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REVIEW

Congenital and childhood myotonic dystrophy: Current aspects of disease and future directions

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Abstract

Myotonic dystrophy type 1 (DM1) is multisystem disease arising from mutant CTG expansion in the non-translating region of the dystrophia myotonica protein kinase gene. While DM1 is the most common adult muscular dystrophy, with a worldwide prevalence of one in eight thousand, age of onset varies from before birth to adulthood. There is a broad spectrum of clinical severity, ranging from mild to severe, which correlates with number of DNA repeats. Importantly, the early clinical manifestations and management in congenital and childhood DM1 differ from classic adult DM1. In neonates and children, DM1 predominantly affects muscle strength, cognition, respiratory, central nervous and gastrointestinal systems. Sleep disorders are often under recognised yet a significant morbidity. No effective disease modifying treatment is currently available and neonates and children with DM1 may experience severe physical and intellectual disability, which may be life limiting in the most severe forms. Management is currently supportive, incorporating regular surveillance and treatment of manifestations. Novel therapies, which target the gene and the pathogenic mechanism of abnormal splicing are emerging. Genetic counselling is critical in this autosomal dominant genetic disease with variable penetrance and potential maternal anticipation, as is assisting with family planning and undertaking cascade testing to instigate health surveillance in affected family members. This review incorporates discussion of the clinical manifestations and management of congenital and childhood DM1, with a particular focus on hypersomnolence and sleep disorders. In addition, the molecular genetics, mechanisms of disease pathogenesis and development of novel treatment strategies in DM1 will be summarised.

Key words: Clinical manifestations; Myotonic dystrophy type 1; Childhood myotonic dystrophy; Congenital myotonic dystrophy; Natural history; Management

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Core tip: Type 1 myotonic dystrophy is an often undetected neuromuscular disease in paediatric patients with variable clinical manifestations and burden of disease. We review the current understandings of disease pathogenesis, symptoms and management in congenital and childhood myotonic dystrophy with a particular focus on hypersomnolence and sleep disorders. Future directions should target standardised care and regular surveillance, understanding pathophysiology and new treatment strategies.

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a multisystem genetic disease that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous systems (CNS) caused by expansion of a CTG trinucleotide repeat in the non-coding region of the dystrophia myotonica gene (*DMPK)*. The phenotype is variable and encompasses a broad spectrum of severity from mild to severe. It is the most common adult muscular dystrophy, with an estimated worldwide prevalence of one in eight thousand, but age of onset varies from prenatal to adulthood. While the clinical manifestations and natural history of DM1 in adulthood are well established, the manifestations and management of DM1 in children warrants further evaluation. Multidisciplinary care including proactive respiratory care and nutrition optimisation have seen changes in the natural history of a number of neuromuscular disorders[1-3]. It is critical to develop a better and focused understanding of the unique issues encountered in the management of DM1 in paediatrics and neonatology to optimise outcomes and develop standards of care. Accordingly, this review will summarise the current understandings of congenital and childhood DM1, with a particular focus on sleep and hypersomnolence.

CLINICAL CLASSIFICATION AND NATURAL HISTORY

There are five clinical phenotypes of DM1 that generally correlate with CTG repeat size (Table 1), including premutation, mild adult DM, classical adult DM, childhood-onset DM and congenital DM.

Congenital myotonic dystrophy (CDM) is characterised by severe hypotonia and weakness at birth, often with respiratory insufficiency. The incidence of CDM is up to 1 in 47619 live births[4] and the mortality in the neonatal period may be 30%-40%[5].

Childhood-onset DM is initially clinically apparent between ages 1-10, however diagnosis may occur later, and predominantly affects muscle strength, cognition, respiratory, central nervous and gastrointestinal systems (Table 2). Juvenile DM is apparent between 10-20 years, however onset may be vague and manifestations overlap between childhood and classic DM. Patients with childhood and juvenile DM survive into adulthood, however the natural history remains to be fully determined, with recent advances in supportive care. Adult type problems arise in later life. Severe CDM demonstrates a unique "biphasic" course, whereby neonatal symptoms improve or stabilise in surviving neonates, before adult-type symptoms present in later life[6]. Echenne and Bassez[5] also observe a "continuum", where CDM survivors and childhood-onset/juvenile types develop the same clinical picture before eventually showing classical adult-onset manifestations. Consequently developing standards of care focusing on the neonatal and childhood periods of DM1 in addition to adult DM are needed. In addition, developing guidelines on transitioning to adult medical care for patients with congenital and childhood DM is necessary.

CLINICAL MANIFESTATIONS OF DM1 IN NEONATES AND CHILDREN

Neonatal period in CDM

Polyhydramnios, reduced foetal movements and preterm delivery often complicate CDM gestation[7]. Classically, neonates are born with hypotonia and immobility, bilateral talipes, contractures, arthrogryposis, facial dysmorphia (carp mouth, ptosis, long neck and face, temporal muscle atrophy), hyporeflexia, a weak cry, sucking and respiratory difficulties. Cases of premature (less than 36 wk gestation) and small for gestational age DM1 babies have also been reported[6]. The presence of respiratory distress is sometimes used to distinguish between mild and severe CDM[8]. Respiratory difficulties were present in about 50% of neonates (Wallgren-Petterson, Bushby, Mellies, and Simonds, 2004) and are the main cause of neonatal mortality which ranges between thirty and forty percent[9].

Musculoskeletal manifestations

Muscle weakness in DM1 is typically distal but may be proximal, the latter indicating a poorer prognosis[10]. Following initial improvement in the neonatal period, the natural history of progressive muscle weakness is variable. While strength is typically stable until adolescence with gradual deterioration subsequently evident, rarely rapid increasing weakness may occur in young adults[8,11]. Complications of muscle weakness may include scoliosis and contractures, particularly at the tendo-achiles producing foot deformity and toe walking. Bulbar muscle weakness may also produce

Table 1 Myotonic dystrophy type 1 clinical phenotypes

Phenotype	Clinical characteristics	CTG repeat length	Age of onset (yr)
Premutation	Not applicable	38-49	Not applicable
Mild/late onset adult	Mild myotonia Cataracts	50-100	20 to 70
Classical adult	Myotonia Muscle weakness Cataracts Conduction defects Insulin resistance Respiratory failure	50-1000	10 to 30 (median 20 to 25)
Childhood onset	Facial weakness Cognitive defects Psychosocial issues Incontinence	> 800	1-10
Congenital	Hypotonia Respiratory distress Cognitive defects Motor and developmental delay Feeding difficulties	> 1000	Birth

swallowing difficulties, speech and language difficulties, separate to cognitive impairment and may initiate consideration of DM1. In contrast to adult DM1, severe myotonia is not common in children but is present to some extent in most children by age 10 years[11-13]. The worsening facial dysmorphia and "carp" mouth appearance seen in CDM neonates is not a feature at birth for childhood-onset cases[12]. These patients may experience facial weakness but to a lesser severity.

Sleep disturbances

Sleep disorders are a significant complaint in both adult and childhood DM1 (Table 3) and may adversely affect learning, memory, high-level cognitive processing and physical functioning, thereby exacerbating psychomotor and cognitive delays in DM1[14,15]. Consequently, understanding sleep pathophysiology and assessment approaches are important in determining management in DM1. Normal sleep is maintained through CNS regulation of breathing and sleep-wake cycles and respiratory muscle integrity.

CNS disturbances in DM1 can affect sleep through central deregulation of breathing whilst sleeping, resulting in hypoventilation and subsequent sleep fragmentation, producing excessive Daytime Sleepiness (EDS)[16]. EDS in DM1 is characterised by persistent sleepiness, more likely during situations requiring less attention, and is not improved by naps and has been reported in approximately 50% of children with DM1[17]. It occurs concurrently and may be attributed to other sleep disorders including sleep apnoea, periodic limb movement disorders (PLMs) and rapid eye movement (REM) sleep dysregulation. Neuronal loss and gliosis in the reticular activating system and brainstem may underlie central deregulation of ventilation[18,19]. Immunoendocrine causes with abnormal levels of growth hormone, cortisol and cytokinesin DM1 may also affect sleep control[20,21]. MRI studies indicate white matter changes are evident; however, the changes do not correlate with severity of EDS[22].

Sleep disordered breathing (SDB) can arise from obstructive causes (apnoeas - airway hypotonia or tonsillar hypertrophy) or central ventilator dysfunction in DM1. Muscle weakness can contribute to obstructive sleep disorders. Apnoea-Hypnoea indices are raised in adult DM1 patients[23]. This causes nocturnal hypoxemia and hypoventilation, subsequent sleep fragmentation and EDS[24,25]. EDS and apnoeas, however have been noted to occur independently, and correction of hypoventilation does not always improve EDS[16]. Sympathetic hyperactivity associated with cardiac conduction disturbances are suspected to be linked to PLMs[26]. Thus conduction deficits seen in DM1 could in part explain sleep fragmentation and subsequent EDS by increasing the occurrence of PLMs.

Cognitive impairment

Cognitive impairment is one of the most common manifestations and challenging management aspects of childhood DM1. This may be the presenting characteristic in children, ranging from mild to moderate intellectual impairment. Overall, both groups have lower than average IQ. CDM patients are more severely affected and full-scale IQ ranges from 40-80, with a mean below 70[12]. Childhood-onset patients have a wider range from 42 to 114 and a mean of about 70-80[27-29]. It is highly possible that patients' IQ is underestimated however, due to the false impressions given by apathy and reduced facial expression commonly seen in DM1. Cognitive impairment correlates with severity of muscle weakness, size of CTG repeat and maternal transmission[27,28].

Psychosocial function

Approximately half of children with DM1 have at least one DSM-IV psychiatric diagnosis[27], with internalising disorders (phobia, depression, anxiety) and attention deficit hyperactivity disorders being common. Avoidant personality types, apathy and autistic features may also be evident[30,31]. Brain imaging of (CT, MRI) CDM and JDM patients often reveal ventricular dilatation, cortical atrophy, and hypoplasia of the corpus callosum, and hyper-intense white matter in cortical regions seem to be specific to CDM[32]. While not evident during paediatric management, these may relate to subsequent development of dementia, and are important considerations in further understanding pathogenic mechanisms of neuro-degeneration.

Respiratory

Respiratory manifestations, related to inspiratory and expiratory muscle weakness, are a major feature of CDM and remain important in childhood. These include sleep breathing disorders, recurrent infections, weak cough

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

System	Congenital (CDM)	Childhood-onset/juvenile onset
Prenatal	Polyhydramnios	Not applicable
	Reduced foetal movements	
	Preterm delivery	
Muscular	Hypotonia at birth	Facial dysmorphia (may be subtle)
	Talipes	Generalised muscle weakness
	Contractures	Myotonia, usually after 1st decade
	Scoliosis, lordosis, kyphosis	Muscle atrophy
	Arthrogryposis	Brisk reflexes
	Characteristic facial dysmorphia	Mild talipes and contractures Motor delay
	Hyporeflexia	
	Generalised muscle weakness (distal > proximal)	
	Muscle atrophy	
	Motor delay	
Vision	Visual impairment	Visual impairment
	Strabismus	Strabismus
	Reduced visual acuity	Reduced visual acuity
	Lens pathology	Lens pathology
Respiratory	Respiratory distress at birth	Recurrent infections (weak cough)
	Raised right hemi-diaphragm	Sleep apnoea and sleep disordered breathing
	Pulmonary hypoplasia	
	Bronchopulmonary dysplasia	
	Aspiration pneumonia	
	Sleep apnoea and sleep disordered breathing	
	Pneumothorax	
	Recurrent infections	
	Impaired central respiratory control	
Gastrointestinal and feeding	Sucking difficulties from birth	Recurrent abdominal pain
	Gastroparesis	
	Gastroesophageal reflux and aspiration	
	Constipation	
	Recurrent diarrhoea	
	Faecal incontinence	
	Anal dilatation	
	Persistent abdominal pain	
CNS	Increased sensitivity to anaesthesia	Hypersomnolence and fatigue
	Neuroendocrine disturbance	Periodic limb movements
	Psychiatric disorders (ADHD, anxiety, depression)	Psychiatric disorders
	Autism	Autism
	Hypersomnolence and fatigue	
Cognitive function	Lower IQ	Lower IQ
	Full scale ranges between 40-80	Full scale ranges from 42 to 114
	Mean less than 70	Mean between 70 and 80
Cardiac	Conduction disturbances	Conduction disturbances
	Structural abnormality, valve defects (most commonly mitral)	Structural abnormality, valve defects (More common in older patients)
Endocrine	Testicular atrophy	Testicular atrophy
	Hormone abnormalities: growth hormone, hypothyroidism (late teens)	Later onset: hormone abnormalities
Hearing	Recurrent otitis media	Recurrent otitis media (less common)
Oral health	Dental caries, plaque, gingivitis decay/trauma	Dental caries, plaque, gingivitis decay/trauma
Speech and language	Nasal voice and dysarthria	Speech delay
	Speech delay	Nasal voice and dysarthria
Life expectancy	30%-40% death rate within neonatal period	Mortality similar to adult-onset
	Mean life expectancy: 45 yr	Mean life expectancy: approximately 60 yr

CDM: Congenital myotonic dystrophy; ADHD: Attention-deficit/hyperactivity disorder; CNS: Central nervous system; IQ: Intelligence quotient.

and aspiration pneumonia[8,12,33]. It is also important to appreciate DM1 patients have hypersensitivity to anaesthesia, which arises from respiratory muscle compromise and central dysregulation of breathing[34]. Separately, obesity may adversely affect pulmonary function and sleep-disordered breathing in adults with DM1, although this remains to be defined in paediatric DM1 patients. Cognitivive impairment may affect an individual's ability to reliability undertake conventional respiratory function tests. Consequently sniff nasal inspiratory pressure (SNIP), which correlates with pulmonary function, may provide an easier and more accurate measurement[35].

Gastrointestinal symptoms

Gastrointestinal complaints often predate diagnosis of DM1 and significantly contribute to morbidity. Previous studies have determined that forty per cent of

Table 3 Sleep disorders in myotonic dystrophy type 1 that contribute to hypersomnolence

Sleep disorder	Description and components
Excessive daytime sleepiness	Greater susceptibility to falling asleep, especially when in situations requiring less attention Naps are long, frequent and unrefreshing
Long night time sleep	Sleep often does not feel sufficient or restorative Sleep fragmentation and frequent arousals
Sleep related breathing disorders	Sleep apnoea or hypopnoea: Obstructive and/or central Hypercapnoea and hypoxemia in both day and night time
RLS and PLM	RLS refers to the urge to move limbs while both awake and asleep, while PLM refers to uncontrolled limb movements during sleep. Both commonly co-exist
REM sleep dysregulation	Abnormal periods of SOREMPs during MSLTs Increased density and frequency of REM sleep nocturnally

RLS: Restless leg syndrome; PLM: Periodic limb movements; SOREMPs: Sleep-onset REM periods; MSLTs: Multiple sleep latency tests; REM: Rapid eye movement.

children and young adults regularly experience faecal incontinence, with twenty per cent stating this was their worst symptom[36]. Up to a third may also report constipation and irregular bowel habits[37]. Recurrent or persistent diffuse abdominal pain are common[38]. In both adults and children, dysphagia, gastroesophageal reflux and choking have been observed[4,39,40]. Dyspeptic symptoms of nausea, vomiting, and early satiety may be attributed to delayed gastric emptying. Lower tract problems also include faecal incontinence, episodic and recurrent diarrhoea, with significant social implications[37,39].

There are multiple factors that cause the gastrointestinal disturbances, including reduced peristalsis and secondary bacterial overgrowth. The latter is a mechanism of diarrhoea which may be overcome with antibiotics[41,42]. Delayed gastric emptying may also be related to gut hormone abnormalities guiding future management strategies[43,44].

Other systems

Many key features of adult "classic" DM are not evident in childhood, including cataracts, significant cardiac disorders and diabetes mellitus. Even so, lens pathology may be evident in 41% of patients, and may be predictive of future cataract development[45]. Conduction disturbances observed on electrocardiography are not uncommon in children, however they do not often present symptomatically with dyspnoea, palpitations or syncope. Valve abnormalities have also been observed, but again, are not clinically significant. Hypothyroidism, hypogonadism, growth hormone imbalance and androgen insensitivity have been observed but are rare[8,46]. In contrast, testicular atrophy and infertility are common amongst CDM males. Females with severe CDM patients may experience very irregular periods and prolonged episodes of amenorrhoea[46].

CURRENT TREATMENT AND MANAGEMENT

Management of childhood DM1 is currently adapted from approaches to adult myotonic dystrophy. A multidisciplinary team approach is critical in providing supportive care to manage manifestations, reduce complications, optimise function and undertake health surveillance (Table 4). This includes involvement of genetic counsellors, nurses, educators, physiotherapists, speech therapists, occupational therapists, social workers, and dieticians in addition to medical specialists. Standards of care for other rare neuromuscular disorders, for example spinal muscular atrophy and Duchenne Muscular Dystrophy, have been established and are easily accessible to health care professionals and patients[1-3]. Advances in the management of respiratory impairment and nutrition have seen an evolution in the natural history of these disorders[47]. The multisystemic nature of DM1 brings about similar complex care, yet the unique cognitive and psychological manifestations of DM1 may limit ongoing engagement with medical services. Patients may present ad hoc to clinicians unfamiliar with DM1. Consequently creating standards of care, encompassing the specific needs of children with DM1 and anticipating transition to adult services, for best practice is critical. Further these need to be accessible and practical to primary care physicians and converted into individual health care plans.

In severe CDM, neonatal intensive care is often required to provide respiratory support. Chest radiography may demonstrate diaphragm elevation, prompting additional management of pulmonary hypoplasia. Nutrition and feeding may require enteral supplementation. Oesophageal function should be evaluated with barium studies and speech pathology assessments to consider aspiration. Cerebral ultrasounds or head CT may be undertaken for concurrent birth related hypoxia or cerebral haemorrhage. Splinting of talipes is also commenced[48].

Recognising cognitive impairment and psychiatric/psychological manifestations are critical in guiding overall management and planning appropriate educational support. Formal cognitive testing and psychological assessments are essential. Special education is common and previous studies have revealed that more than two thirds of DM1 children have repeated a grade at

Table 4 Current management strategies in congenital and childhood myotonic dystrophy type 1

Clinical problem	Management strategies
Muscle weakness	
General	Exercise and physical therapy
	Possible drug therapy (DHEA, IGF-1, BP3, Creatinine use has shown possible benefits but this is not routinely done)
Talipes, foot drop, osteopenia, contractures	Orthopaedic surgery (*e.g.*, tendon transfer, if required)
	Mobility aids
	Physiotherapy, ankle foot orthoses, splints
(Scoliosis, kyphosis)	Optimise vitamin D and calcium
	Physiotherapy, stretches and splints
Speech (dysarthria)	Orthopaedic surgery
Swallowing/feeding	Speech therapy
	Speech therapy
	Modification of food consistency
	Physiotherapy to enhance swallowing
Myotonia	Occupational therapy – adaptive devices
	Drug therapy (Mexiletine, anti-epileptics, amino acids, antidepressants)
Respiratory	
Chest wall weakness and respiratory function	Regular surveillance screening with a symptom checklist including:
	Orthopnoea, dyspnoea with ADLs, sleep disturbances, morning headaches, apnoea, reduced cognition, EDS, fatigue, recent chest infections
	Respiratory function tests including
	Regular forced vital capacity, FEV1, pulse oximetry and peak expiratory cough flow
	Elective monitoring also includes mean inspiratory and expiratory pressures, and arterial blood gas analysis
	Imaging may include chest radiography or ultrasound for detection of motion abnormalities and thinning of diaphragm
	Nocturnal non-invasive ventilation: BiPAP or CPAP (in more obstructive cases)
Weak cough	CDM: Intubation and ventilation during neonatal period
Greater	Physiotherapy incorporating airway clearing techniques, manual assisted cough and postural drainage of secretions
Susceptibility to infections/recurrent infections	Antibiotics for management of acute infections
	Prophylactic vaccinations
	Respiratory physician consultation
	Prophylactic antibiotics
Cardiac	
Conduction disorders	Annual surveillance with ECG and echocardiography
	Holter monitoring
	Pacemaker or defibrillator insertion if indicated
Sleep	
Sleep related breathing disorders	Respiratory function testing
	Overnight pulse oximetry
	Polysomnography
	Non-invasive ventilation
Upper airway obstruction/apnoea	Total tonsillectomy or adenoidectomy may be beneficial
Periodic limb movements	Assessment of serum iron and ferritin
	Consider dopaminergic agents
Excessive daytime somnolence	Thorough assessment (questionnaires, actigraphy)
	Drug therapy/psychostimulants (Modafanil)
Hearing	Regular assessment
	Antibiotics for otitis media
	Grommets for recurrent otitis media
Gastrointestinal	
Nutrition	Monitoring growth
	Assessment of micronutrients (*e.g.*, iron and vitamin D) and supplementation as needed
	Dietician consultation
Irritable bowel syndrome type symptoms	Antibiotics to counteract bacterial overgrowth
Diarrhoea	Antibiotics (erythromycin)
	Drug therapy (cholestyramine)
Constipation	Stool softeners
	Laxatives/stimulating agents
	Regular toileting routine assisted by bulking agents and laxatives
Faecal incontinence	Cholestyramine
(Anal dilatation)	Colostomy (last resort)
Abdominal Pain	Pain medication (NSAIDs)
	Cholestyramine
Anaesthesia	

Hypersensitivity with risk of respiratory depression	Detailed anaesthetic work up and assessment that may include ultrasound examination of gastric volume for risk of aspiration Establish airway: modified rapid induction, tracheal tube/supra-glottic device
Increased risk of intraoperative myotonia	Avoid opioid infusions and intravenous administrations Consider local anaesthetia as an alternative (Caudal, spinal and epidural) Extensive post-operative monitoring and support Paracetamol and NSAIDs
Poor oral health	Regular dental hygiene Regular visits to general and specialist dental clinics Good home care techniques: cleaning, plaque removal
Vision	Early and regular screening Prevention of amblyopia Early correction of hyperopia and astigmatism
Psychological	
Cognitive deficits and mental retardation	Cognitive assessment Planning of appropriate education environment and support
Neuropsychiatric comorbidities (Attention deficit, personality disorders)	Psychotherapy, social skills training Drug therapy (*e.g.*, stimulants for ADHD)
Social issues	Specialised school or special arrangements

DHEA: Dehydroepiandrosterone; IGF: Insulin-like growth factor; EDS: Excessive daytime sleepiness; BiPAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; CDM: Congenital myotonic dystrophy; NSAIDs: Non-steroidal anti-inflammatory drugs; BP3: Binding protein 3; ADL: Activities of daily living; FEV1: Forced expiratory volume in 1 s; ECG: Electrocardiogram; NSAIDS: Non-steroidal inflammatory drugs; ADHD: Attention deficit hyperactivity disorder.

school[27]. Anticipating economic and vocational support are critical, with unemployment common in young adults. Taken together, special education, psychotherapy, social and vocational skills training should be utilised to maximise functionality. Stimulant medication may be prescribed for management of attention deficit hyperactivity disorder, a common comorbidity, with attention to screening for cardiac rhythm disorders.

Muscle weakness is rarely progressive in childhood; however physiotherapy, occupational therapy and orthopaedic surgery are important to limit and manage complications (contractures, pain and scoliosis) and maximise function. This includes regular assessments of strength, range of motion and function. Stretches, orthoses and assistive devices may be utilised. Tendo-achilles lengthening and scoliosis surgery may be indicated. Even though exercise therapy is commonly used, studies have shown neither benefit nor harm[49]. A Cochrane review published in 2006[50] found limited evidence supporting drugs for myotonia. Agents analysed included sodium channel blockers (such as procainamide and mexiletine), calcium channel blockers (nifedipine), benzodiazepines (diazepam), taurine and tricyclic antidepressants (clomipramine and imipramine). A more recent study has found that mexiletine is effective and well tolerated for improving debilitating grip myotonia in adults[51]. Facial weakness worsens with age and swallowing dysfunction may be assisted with diet modification and speech pathology. Speech therapy will also assist in language development. In addition facial weakness and an open mouth posture may cause more plaque, gingivitis and caries such that more frequent brushing, dental hygiene and regular dental reviews are important[52].

Regular surveillance for respiratory and cardiac complications is important in childhood. The most recent European Neuromuscular Centre workshop (ENMC) for chronic respiratory disease in DM1 describes consensus recommendations for assessment, management and follow-up based on current evidence and clinician experience[53]. Interviews with patient and carer should include a checklist for symptoms of orthopnoea, dyspnoea while performing activities of daily living, sleep disturbances, morning headaches, apnoea, reduced cognition, EDS, fatigue and chest infections since last review to identify and quantify respiratory insufficiency[53]. Accompanying tests should include respiratory function testing, pulse oximetry and polysomnography (Table 4). Management should include routine vaccination for pertussis, pneumococcus and influenza in preventing respiratory infections. Airway clearance techniques are beneficial in management of weak cough. Respiratory support is more commonly indicated in neonates than in childhood. Non-invasive ventilation may improve quality of life when there is hypoventilation or apnoea, however clinicians still debate its efficacy and further studies will clarify utility[53]. While Bi-level positive airway pressure (BiPAP) use is first line, continuous positive airway pressure (CPAP) should be used when there is a predominantly obstructive component in respiratory insufficiency. CPAP use should be accompanied with careful monitoring of blood gases[53]. Importantly, there may be a possible relation between apnoea and dysrhythmia[54] such that cardiac monitoring should accompany appropriate respiratory management when spontaneous apnoea is present[53].

Routine electrocardiography and echocardiogram should be performed and Holter monitoring may be undertaken if clinically indicated to assess for arrhythmia. Cardiac interventions, such as pacing or implanted defibrillator, are more likely to be needed closer to adulthood.

Recurrent and persistent otitis media is common

in CDM[12] and should be referred to ear, nose and throat (ENT) specialists for assessment of hearing and management. Likewise, gastrointestinal problems are an important management issue. Supportive therapies such as stool softeners/bulking agents, laxatives, antibiotics for bacterial growth, and pain medication are useful. Some drug therapies have also proven effective in remediating symptoms (Table 4). Bile acid sequestrator agents, such as cholestyramine, have been noted to reduce diarrhoea, incontinence and abdominal pain[33].

Genetic counselling is crucial in understanding the nature and inheritance pattern of DM1[55]. Multiple family members are commonly affected, and early counselling allows for surveillance and early intervention in these individuals as well as family planning with foetus risk assignment depending on parental disease. Genetic anticipation, the occurrence of decreasing age of onset and increasing severity in successive generations related to expansion of CTG repeats during meiosis, is an important consideration in genetic counselling. Notably, women have a higher risk of CDM offspring and risk factors include length of triplet repeats, symptoms during pregnancy and severity of their clinical presentation. Previous studies vary in estimation of CDM risk related to maternal CTG repeat length, rendering specific risk assessments difficult. Maternal alleles longer than 300 repeats have been demonstrated to have a 59% risk of CDM, compared with a 10% risk when CTG repeats are less than 300[56]. Different studies have found a maternal CTG length greater than 100 may have a 63% risk of CDM[57,58]. Anticipation with paternal inheritance is also possible and risk factors include onset less than aged 30 years and previous CDM pregnancies[59,60]. A parent may be identified with DM1 following diagnosis in their child and is of significance in planning of health care for the family.

Management of sleep disturbances

Sleep disturbances have been shown to be linked to greater psychosocial issues, depressive symptoms and lower quality of life[16,61,62]. Further, it is a condition faced in both adult and paediatric populations; hence early management is highly beneficial. Current management involves a thorough assessment and quantification of the sleep problem with appropriate tests. This includes polysomnography, lung function, and subjective questionnaires to assess daytime sleepiness, quality of life assessments and monitoring activity and rest cycles through non-invasive actigraphy. If a SDB is suspected, supportive ventilation with CPAP, BiPAP, sero-ventilation can improve arterial blood gases and prolong survival but may not always alleviate EDS[62]. Use of psychostimulants remains debated. A Cochrane review[63] found that evidence was inconclusive to support psychostimulant use in hypersomnia, but subjective clinician experience and other studies have found modafinil to be beneficial for EDS[64,65]. The American Academy of Sleep Medicine recognises modafinil as a therapeutic option for EDS in adult DM1, and states the current dosing recommendation as 200 mg once daily for treatment of EDS in narcolepsy[66]. There are limited clinical trials and safety information for modafinil use in children, hence modafinil is not approved by regulatory bodies for use in young children. Further studies in this group are needed to determine safety and efficacy.

GENETICS AND PATHOGENESIS OF DM1

DM1 has autosomal dominant inheritance and penetrance is variable (Figure 1). It is caused by a CTG repeat expansion of the non-coding DNA segment on the *DMPK* gene on chromosome 19q13.3. In unaffected individuals, the *DMPK* gene segment is highly polymorphic and can range from 5-27 copies[67]. There can be greater than 2000 CTG repeats in DM1[68]. Larger repeats correlate with greater symptom severity and earlier age of onset (Figure 2). One study demonstrated that in severe congenital DM1, 44% had more than 4.5 kb (up to 2000 repeats), however the largest repeat was not conditional for congenital disease[69].

DM1 demonstrates anticipation, as the CTG repeat expansion in *DMPK* may increase and become unstable with each generation. Even though amplification occurs regardless of the parental sex, offspring repeat size seems to increase more in paternally transmitted cases when the father has smaller repeats[70], but instability is greater when the mother has an expansion of more than 0.5 kb[71]. Many studies have also found occasional contractions in repeat size and variants to the repeats, but it has yet to be established if variants or interruptions in the repeats alters pathogenesis[72,73]. A sound understanding is especially important in management with regard to family planning. Adequate counselling of women who are considering pregnancy is crucial and foetal risk of disease should be assessed based on parental repeat size and presence of siblings with DM1 as mentioned before[59].

MOLECULAR PATHOGENESIS

The molecular pathogenesis of DM1 is mediated by toxic RNA with disruption of splicing of pre-mRNA transcripts including CUG binding protein (CUG-BP) and Musclebind-like protein (MBNL) (Figure 3). The CTG DNA expansion produces transcription of mutant (CUG) RNA repeats which bind to splice-regulating proteins producing aggregation and formation of ribonuclear inclusions[74,75]. Deregulated alternative splicing of pre-mRNAs has been attributed to abnormal levels of splice-regulating proteins. MBNL and CUG-BP are the two main proteins indicated[76], and the RNA toxicity mediated process is commonly known as "spliceopathy". It is uncertain as to how many other RNA-binding proteins/splice-regulating proteins are involved in DM1 pathogenesis.

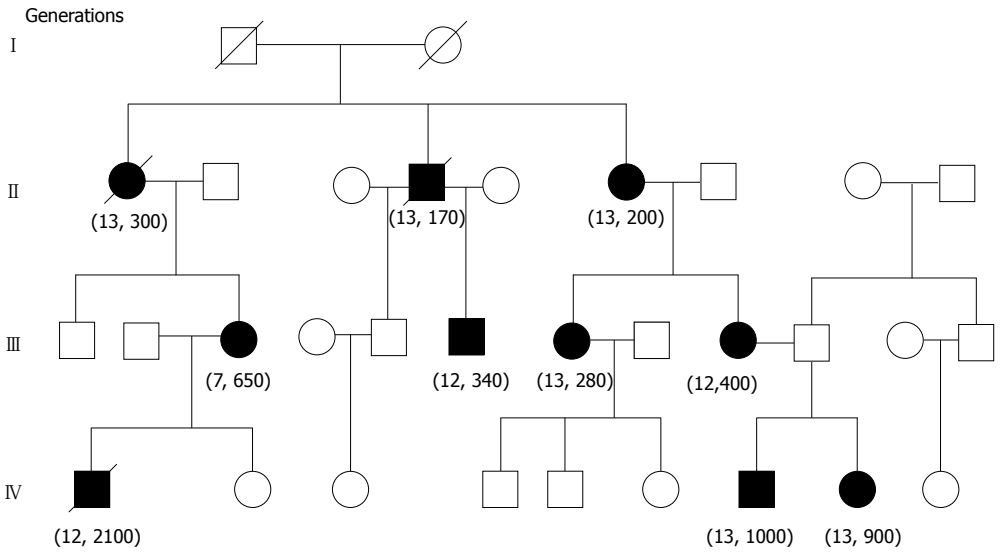

Figure 1 Genogram of family with myotonic dystrophy type 1 illustrating autosomal dominant inheritance. The numbers in brackets indicate the number of CTG triplet repeats in the 3' untranslated portion of the *DMPK* gene of affected individuals. Square = male; Circle = female; Black symbol = DM1 affected individuals; Strikethrough symbol = deceased.

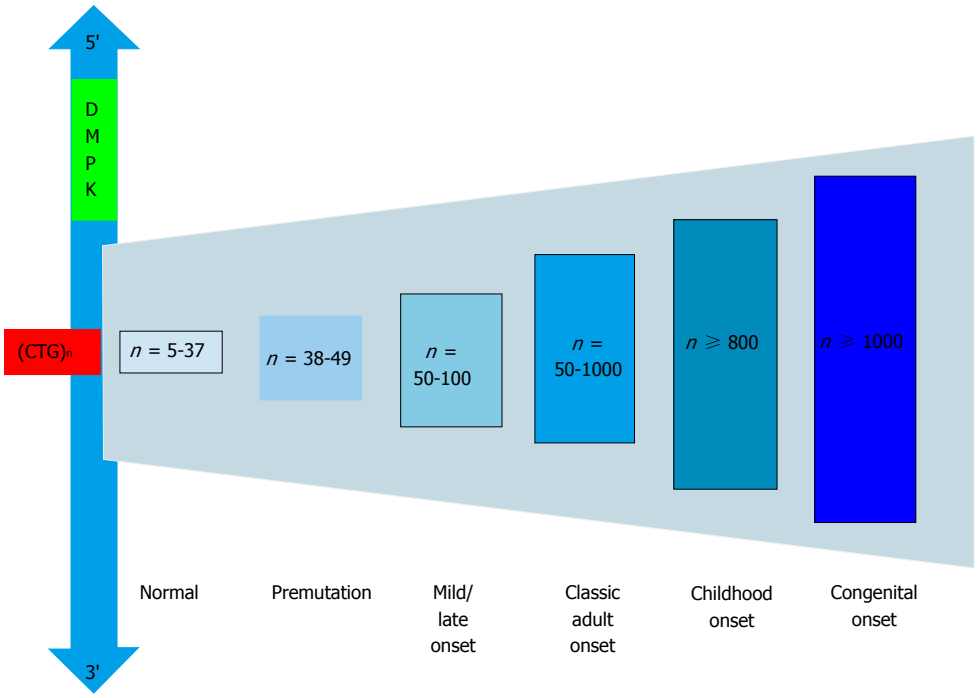

Figure 2 The genetic basis of myotonic dystrophy type 1. In DM1 there is an unstable CTG expansion at the DM1 locus, DMPK. Repeat size correlates with phenotype of DM1. DM1: Myotonic dystrophy type 1; DMPK: Dystrophia myotonica protein kinase.

MBNL 1 is most abundant in skeletal muscle, whilst MBNL 2 abnormalities have been identified in brain tissue[77,78]. In DM1, they are sequestered in the nucleus and unable to be utilised by the cell (RNA "loss of function"). CUG-BP, conversely is elevated in DM1 (RNA "gain of function") *via* increased activation and phosphorylation through several other protein mediators such as protein kinase C[79]. CUG-BP has been noted to bind to human cardiac troponin pre-mRNA[80], explaining cardiac abnormalities. Elevated CUB-BP also forms abnormally spliced insulin receptor (IR) pre-mRNA resulting in a switch to IR-A which is an abnormal isoform, thus explaining insulin resistance in adult DM1[81]. Furthermore, CUG-BP elevation has been noted to inhibit myoblast differentiation, form stress granules which reduce DNA repair, and result in loss of CIC-1 chloride channels through disruption of alternative splicing[75,82,83]. Other mechanisms identified include: overexpression of miRNA (non-coding RNA that modulates gene expression post-transcriptionally), increased myoblast cell decay, increased repeat-associated non-ATG translation (translation without an ATG

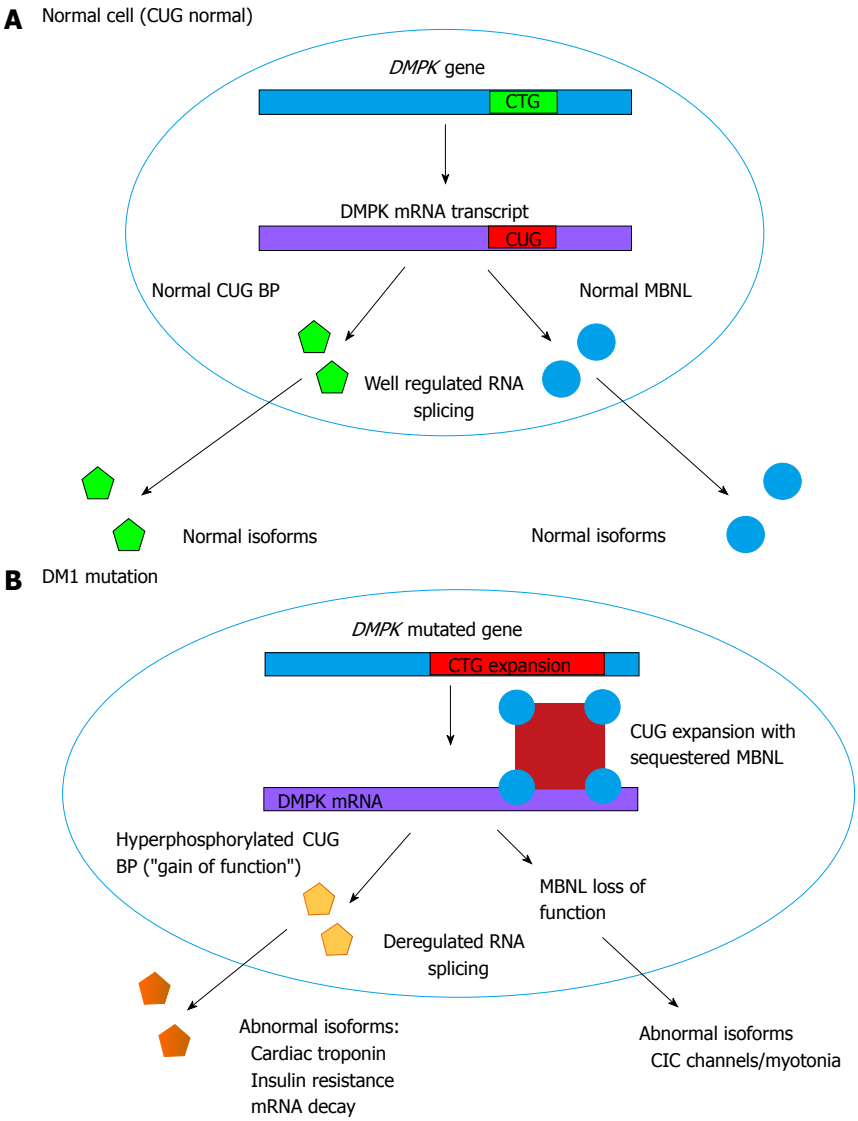

Figure 3 Pathogenic mechanisms in myotonic dystrophy type 1: (A) Normal RNA processing in cell with normal CTG repeats at the myotonic dystrophy type 1 locus; (B) Effects of expanded CTG repeat at the DM1 locus. A: Normal actions of MBNL and CUG BP in regulating alternative splicing within a cell; B: Pathogenic mechanisms involving MBNL and CUG BP, resulting in deregulated alternative splicing. While DM1 mutation is an untranslated CTG expansion, it is expressed at the RNA level and the CUG binds with two RNA binding proteins (CUGBP and MBNL) to disrupt RNA processing and splicing of other genes. For example, altered splicing of chloride channel and insulin receptor transcripts leads to myotonia and insulin resistance, respectively. DM1: Myotonic dystrophy type 1; MBNL: Musclebind-like protein; CUG BP: CUG binding protein.

start code resulting in abnormal protein aggregates), and there may even be a role for promoting oxidative stress[84-87].

NOVEL THERAPIES

There is exciting research in gene therapy that holds much promise for the treatment of myotonic dystrophy. Current management is supportive, but gene therapy may modify disease in the future. Most studies are RNA-based and focus on the RNA mediated pathways of disease (Figure 4). The most promising is antisense therapy. Strands of nucleic acid [called antisense oligonucleotides (AONs)] complimentary to target mutations are synthesised, in the hope that the target mutant sequence is silenced. Studies have effectively targeted exon 7a which codes for the defective chloride channel involved in DM1[88]. Others have effectively inhibited RNA sequestration by binding to CUG mRNA expansions[89] and sites for abnormal MBNL binding[90]. AONs have also been used to degrade the RNA expansions and the mutant DMPK allele through enzymatic actions[91-94]. Effective delivery of AONs remains the main problem with such therapies. Systemic delivery is ideal but AON levels have to be sufficiently abundant to penetrate muscle tissue and have an effect. This is greatly limited by the intact muscle surface membrane, and currently only mouse models have successfully enhanced AON uptake in muscle fibres with systemic administration[95]. Further, the effects of these novel drugs can be very specific and targets only myotonia in muscles, and thus not addressing the multi-

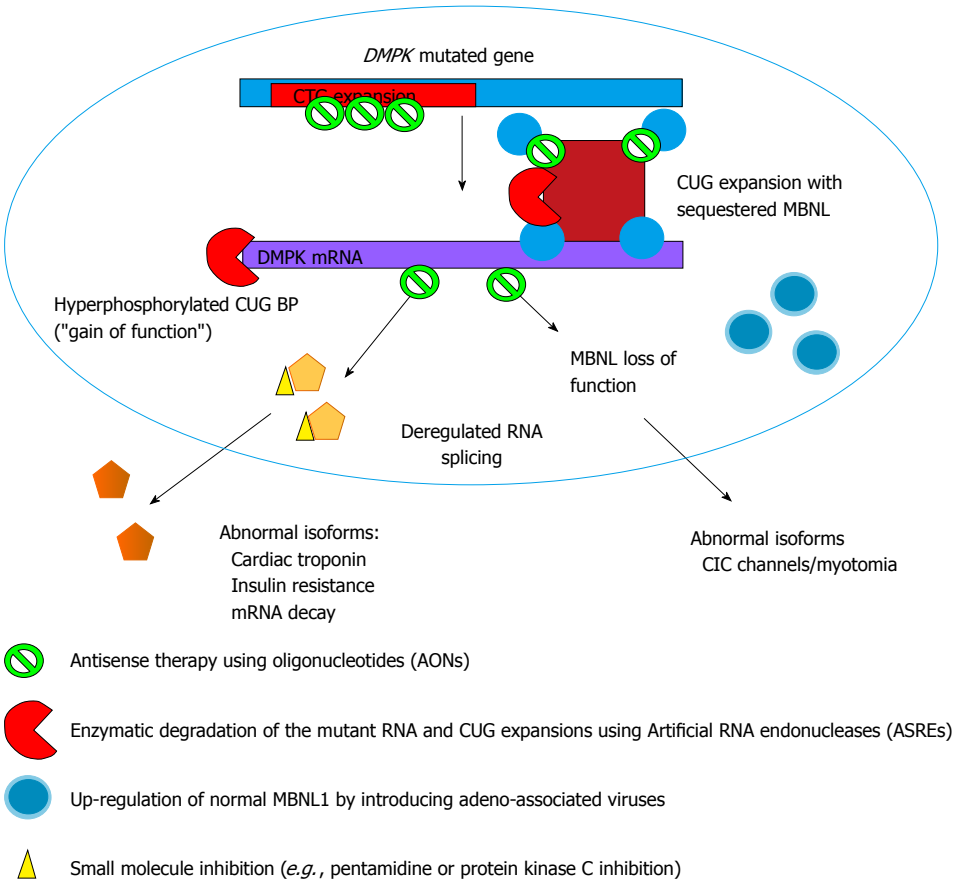

Figure 4 Novel therapies using RNA-based mechanisms to mediate RNA toxicity in a myotonic dystrophy type 1 cell. Promising trials have shown various means and targets of RNA mediated therapy with the aim of reversing or modifying "spliceopathy" and normalising cellular splice protein levels and actions. MBNL: Musclebind-like protein.

systemic problems.

MBNL-1 loss of function is well established as a feature of DM1 pathogenesis and studies have also explored means to up-regulate this splice mediator since it is abnormally sequestered in DM1. AONs have also been used for this but MBNL1 up-regulation has also been achieved in transgenic mice through the introduction of adeno-associated virus. This stimulates the overexpression of MBNL1, overcoming the sequestration and normalising MNBL function[96]. CUG-BP1 activity is increased in DM1, and down-regulation strategies by direct inhibition *via* small molecules like pentamidine or by inhibiting protein kinase C (involved in activating CUG-BP1) which potentially normalises CUG-BP1 levels[79,97]. There have also been studies looking specifically at reducing muscle weakness by introducing anabolic stimuli. Agents studied include testosterone, creatine[98-100], dehydroepiandrosterone[101] and recombinant insulin-like growth factor (IGF-1)[102]. Studies have yet to show improvements in muscle function in patients. Myostatin is known to down-regulate muscle growth and function, and inhibiting its production may be beneficial to DM1 patients; although no trial has been done specifically in DM1[95]. Future therapies will need to address the issues of efficient delivery and global effectiveness, especially in the CNS as this aspect is often most concerning for patients.

CONCLUSION

DM1 is a multisystem disease that predominantly affects muscle strength, cognition, respiratory, central nervous and gastrointestinal systems in neonates and children. Sleep disorders are often under recognised yet a significant morbidity. No effective disease modifying treatment is currently available and neonates and children with DM1 may experience severe physical and intellectual disability, which may be life limiting in congenital DM1. Novel therapies, which target the gene and the pathogenic mechanism of abnormal splicing, are emerging, but multidisciplinary management is currently supportive, incorporating regular surveillance and treatment of manifestations. It is important to develop a standard of care of congenital and childhood-onset patients to optimise outcomes.

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