 70.0%; JDM1 3/10, 30.0%) and neuromuscular function (CDM1 30/30, 100.0%; JDM1 25/30, 83.3%) were evident.

Conclusion The health consequences of DM1 in childhood are diverse, highlighting the need for paediatric multidisciplinary management approaches that encompass key areas of cognition, musculoskeletal, gastrointestinal, respiratory, cardiac and sleep issues.

What is already known on this topic?

- Paediatric myotonic dystrophy type 1 (DM1) is characterised by a broad clinical spectrum and complex phenotype.
- The clinical spectrum of disease in childhood differs from classical adult-onset DM1.

What this study adds?

- People with congenital myotonic dystrophy exhibit more severe health issues than childhood-onset/juvenile patients.
- Substantial difficulties with intellectual, fine motor, gastrointestinal and neuromuscular function occur in children and adolescents with myotonic dystrophy.
- Paediatric multidisciplinary management is recommended to provide comprehensive, coordinated clinical care.

INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a multisystem disease with a broad spectrum of severity that arises from an autosomal-dominant expansion of CTG trinucleotide repeats in the non-coding region of the dystrophia myotonia gene (*DMPK*).[1–3] Various diagnostic classifications have been proposed based on age of onset and severity including congenital, infantile/childhood, juvenile, adult-onset and later adult/asymptomatic[4 5]; however, DM1 likely represents a continuum of disease severity. With a worldwide prevalence of approximately 1 in 8000,[6] DM1 is the most common type of adult-onset muscular dystrophy. Symptoms in adult-onset DM1 include progressive muscle weakness and myotonia with daytime sleepiness, fatigue, cataracts, endocrine disturbances and cardiac arrhythmias also common.[6] In contrast, congenital myotonic dystrophy (CDM1) is characterised by severe hypotonia and weakness at birth, often with respiratory insufficiency and can have feeding difficulty, respiratory failure, intellectual disability and autistic features as they get older.[6 7] Childhood-onset DM is initially clinically apparent between ages 1 and 10 years[8]; however, diagnosis may occur later and frequently demonstrates failure to thrive accompanied by abdominal symptoms, muscle hypotonia, variable degree of cognitive impairment, altered psychosocial function, dysarthria and excessive sleepiness.[7 9–11] Many of the symptoms characteristic of adult DM are different to that observed with congenital and childhood DM1, likely related to the relatively more severe phenotype associated with early-onset DM1.[12] While the phenotype and natural history of paediatric myotonic dystrophy has previously been described, it is timely to comprehensively revisit this given advances in multidisciplinary care have improved the natural history of many neuromuscular disorders and novel treatment approaches are being developed. Further research supporting and expanding the known clinical characteristics of this complex genetic disorder is essential to strengthening the data necessary to develop paediatric-specific standards of care that are currently not available for DM1. As such the present study aims to comprehensively describe the clinical manifestations of congenital and childhood DM1 and proposes paediatric-specific management guidelines. Additionally, as novel DM1 therapies are developed these insights will also promote clinical trial readiness and development of pertinent outcome measures.

METHODS

Paediatric patients (0–18 years) with DM1 managed at the Sydney Children's Hospital neuromuscular clinic from 2000 to 2015 were included in this study.

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Inclusion criteria included diagnosis confirmed by triplet repeat primed PCR demonstrating expanded CTG repeat in the DMPK gene and/or Southern blot for quantitation of triplet repeats and age 18 years or younger. Classification of DM1 was based on age of onset of clinical symptoms as follows: patients with CDM1 had clinical symptoms evident before age 12 months; childhood/juvenile onset DM1 (JDM1) manifested symptoms after the first year of life.

From patient records and clinical investigations, a retrospective study described classification of DM1, gender, molecular genetics/triplet repeat size, gestational and neonatal, musculoskeletal/orthopaedic, respiratory, gastrointestinal/nutritional, cognitive, behavioural, psychological, cardiac, endocrine, ophthalmological and sleep issues in DM1. Intellectual function was determined by assessments including Weschler Intelligence Scale for Children and Griffiths Mental Development Scales. Patients were reviewed annually by neurologists, respiratory physicians, cardiologists and ophthalmologists.

Written informed consent was provided by participant's parent or legal guardian.

Data analysis

Descriptive statistics were used to describe clinical features by subtype and expressed as number (percentage) and mean±SD. Cross-sectional data were normally distributed and analysed using IBM SPSS V.22. A p value of <0.05 was considered statistically significant.

RESULTS

A clinical and genetic diagnosis of DM1 was confirmed in 40 infants and children, including 30 patients with CDM1 and 10 patients with JDM1. There were 12 females and 28 males (mean age at last assessment 12.8 years, range 2–19 years) and total patient-years were 513 (table 1).

The most common initial clinical manifestations in CDM1 were severe neonatal hypotonia 19/30 (63.3%), feeding difficulties 17/30 (56.7%), bilateral talipes 17/30 (56.7%) and neonatal ventilation 13/30 (43.3%). Common initial parental concerns among children with JDM1 included difficulties with learning, school performance and hand function. Average gestational age at birth was 36.7±2.5 weeks (range 29–41) and 38.5±1.6 weeks (range 37–41) for CDM1 and JDM1, respectively. Importantly pregnancy complications were greater in CDM1, including antenatal history of polyhydramnios 13/30 (43.3%), reduced fetal movements 5/30 (16.7%) and prematurity 6/30 (20.0 %); none of these was evident in JDM1. Furthermore, births required greater intervention in CDM1, comprising emergency caesarean section (CDM1 5/30, 16.7%; JDM 1/10) or forceps/ventouse-assisted vaginal delivery (CDM1 2/30, 6.7%; JDM1 0). Notably, an expansion of >1500 base pairs was universally related to CDM1, otherwise expansion size did not determine DM1 type or severity. Maternal inheritance was more prominent among our cohort 34/40 (85%), with paternal inheritance occurring more frequently in non-congenital groups (3/10, 30%) compared with CDM1 (3/30, 10%).

Table 1 Demographic data

Characteristic	CDM1	JDM1
Children studied, n	30	10
Children with DM, sex (%)		
Male	21 (70%)	7 (70%)
Female	9 (30%)	3 (30%)
Sex of parent with DM (%)		
Male	3 (10%)	3 (30%)
Female	27 (90%)	7 (70%)
Mean age at last appointment, years (SD)	12.6 (5.1)	13.5 (3.5)
Mean age of diagnosis, years (SD)	2.01 (3.5)	7.9 (4.4)
Mean CTG repeat length (range)	1277.5 (100–1500)	958.9 (300–1365)
Mean gestational age of child (SD)	36.7 (2.5)	38.5 (1.6)

CDM1, congenital myotonic dystrophy; JDM1, juvenile onset DM1.

Health outcomes from childhood to adolescence in congenital and juvenile myotonic dystrophy

Overall, there was a broad spectrum of clinical manifestations and severity for infants and children with DM1 involving multiple systems (table 2).

Intellectual function and behaviour

Intellectual disability was evident in the majority of school-aged patients with CDM1 and JDM1, occurring in 25/26 (96.2%) and 9/10 (90.0%), respectively. While 25/26 patients with CMD1 had intellectual disability, the severity was more pronounced with 8/25 (30.0%) patients with CMD1 having moderate to severe impairment, contrasting with a mild disability evident in 9/10 (90.0%) patients with JDM1. Consequently, 25/26 (96.2%) of CDM1 children used educational support and 24/30 (80.0%) used speech therapy for speech and language delay. In addition, similar rates of autism spectrum disorders were evident in both CDM1 (6/30, 20.0%) and JDM1 (2/10, 20.0%).

Motor and musculoskeletal

Symptoms related to muscle weakness were common in both subtypes. Facial diplegia and bulbar dysfunction due to muscular weakness were present in 30/30 (100%) patients with CDM1 and 7/10 (70%) patients with JDM1. The clinical effects were greater in CDM1, including dysarthria (CDM1 23/30, 76.7%; JDM1 2/10, 20%) and drooling (CDM1 12/30, 40.0%; JDM1 1/10, 10%).

Muscle weakness persisted past the neonatal period in 27/30 (90.0%), with distal dominance in 25/30 (83.3%) of patients with CDM1 most evident in ankle dorsiflexion and hands. Initiation of independent walking after 18 months was observed in 24/30 (80.0%) CDM1 contrasting with 0/10 (0%) patients with JDM1 (age of independent ambulation: CDM1 24.3±11.4, range 12–60 months; JDM1 14.8±2.9, range 11–18 months). Subsequent effects of motor weakness were more disabling in the CDM1 group. Fatigue was comparable in both phenotypes (CDM1 18/30, 60.0%; JDM1 5/10, 50.0%); however, the impact was greater in CDM1 with 6/30 (20.0%) using a wheelchair for long distances, contrasting with 0/10 patients with JDM1. Scoliosis was present in 7/30 (23.3%) patients with CDM1 but not in JDM1 (0/10). Both groups also experienced contractures, predominantly of the Achilles tendon (CDM1 11/10, 36.7%; JDM1 2/10, 20%) and musculoskeletal pain (CDM1 5/30, 16.7%; JDM1 1/10, 10%).

Fine motor function was not age appropriate and included difficulties with buttoning, handwriting and using utensils, evident in 23/30 (76.6%) CDM1, and disturbed activities of daily living in 13/30 (76.6%) CDM1 and 6/10 (60.0%) JDM1. In addition to distal weakness, myotonia affected fine motor control. This was more prevalent in JDM1, reported in 9/10 (90.0%) patients with JDM1 at last assessment compared with 23/30 (76.7%) of CDM1. The earliest age of myotonia onset observed was 5 years.

Table 2 Summary of the clinical manifestations of myotonic dystrophy type 1 in congenital and childhood/juvenile onset patients

		Congenital	Childhood/ juvenile
System	**Clinical issue**	**n=30 (%)**	**n=10 (%)**
Intellectual function and behaviour	Normal intellectual function	1 (3.8)	1 (10.0)
	Mild intellectual disability*	**17 (65.4)**	**9 (90.0)**
	Moderate to severe intellectual disability	8 (30.8)	0
	Speech delay	**24 (80.0)**	1 (10.0)
	Autism spectrum disorder	**6 (20.0)**	2 (20.0)
Motor and musculoskeletal	**Facial diplegia**	**30 (100.0)**	**7 (70.0)**
	Dysarthria	23 (76.7)	2 (20.0)
	Drooling	28 (60.0)	1 (10.0)
	Muscle weakness	**27 (90.0)**	**6 (60.0)**
	Myotonia	**23 (76.7)**	**9 (90.0)**
	Delayed gross motor milestones	**24 (80.0)**	2 (20.0)
	Fine motor difficulties	**23 (76.6)**	**6 (60.0)**
	Fatigue	**18 (60.0)**	**5 (50.0)**
	Contractures	11 (36.7)	2 (20.0)
	Scoliosis	7 (23.3)	0
	Musculoskeletal pain	5 (16.7)	1 (10.0)
	Cerebral palsy	2 (6.7)	0
Respiratory	**Recurrent infections**	**6 (20.0)**	1 (10.0)
	Asthma	5 (16.7)	0
	Pneumonia (≥1 episode)	4 (13.3)	1 (10.0)
Gastrointestinal	**Faecal incontinence**	**17 (70.0)**	**3 (30.0)**
	Constipation	10 (33.3)	3 (30.0)
	Malnutrition/weight loss	6 (20.0)	0
	Dysphagia	6 (20.0)	2 (20.0)
Genitourinary	**Urinary incontinence**	**13 (43.4)**	**3 (40.0)**
	Undescended testes at birth†	8 (38.1)	0
	Irregular menses‡	3 (10.0)	1 (10.0)
Cardiovascular	Abnormal echocardiogram, not clinically significant	7 (23.3)	0
	Arrhythmia requiring intervention	1 (3.3)	0
	Abnormal ECG, not clinically significant	5 (16.7)	1 (10.0)
Head and neck	**Impaired visual acuity**	**10 (33.3)**	2 (20.0)
	Cataracts (early signs)	2 (11.1)	1 (10.0)
	Dental caries	7 (23.3)	1 (10.0)
Sleep	**Subjective EDS**	**10 (33.3)**	**3 (30.0)**
	Obstructive sleep apnoea	**5 (16.7)**	**1 (10.0)**
	Nocturnal hypoventilation	4 (13.3)	1 (10.0)
	Periodic limb movement disorder	2 (6.7)	0

Main health issues are highlighted in bold.
*School-aged children, not less than 5 years of age.
†Males only.
‡Females only.
EDS, excessive daytime sleepiness.

The greater severity of motor symptoms in CDM1 resulted in differences in management between the two groups, with more regular physiotherapy (CDM1 21/30, 70.0%; JDM1 2/10, 20.0%), occupational therapy (CDM1 18/30, 60.0%; JDM1 2/10, 20.0%) and use of ankle–foot orthoses (CDM1 15/30, 50.0%; JDM1 2/10, 20.0%). Surgery related to complications of muscle weakness was only undertaken in patients with CDM1, including Achilles lengthening in 7/30 (23.3%), surgical correction of foot deformities in 2/30 (6.7%) and scoliosis surgery in 1/30 (3.3%).

Respiratory

Chronic respiratory issues in patients with CDM1, included recurrent lower or upper respiratory tract infections (6/30, 20.0%), asthma (4/30,13.3%), one or more previous episodes of pneumonia (5/30, 16.7%) and positive airway pressure respiratory assistance for obstructive sleep apnoea (OSA) (3/30, 10.0%) and for restrictive lung disease (1/30, 3.3%). In contrast, respiratory complications were far less common in patients with JDM1, with only pneumonia and recurrent infections reported in 1 of 10 patients with JDM1 (10.0%).

Gastrointestinal

Gastrointestinal concerns were common in both groups. Faecal incontinence was reported in 17/30 (70.0%) patients with CDM1 and 3/10 (30.0%) patients with JDM1 and resolved at an older age in CDM1, with a 16-year-old patient with CDM1 continuing to experience faecal incontinence. Constipation (CDM110/30, 33.3%; JDM1 3/10, 30.0%) and dysphagia (CDM1 6/30, 20.0%; JDM1 2/10, 20.0%) were equally prevalent in both groups. Other gastrointestinal issues in CDM1 included malnutrition and weight loss (6/30, 20.0%), occasional mild abdominal pain (2/30, 11.1%), gastro-oesophageal reflux requiring medication (3/30, 10.0%) and diarrhoea (1/30, 3.3%). Severe and ongoing dysphagia beyond the neonatal period was evident in 1/30 (3.3%) patients with CDM1, requiring percutaneous endoscopic gastrostomy feeding. Diet modification and supplementation were standard and important management approaches for gastrointestinal issues.

Genitourinary

Overall, 20/30 (66.7%) patients with CDM1 had issues with urinary incontinence in childhood and adolescence in contrast with 4/10 (40.0%) patients with JDM1, highlighting urinary incontinence as an important issue in both phenotypes in childhood. Of those with urinary issues, persistent and frequent urinary incontinence in childhood was an important issue for 13/30 (43.3%) of patients with CDM1 and 3/10 (30.0%) patients with JDM1. In addition, occasional episodes of urinary incontinence occurring less than once a month were reported by 4/30 (13.3%) patients with CDM1. Solely nocturnal enuresis was reported in 3/30 (30.0%) patients with CDM1 and 1/10 (10.0%) patients with JDM1.

Undescended testes at birth were present in 0/7 JDM1 and 8/21 (38.1%) CDM1 males with 5/8 (62.5%) of these surgically corrected.

Cardiovascular

Cardiac arrhythmias were observed in 5/30 (16.7%) patients with CDM1 and 1/10 (10%) patients with JDM1. One of 30 (3.3%) patients with CDM1 had atrial fibrillation that required management with sotalol and ablation. Other conduction disturbances were not clinically significant and included first-degree atrioventricular block managed with annual ECG surveillance. Cardiomyopathy was not identified in any patient.

Ophthalmic, head and neck

Ptosis (CDM1 18/30, 60.0%; JDM1 2/10, 20.0%), impaired visual acuity requiring glasses (CDM1 10/30, 33.3%; JDM1 2/10, 20.0%), hyperopia (CDM1 2/30, 6.7%; JDM1 0), strabismus (CDM1 2/30, 6.7%; JDM1 0), astigmatism (CDM1 2, 6.7%; JDM1 1/10, 10.0%) and early signs of cataract development (CDM1 2/30, 6.7%; JDM1 0) affected vision in children and adolescents with DM1. Poor oral hygiene resulting in dental

Table 3 Proposed multidisciplinary management and treatment approaches in childhood myotonic dystrophy type 1 (DM1)

Respiratory and sleep	
Increased risk of infection	Proactive annual vaccinations (influenza, pneumococcus) Monitoring, regular respiratory consults Physiotherapy—airway clearance, aspiration risk assessment and management
Anaesthetic risk	Awareness and appropriate management: longer postoperative monitoring and support
Sleep-disordered breathing	Respiratory physician assessment and consults PSG Assisted ventilation (eg, CPAP)
Excessive daytime sleepiness	PSG, ESS and other assessments No current drug recommendations
Cognition	
Intellectual delay	Early assessment and education supports
Speech delay	Speech therapy
Autism	Appropriate assessment, referral to specialist services
Other behavioural problems	Appropriate assessment Referral to psychology/psychiatry
Reproductive health	
Menstrual irregularities/ menorrhagia	Oral contraceptives Referral to gynaecology
Genetic counselling	Including cascade testing Family planning and antenatal care for subsequent DM1 families
Endocrine	
Diabetes Hypothyroidism Hypogonadism Growth hormone imbalance Androgen insensitivity	Assess if clinical indication, refer to endocrinologist as required
Gastrointestinal	
Incontinence	Diapers/pads Patient and carer education Bladder training and behavioural interventions Addressing psychological consequences
Constipation	Diet modification Stool softeners
Nutrition	Monitor growth, nutrition/dietetics assistance, assess micronutrients (iron and vitamin D and supplement as indicated)
Swallowing/feeding	Speech therapy Modification of food consistency
Nausea/reflux	Monitor, use of antacids
Abdominal pain	Thorough assessment for potential causes and referral to gastroenterology
Motor	
Gross and fine motor delay and weakness	Aim to optimise mobility and function—adaptive equipment, assistive technology Physiotherapy and occupational therapy Orthoses and stretches surgery (eg, tendon transfer, if required for foot drop) Regular physical activity Falls risk assessment
Myotonia	Mobility aids Adaptive devices Consider medication if debilitating (Mexiletine) Monitor for potential complications (especially cardiac)
Contractures/scoliosis	Physiotherapy, occupational therapy, stretches, orthoses Consider surgical intervention
Facial weakness	Speech pathology referral
Head and neck	
Vision	Early assessment and correction Annual ophthalmology review (for cataract development)
Hearing	Surveillance Management of otitis media (grommets, antibiotics)
Dental	Regular check-ups, maintain hygiene
Cardiac	
Possible conduction/structural abnormalities	Annual ECG and echocardiogram Cardiovascular risk education Holter monitor if, for example, unexplained dizziness, falls, palpitations Pacemaker or defibrillator insertion if indicated

CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; PSG, polysomnography.

caries was problematic for 7/30 (23.3%) patients with CDM1 and 1/10 patients with JDM1 (10.0%).

Sleep

Subjective reports of excessive daytime sleepiness (EDS) were equally present in both subgroups (CDM1 10/30, 33.3%; JDM 1 3/10, 30.0%). Sleep-disordered breathing included OSA (CDM1 5, 16.7%; JDM1 1/10, 10.0%) and nocturnal hypoventilation (CDM1 4/30, 13.3%; JDM1 1/10, 10.0%) managed by adenotonsillectomy for OSA, and positive airway pressure. Periodic limb movement disorder was noted in sleep studies (CDM1 2/30, 6.7%; JDM1 0) and was associated with otherwise unexplained sleep-wake complaint. Narcolepsy was not identified in any patient with two patients completing multiple sleep latency tests.

No disturbances in endocrine function (diabetes mellitus, hypothyroidism, hypogonadism, growth hormone imbalance and androgen insensitivity) were observed with investigations initiated on clinical indication.

DISCUSSION

The present study reveals the diverse spectrum of manifestations and health outcomes in a cohort of infants, children and adolescents with CDM1 and JDM1 in the context of their clinical care.[13 14] Much of the paediatric DM1 literature has focused on discrete symptomatic domains including muscle function,[15 16] cognitive disturbances and autism spectrum conditions,[7 17 18] visual function,[19] orthopaedic manifestations[20] and cardiac abnormalities.[21] Comparing these and studies that have looked more broadly at the clinical presentation of paediatric onset DM1,[4 14 22] our results are generally in agreement further strengthening the existing natural history data. Of prognostic relevance, despite the recognised 'biphasic' course in patients with CDM1,[3] in which the initial manifestations of severe hypotonia, respiratory insufficiency and feeding difficulties gradually improve, diverse health issues continued to be substantial and more marked than JDM1. In both congenital and childhood patients, intellectual disability was a prominent feature with increased severity evident in the congenital form. As such utilisation of educational support was particularly high in the CDM1 cohort. Similarly speech and language delays were frequently reported in this group with a very high proportion of patients receiving speech therapy. One novel aspect of this study that is generally under-reported in the literature was the high incidence

of urinary incontinence. Faecal incontinence was also experienced by a large number of both congenital and childhood-onset patients with rates similar to that described previously.[23 24] Recent parental-reported evidence has identified that aside from the well-described muscle impairment and brain dysfunction, communication issues, bowel control and urinary incontinence are significant contributors to disease burden in daily life.[25] Taken together, these results indicate that a greater focus on the early and proactive management of potentially modifiable symptoms may alleviate some of the high disease burden experienced by patients and their families.

Guidelines for the care of DM1 adults in Canada have been published[26] and recommendations for the development of adult DM1 standards of care with have been proposed in the UK[27]; however, international consensus is lacking. Additionally with the widely recognised phenotypical differences between adult-onset and congenital/childhood forms of this disease, a paediatric-specific standards of care is necessary to develop optimum care through an integrated approach for the management of the various aspects of disease manifestations. A multidisciplinary approach to DM1 management as proposed in table 3 is recommended to provide comprehensive, coordinated clinical care encompassing neuromuscular, pulmonary, cardiac, gastrointestinal, rehabilitative, developmental, orthopaedic and psychosocial care.

Our main goal was to identify the clinical features specific to congenital and childhood DM1 to further contribute to the growing body of evidence necessary to support the development of paediatric-specific standards of care for this complex genetic disorder. Caution is warranted however in the interpretation of the results of this study with the retrospective nature and limited number of participants from a single centre potentially limiting the generalisability of the findings. More large-scale prospective studies investigating the effectiveness of comprehensive management approaches, particularly where symptomatic modification in areas of high disease burden is possible, would be of great value in improving quality of life for these children and their families.

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