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Review Article

Myotonic Dystrophy: Sum and Substance

Ashok Kumar and Sarita Agarwal*
Department of Medical Genetics, SGPGIMS, India

***Corresponding author:** Sarita Agarwal, Department of Medical Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

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Abstract

Myotonic dystrophy is an autosomal dominant, multisystem disorder that is characterized by myotonic myopathy. The unstable repeat expansions of (CTG)n repeat in the 3'-UTR of the DMPK gene and a (CCTG)n repeat in intron 1 of the CNBP (formerly ZNF9) gene cause the two known subtypes of myotonic dystrophy: (i) Myotonic Dystrophy type 1 (DM1) and (ii) Myotonic Dystrophy type 2 (DM2) respectively. This review will focus on the molecular pathophysiology, genetics, diagnosis, management and therapeutics aspect of myotonic dystrophy. The length of the (CTG)n repeat expansion in DM1 correlates with disease severity and age of onset. The symptoms and severity of Myotonic Dystrophy Type 1 (DM1) ranges from severe and congenital forms. In adult patients, cardiac conduction abnormalities may occur and cause a shorter life span. In subsequent generations, the symptoms in DM1 may present at an earlier age and have a more severe course (anticipation). In Myotonic Dystrophy Type 2 (DM2), no anticipation is described, but cardiac conduction abnormalities as in DM1 are observed and patients with DM2 additionally have muscle pain and stiffness. Because of the disease characteristics in DM1 and DM2, appropriate molecular testing and reporting are very important for the optimal counselling in myotonic dystrophy. There is currently no cure but supportive management helps equally to reduce the morbidity and mortality and patients need close follow up to pay attention to their clinical problems.

Keywords: Myotonic dystrophy; Triplet repeat; TP-PCR; Gene therapy

Introduction

Myotonic Dystrophy (DM) is a chronic, slowly progressing, highly variable, inherited multisystem autosomal-dominant disease characterized by marked intrafamilial and interfamilial clinical variability. There are two types of DM, namely myotonic dystrophy types 1 and 2 (DM1 and DM2).

Myotonic dystrophy type 1 (DM1, MIM 160900) is the most frequent adult-onset muscular dystrophy. It was first clinically recognized by Steinert [1], Batten and Gibb [2]. The main characteristics of DM1 are myotonia, progressive muscle weakness and wasting and a broad spectrum of systemic symptoms [3]. Its clinical expression is unusual, characterized by a marked variability between and within pedigrees [3,4] and a striking genetic anticipation [5] where the age-at-onset typically decreases by 25 to 35 years per generation [6]. Based on clinical ascertainment, worldwide prevalence is estimated to be 12.5/100000 [3] but it can be higher as many patients in older generation remain undiagnosed. On the basis of clinical severity the disorder is divided into three groups mid, classical and congenital. Out of these three, the congenital form is the most severe [7].

DM2 (proximal myotonic myopathy) has similar disease manifestations, although they are generally less severe and usually of later onset [8].

In the present review we will emphasize on the molecular pathophysiology, genetics, diagnosis, management and therapeutics aspect of myotonic dystrophy.

Genetic Insight of Disease

DM1 is an autosomal dominant disorder caused by an expansion of an unstable CTG trinucleotide repeat in the 3' Untranslated Region (UTR) of the gene DMPK (Myotonic Dystrophy Protein Kinase) located on chromosome 19q13.3, which codes for a myosin kinase expressed in skeletal muscled 'myotonin protein kinase' [9,10]. The DMPK gene is ~14 kb and encodes 2.3 kb of mRNA with 15 exons and the protein (cAMP-dependent serine-threonine kinase) of 624 amino acids [11,12].

Normal individuals have between 5 and 37 CTG repeats. CTG repeat lengths exceeding 37 are abnormal. Patients with between 38 and 49 CTG repeats are asymptomatic but are at risk of having children with larger, pathologically expanded repeats [13]. This is called a 'pre-mutation' allele. Full penetrance alleles occur with repeats greater than 50 CTGs and are nearly always associated with symptomatic disease although there are patients who have up to 60 repeats who are asymptomatic into old age and similarly patients with repeat sizes up to 500 who are asymptomatic into middle age. CTG repeat sizes in patients range from 50 to 4000. Molecular genetic testing detects mutations in 100% of affected individuals. Allele sizes were established by the Second International Myotonic Dystrophy Consortium (IDMC) in 1999 [14]. The disorder shows a phenomenon of genetic anticipation in which affected individuals in succeeding generations have an earlier age of onset and a more severe clinical course [15] due to the expansion of the repeat number during gametogenesis.

DM2 is an autosomal dominant disorder caused by a mutation in the ZNF9 (zinc finger protein 9) gene on chromosome 3q21. The

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first intron in ZNF9 contains a complex repeat motif (TG)n(TCTG) n(CCTG)n. Expansion of the CCTG repeat causes DM2 [16,17]. The repeat expansion for DM2 is much larger than for DM1, ranging from 75 to over 11000 repeats. Unlike DM1, the size of the repeated DNA expansion does not correlate with age of onset or disease severity in DM2. Anticipation is less evident clinically in DM2. A congenital form of DM2 has not been reported.

Molecular pathogenesis of disease

In DM1, the expanded CTG repeat is transcribed into DMPK mRNA but it does not affect DMPK protein structure. Rather, this expansion leads to production of a mutant DMPK mRNA which forms aggregates in affected nuclei [18] and the relative haploinsufficiency of the DMPK protein is not responsible for disease phenotype [19]. How does an accumulation of aberrant RNA lead to disease? It is proposed that many clinical manifestations of the disease are caused by alterations in the levels and activity of specific RNA-binding proteins involved in RNA splicing and those changes in levels and stability of these proteins then lead to aberrant splicing of many downstream RNA targets [20,21]. In general, the resultant spliceopathy leads to a splicing pattern more consistent with fetal expression than normal adult splicing patterns. Specifically, Muscleblind-like protein 1 (MBNL1) protein has been found to co-localize with mutant DMPK mRNA foci and this cause sequestration of MBNL1 by the RNA foci resulting in a loss of function that ultimately affects downstream targets [22,23]. Recent analysis has suggested that at least 200 targets are mispliced in a mouse model of DM1 and that >80% of these misplicing events are likely due to functional MBNL1 loss [24]. In support of this, genetic deletion of MBNL1 leads to a subset of the phenotypes seen in DM1, like cataracts, splicing alterations, myotonia and changes in muscle histology [25]. Interestingly, MBNL1 is sequestered with RNA foci in DM2 as well, and many aspects of the spliceopathy seen in DM1 are also found in DM2 [26]. In addition to MBNL1 sequestration, the levels of another RNA binding protein, CUG-Binding Protein 1 (CUGBP1) are increased in affected tissues. This is thought to be mediated by Protein Kinase C (PKC) phosphorylation and resultant stabilization of CUGBP1, although the details of this mechanism are poorly understood [27]. CUGBP1, like MBNL1, has important roles in RNA splicing and is thought to be antagonistic to MBNL1 for many of the splicing defects observed in DM1. Thus, the increase in CUGBP1 could synergize with the functional loss of MBNL1. CUGBP1 also has additional roles in RNA stability and translation [28-31]. Missplicing of certain downstream targets is then considered directly responsible for at least some of the observed phenotypes of DM1, and new targets are continually being discovered. For example, it has been elegantly shown that mis-splicing of the muscle-specific chloride channel ClC1 is responsible for the myotonia observed in DM1 models and patients. Aberrant splicing of the ClC-1 pre-mRNA leads to inclusion of exon 7a into the mature mRNA (a pattern more consistent with embryonic ClC-1 expression). Exon 7a inclusion ultimately results in a premature stop codon, resulting in rapid decay of the mis-spliced transcript [32,33]. Other splicing abnormalities may be responsible for insulin resistance (aberrant splicing of insulin receptor), some of the cardiac phenotypes (cTNT), and likely some of the central nervous system cognitive effects [34-37].

Diagnosis of DM1

System, muscular skeletal, cardiovascular, GI, Endocrinology, CNS etc. features and diagnosis: After contraction of the muscle relaxation is greatly delayed. This is the clinical manifestation of the disease. It may be troublesome in some while other patients may not be aware of it. Muscle weakness is variable. Weakness of facial muscles gives facial change, pain in abdomen and constipation may be symptoms in some of them. The severity and age of onset of symptoms correlates well with number of triplet repeats. The CTG repeat size is positively correlated with severity of the disease and inversely correlated with age of onset of symptoms [38-41]. The cases with 50 to 150 repeats have mild manifestations in the sixth decade or later while the classical cases manifesting at a young age have 150 to 1000 repeats. The third variety is congenital and is associated with prenatal hydramnios, joint contracture and severe hypotonia at birth. These cases have more than 2000 repeats and the diseased allele is transmitted through the mother. Some of the neonatal DM1 succumb to respiratory failures while some survive but have developmental disability. Other symptoms are also involved in myotonic dystrophy and features include cardiac rhythm abnormalities, cataract, diabetes mellitus, testicular atrophy and prenatal balding [3,42,43]. In cases without clinically obvious myotonia electromyogram is useful to demonstrate myotonic discharges. Creatinine phosphokinase may be mildly elevated in DM1 and muscle biopsy is only rarely required but required in cases with neuromuscular complaints and with negative genetic analysis [42,44]. However, clinical diagnosis is possible in most of the cases but molecular diagnosis is needed to differentiate between DM1 and DM2. In some cases it is difficult to differentiate from myotonia congenital and myopathies.

Molecular diagnosis: The detection of expansion of triplet repeat traditionally is done by Southern blot analysis [45,46]. However, Triplet Primed PCR (TP-PCR) based testing is found to be a reliable non-radioactive method as a replacement of the Southern blot [47-50]. The number of triplet repeats correlates with the phenotype and hence, it is important for prediction of severity of the disease [38-41]. In the clinical scenario of DM, if DM1 mutation is not detected, the mutation in DM2 should be tested. The mutation detection helps in the confirmation of the diagnosis, predicting severity and providing genetic counselling. After molecular confirmation of the diagnosis in the proband, the family can be counselled for prenatal diagnosis and diagnosis can be offered to presymptomatic carriers in the family. Mutation detection is necessary to differentiate between DM1 and DM2 as in this era linkage analysis for prenatal or presymptomatic diagnosis has a limited role. The application of TP-PCR [49] and multiplex PCR over Southern blotting [45] for screening of triplet repeat expansion in DM1 is now recommended.

Molecular Pathogenesis of Disease

A summary of the steps in the pathogenesis of DM1 is shown in Figure 1, and the instances in which molecular or symptomatic therapy have been attempted are noted. General concepts in therapeutic design strategy are detailed in Figure 2. Targeting the earliest stage of aberrant pathophysiology is often the most difficult and technically challenging approach (in this case targeting DNA repeat expansion), although it has the potential for the greatest therapeutic benefit since all downstream effects are then modified.

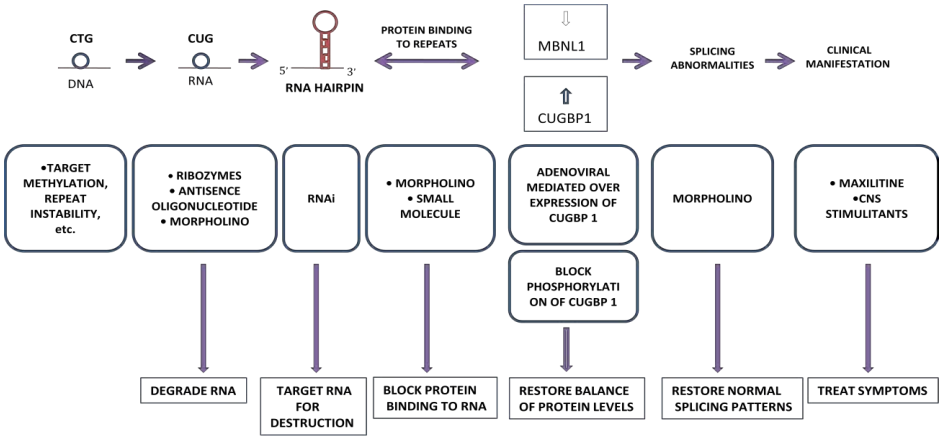

Figure 1: Steps in pathogenesis and potential therapeutic targets in DM1.
Myotonic Dystrophy results from the expansion of CUG repeats in the mutant RNA, rather than from reduced or dysfunctional protein levels. These repeats form a hairpin structure that can bind and sequester MBNL1 and potentially other RNA-binding proteins. Through mechanisms that are still poorly understood, this toxic RNA also causes hyperphosphorylation and stabilization of CUGBP1. The functional loss of MBNL1 and increase in available CUGBP1 are thought to result in misplicing of downstream RNA targets (largely to fetal isoforms) causing many, if not all, of the observed phenotypes. Attempts have been made to target each of the steps in pathogenesis, although the current effective therapy is limited solely to symptom management.

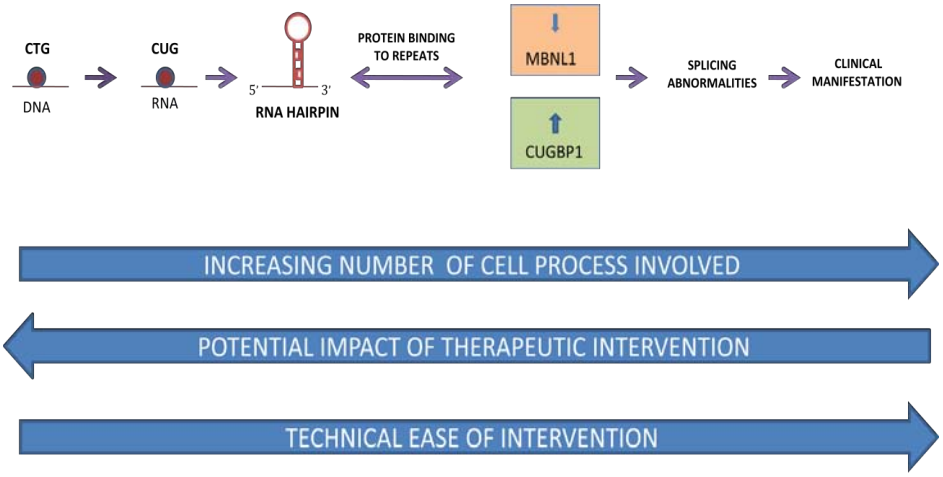

Figure 2: Therapeutic Design approach.
DM1 is caused by a repeat expansion in the DNA which is then incorporated into a mutant RNA. This toxic RNA then leads to a cascade of mispliced RNA transcripts and multisystem manifestations of disease. The mechanism of pathogenesis is simplest at the stage of the expanded DNA repeat and becomes increasingly more complicated as more cellular processes and pathways are involved in the downstream effects. Thus, intervention at the level of the DNA provides the most therapeutic benefit but is least technically feasible. Conversely, intervention at the level of one mis-spliced target may be most technically approachable, but therapeutic impact is then limited to only one portion of the disease phenotype.

As one targets further down the cascade, potential therapies may be easier to design and implement, however, only a subset of pathology would be treated. For example, targeting splicing abnormalities in the chloride channel mRNAs in DM1 patients may be more feasible than targeting DNA repeat expansions. The resultant effect, however, would address only the myotonia in skeletal muscle, and other systemic complications would still be present. Thus, an ideal therapy would need to strike a pragmatic balance to allow for substantial benefit, relative ease of technical approach, and minimal effect on unrelated cellular mechanisms. Theoretically, and in practice, each of the abnormal steps in the pathogenesis of DM1 could be targeted for interventional modification. There is very little specific treatment that is distinct for DM2 and the multisystem pathologies of DM2 are similarly treated and monitored. Below we will discuss the varied therapeutic approaches as well as their potential applications and limitations to human disease.

DM1 and DM2 have 3 different problems: (1) myotonia, (2) muscle weakness, (3) systemic manifestations like cataracts, diabetes mellitus, cardiac arrhythmia, and others (Table 1). Both DM1 and DM2 progress through defect in chloride (Cl) channel. To date we do not have any medication to open Cl channels of the skeletal muscles; therefore we have been using Na channel blocker for myotonia. Mexiletine, Procainamide, Phenytoin, Carbamazepine are all Na channel blockers which were originally developed for cardiac arrhythmia, or seizure disorders. Since myotonic dystrophy has progressive muscle weakness due to the dystrophic nature of this disorder, even if myotonia is reduced, muscle weakness is a bigger problem. Na channel blockers tend to reduce muscle power

Table 1: Treatment (Tx) for Myotonic Dystrophy Type 1 (Includes Treatment for Myotonia, Muscle Weakness, and Systemic Manifestations).

Tx for myotonia	Tx for muscle weakness	Tx for systemic manifestations
ACTH **Corticosteroid (cortisone, prednisone)** **Procaine amide** **Mexiletine** **Phenytoin** **Carbamazepine** **Dehydroepiandrosterone sulfate (DHEAS)** **Dexamethasone** **Nifedipine**	No effective medicine available. Trials with Creatine and DHEAS: some improvement	(1) Cataract: operation and implanting artificial lens (2) Cardiac arrhythmia: cardiac pacemaker as needed and Coenzyme Q10 (3) Respiratory problem therapeutics: modafinil (200–400mg/day) and dexamphetamine or methylphenidate are used (4) Diabetes mellitus: metaformin and Troglitazone (5) Hypothyroidism:thyroxine (6) Hypogonadism: hormonal replacement is not usually done

by decreasing muscle action potentials and these unwanted effects of Na channel blockers are the problem. Therefore, it is important to develop medications for myotonic dystrophy which can reduce myotonia and yet maintain the muscle strength as it is.

Treatment for myotonia

Dehydroepiandrosterone Sulphate (DHEAS) [51] and Nifedipine [52] used for myotonia control in DM1. The 250 mg/day dose of DHEAS reduced myotonia and improved the activities of daily living [51] DHEAS does not reduce muscle power as much as other drugs (like mexiletine) that have been used for myotonia and ADL in the past. It prevents the cytotoxicity of toxic RNA of expanded CUG repeats in a neural cell line [53].

Some relief of myotonia with quinine procainamide, phenytoin, ACTH (cause movement of potassium out of the muscle cell during contraction) and corticosteroid (cortisone, prednisone) [54,55] but these and some other drugs, showed no beneficial effects on the progressive weakness. In myotonic dystrophy steroids may improve myotonia only, due to its membrane stabilising properties. However, Steroids should be considered for short term use especially when swallowing and respiration are severely impaired. The high dose dexamethasone resulted in a marked improvement on both weakness and myotonia in a patient with myotonic muscular dystrophy [54,55].

Therapeutic trials to improve muscle strength for myotonic dystrophy

Creatine Monohydrate (CrM) therapy: Creatine monohydrate alleviate the symptoms of muscular dystrophy, sand when used in conjunction with corticosteroids, significantly reduce the amount of atrophy associated with the progression of this debilitating disease. A double-blind placebo-controlled study of CrM therapy for 20 DM2 patients for 3 months duration did not have significant effects on muscle strength. However, 2 DM2 patients showed mild improvement in DM2 specific muscle pain, which is more troublesome than myotonia for DM2 patients [56].

CrM therapy was done as an open trial for 20 Japanese muscular dystrophy patients including 14 Myotonic Dystrophy (DM1) cases [57]. Twelve patients had subjective improvement of muscle power. There are minor side effects of creatine including excessive sleepiness, diarrhoea, and sweating. To date, DM2 cases have not been reported in Japan.

Treatment for systemic manifestations

Treatment for cataracts: It is important to evaluate for visual disturbance after cataract surgery for DM1. In DM1, capsulorhexis contracture tends to occur after cataract surgery and causes decreased vision which may occur a few months after the cataract surgery [58]. Therefore, it is important to inform the ophthalmologist before cataract surgery of the diagnosis of myotonic dystrophy.

Treatment for cardiac arrhythmia to avoid sudden death: Tachyarrhythmia and conduction block may be responsible for up to 30% of fatalities in DM1 [59]. In more advance condition of fatal arrhythmias invasive electrophysiological testing of the heart may be required [60]. When ECG shows an increased PR interval, measurement of HV interval (infra-nodal conduction delay; HV >70 ms) may help to decide the need for Pacemaker (PM) implantation to prevent sudden death of patient [61]. The PM protects the patient against the clinical consequences of paroxysmal profound bradycardia and facilitates the diagnosis and management of frequent paroxysmal tachyarrhythmia [61]. On the other hand, the oral administration of coenzyme Q10 (CoQ10) improves muscle strength and impaired myocardial function [62]. Thus, CoQ10 offers a safe and improved quality of life for DM1 patients.

Treatment for diabetes mellitus: In myotonic dystrophy, insulin resistance and hyperinsulinism is present. Drug Metaformin control hyperglycemia of DM1, since Metaformin increases glucose uptake of the skeletal muscles independently [63]. Another drug, Troglitazone reduces insulin resistance and improves myotonia in DM1 patients [64].

Treatment for excessive daily sleepiness: Modafinil (Provigil) is approved for treating excessive daytime sleepiness associated with narcolepsy, for shift-work sleep disorder, and as an adjunctive treatment in patients with obstructive sleep apnea syndrome who have residual daytime sleepiness despite optimal treatment with continuous positive airway pressure. Although modafinil improves measures of sleepiness, it does not generally normalize them, and it may be less effective than other stimulants for some narcoleptic patients. The recommended dosage of Provigil for patients with narcolepsy or Obstructive Sleep Apnea (OSA) is 200 mg taken orally once a day as a single dose in the morning. Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose. Modafinil is an effective drug and do not have any cardiovascular complications [65].

Experimental therapeutic trials to decrease CTG repeat: Future essential treatment for DM1

Targeted molecular treatment: Antisense molecules: The development of targeted molecular treatments (especially antisense therapy) has achieved great success in vitro and in animal models. Preferential reduction of mutant DMPK causes reversal of the

abnormal phenotype in DM1 myoblasts [66]. Alterations in splicing of the muscle specific chloride channel 1 (ClCN-1) cause the myotonic phenotype of DM1. Morpholino (a small antisense molecule to alter gene expression) reverses the altered splicing of ClCN-1 mRNA [67]. It carries a complementary base sequence to the expanded RNA and it bind to the expanded RNA (the cause of myotonic dystrophy). The interaction prevents RNA from trapping and interacting with another molecule and muscle blind protein (MBNL) which is central to the disease process in DM1. Though still far away from successful clinical use, gene therapy may become a valuable therapeutic approach in future.

Chemotherapeutics and other treatment in DM1: Chemotherapeutic agents like Ethylmethanesulfonate (EMSO), Mitomycin C Mitoxantrone, and Doxorubicin etc. reduced expanded CTG repeat in lymphoblast cells of DM1 patients [68]. This may be eventually applicable to 17 neurological intractable diseases including spinocerebellar degeneration in addition to DM1.

Conclusion and Future Prospective

Much progress has been made regarding the development of molecular therapeutics for myotonic dystrophy, and there is great promise inherent in many of these approaches. However, before we are able to move these therapies forward into clinical trials, we must first identify the appropriate outcome measures to be used as markers for therapeutic efficacy. In addition, it will require the identification of molecular disease biomarkers that can be used to follow the extent of disease modification with therapeutic intervention. Clearly, if the outcome measures chosen in the clinical trial design do not adequately reflect changes in disease state, then these new therapies may be deemed to be ineffective despite real benefit. New initiatives are being developed to identify appropriate biomarkers and to uncover which outcome measures are most reliable and meaningful for the purpose of clinical trials. Research in DM1 has opened up new frontiers in medical research. About 20 years after the discovery of the first DM1 mutation, there is better understanding of the molecular pathology. A series of promising and effective Antisense Oligonucleotides (AONs), drugs and small molecules are in the pipeline of development but much work still needs to be done. A second important challenge in treating DM1 is its multisystemic nature which is highly variable and makes it difficult to define target tissues and to develop reliable biomarkers for clinical trials.

In summary, although much progress has been made, additional basic and translational studies will be required to understand the molecular pathogenesis of DM1 and to develop safe and effective treatment strategies.

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