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Review

Myotonic dystrophies: An update on clinical aspects, genetic, pathology, and molecular pathomechanisms☆

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ABSTRACT

Myotonic dystrophy (DM) is the most common adult muscular dystrophy, characterized by autosomal dominant progressive myopathy, myotonia and multiorgan involvement. To date two distinct forms caused by similar mutations have been identified. Myotonic dystrophy type 1 (DM1, Steinert's disease) is caused by a (CTG)n expansion in *DMPK*, while myotonic dystrophy type 2 (DM2) is caused by a (CCTG)n expansion in *ZNF9*/*CNBP*. When transcribed into CUG/CCUG-containing RNA, mutant transcripts aggregate as nuclear foci that sequester RNA-binding proteins, resulting in spliceopathy of downstream effector genes. However, it is now clear that additional pathogenic mechanism like changes in gene expression, protein translation and micro-RNA metabolism may also contribute to disease pathology. Despite clinical and genetic similarities, DM1 and DM2 are distinct disorders requiring different diagnostic and management strategies. This review is an update on the recent advances in the understanding of the molecular mechanisms behind myotonic dystrophies. This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

1. Introduction

Myotonic dystrophies (DMs) are autosomal dominant, multisystemic diseases with a core pattern of clinical presentation including myotonia, muscular dystrophy, cardiac conduction defects, posterior iridescent cataracts, and endocrine disorders [1]. In 1909 Steinert and colleagues first clearly described the "classic" type of myotonic dystrophy which was called Steinert's disease (OMIM 160900). The gene defect responsible for myotonic dystrophy described by Steinert was discovered in 1992 and found to be caused an expansion of an unstable CTG trinucleotide repeat in the 3′ untranslated region (UTR) of the *myotonic dystrophy protein kinase* gene (*DMPK*; OMIM 605377) which codes for a myosin kinase expressed in skeletal muscle. The gene is located on chromosome 19q13.3 [2–4]. Subsequently, in 1994, a different multisystemic disorder was described with dominantly inherited myotonia, proximal greater than distal weakness, and cataracts but lacking the gene defect responsible for Steinert's disease [5–8]. In Europe, the disease was termed proximal myotonic myopathy (PROMM, OMIM*160900) [5] or proximal myotonic dystrophy (PDM) [8] while in the United States it was termed myotonic dystrophy with no CTG repeat expansion or myotonic dystrophy type 2 (DM2) [6]. Later studies demonstrated that many of the families identified as having myotonic dystrophy type 2, PROMM or PDM had the same disease, a disorder caused by an unstable tetranucleotide repeat expansion, CCTG, in intron 1 of the *nucleic acid-binding protein* (*CNBP*) gene (previously known as *zinc finger 9* gene, *ZNF9*) on chromosome 3q21 [9,10]. Due to the existence of different types of myotonic dystrophy, the International Myotonic Dystrophy Consortium developed a new nomenclature and guidelines for DNA testing [11]. The Steinert's disease, the classic form of myotonic dystrophy that results from an unstable trinucleotide repeat expansion on chromosome 19, is now termed myotonic dystrophy type 1 (DM1). Patients with the clinical picture of myotonic dystrophy type 2/proximal myotonic myopathy, who have positive DNA testing for the unstable tetranucleotide repeat expansion on chromosome 3, are now classified as having myotonic dystrophy type 2 (DM2) [6,12,13].

Although DM1 and DM2 have similar symptoms, they also present a number of very dissimilar features making them clearly separate diseases (Table 1).

2. Clinical features

Myotonic dystrophy type 1 is the most common inherited muscular dystrophy in adults with an estimated prevalence of 1/8000. Patients with DM1 can be divided into four main categories, each presenting specific clinical features and management problems: congenital,

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Table 1
Comparison of clinical manifestations between DM1 and DM2.

Clinical Features	DM1	DM2
General features		
Epidemiology	Widespread	European
Age of onset (years)	0 to adult	8–60
Anticipation	Always present	Exceptional
Congenital form	Present	Absent
Life expectancy	Reduced	Normal range
Core features		
Clinical myotonia	Evident in adult-onset	Present in <50%
EMG myotonia	Always present	Absent or variable in many
Muscle weakness	Disabling at age 50	Onset after age 50–70
Cataracts	Always present	Present in minority
Muscle symptoms		
Facial and jaw weakness	Always present	Usually absent
Bulbar weakness-dysphagia	Always later	Absent
Respiratory muscles weakness	Always later	Exceptional
	Always prominent	Only flexor digitorum profundus, rare
Distal limb muscle weakness	May be absent	Main disability in most patients, late
	Always prominent	Prominent in few
Proximal limb muscle weakness	Absent or mild	Most disabling symptom in many
Sternocleidomastoid weakness	Face, temporal, distal hands and legs	Usually absent
Myalgic pain	Absent	Present in ≥50%
Systemic features		
Tremors	Absent	Prominent in many
Behavioral change	Early in most	Not apparent
Cognitive disorders	Prominent	Not apparent
Hypersomnia	Prominent	Infrequent
Cardiac arrhythmias	Always present	From absent to severe
Male hypogonadism	Manifest	Subclinical in most
Manifest diabetes	Frequent	Infrequent

childhood-onset, adult-onset and late-onset/asymptomatic. Table 2 summarizes these subtypes.

Congenital DM1 (CDM) shows a distinct clinical phenotype with distinct clinical features therefore it is not to be considered a severe early form of 'classical' DM1. CDM often presents before birth as polyhydramnios and reduced fetal movements. After delivery, the main features are severe generalized weakness, hypotonia and respiratory compromise. One feature of affected infants is the "fish-shaped" upper lip an inverted V-shaped upper lip which is characteristic of severe facial weakness. Mortality from respiratory failure is high. Surviving infants experience gradual improvement in motor function, almost all CDM children are able to walk. Cognitive and motor milestones are delayed and all patients with CDM develop learning difficulties and require special need schooling. Cerebral atrophy and ventricular enlargement are often present at birth [14,15]. A progressive myopathy and the other features seen in the classical form of DM1 can be develop although this does not start until early adulthood and usually progresses slowly [16]. Clinical myotonia is neither a feature presented in the neonatal period nor can it be disclosed in the electromyogram (EMG). Patients often develop severe problems from cardiorespiratory complications in their third and fourth decades.

The diagnosis of the DM1 childhood onset form is often missed in affected adolescents or children because of uncharacteristic symptoms for a muscular dystrophy and apparently negative family history [17]. These patients have cognitive deficits and learning abnormalities [18] and, as in the congenital cases, degenerative features often develop as these children reach adulthood. There is increasing evidence of early heart conduction abnormalities thus annual electrocardiograms and consideration of electrophysiological studies should be a part of routine management.

The core features in classic adult-onset DM1 are distal muscle weakness, leading to difficulty with performing tasks requiring fine dexterity of the hands and foot drop, and facial weakness and wasting, giving rise to ptosis and the typical myopathic or 'hatchet' appearance. The neck

Table 2
Summary of myotonic dystrophy type 1 phenotypes, clinical findings and CTG length.

Phenotypes	Clinical findings	CTG length	Age of onset
Congenital	Infantile hypotonia Respiratory failure Learning disability Cardiorespiratory complications	>1000	Birth
Childhood onset	Facial weakness Myotonia Low IQ Conduction defects	50–1000	1–10 years
Adult onset "classic DM1"	Weakness Myotonia Cataracts Conduction defects Insulin resistance Respiratory failure	50–1000	10–30 years
Late onset/asymptomatic	Mild myotonia Cataracts	50–100	20–70 years
Pre-mutation	None	38–49	N/A

flexors and finger/wrist flexors are also commonly involved. Grip and percussion myotonia are regular features; however, myotonia affects other muscle including bulbar, tongue or facial muscles, causing problems with talking, chewing, and swallowing. Elevation of the serum creatine kinase is sometimes present. Cardiac involvement is common in DM1 and includes conduction abnormalities with arrhythmia and conduction blocks contributing significantly to the morbidity and mortality of the disease [19–22]. In some patients and families, a dilated cardiomyopathy may be observed. Posterior subcapsular cataracts develop in most patients and some patients may develop cataract at an early age without any other symptoms [23]. CNS dysfunctions with a characteristic of cognitive and neuroimaging involvement are also present [24] Nocturnal apnoeic episodes and daytime sleepiness are common manifestations. Gastrointestinal tract involvement covers irritable bowel syndrome, symptomatic gall stones and gamma-glutamyltransferase elevations. Finally, endocrine abnormalities include testicular atrophy, hypotestosteronism, and insulin resistance with usually mild type-2 diabetes.

In late-onset or asymptomatic DM1 patients myotonia, weakness and excessive daytime sleepiness are rarely present. Before DNA tests became available, there were many examples of incorrect ascertainment, even when using markers such as EMG evidence of myotonia and slit-lamp examination for the characteristic cataracts [25]. In late-onset patients, the search for cataracts is helpful for identifying the transmitting person.

The prevalence of DM2 is not well established, but estimated to be similar to DM1 in European populations [26]. The most important discrepancy between DM1 and DM2 is the absence of a congenital form in DM2 [13,27] and the clinical presentation is a more continuum from early adult-onset severe form to very late-onset mild symptoms (paucisymptomatic).

Clinically based ascertainment of DM2 patients is even more difficult because of the large phenotypic variability and a large number of individuals with milder symptoms who remain undiagnosed. Moreover, milder phenotypes with prominent myalgia may easily be misdiagnosed as fibromyalgia [28] and patients with the onset of slowly progressive proximal muscle weakness after the age of 70 years may not be referred for neuromuscular investigations.

DM2/PROMM typically appears in adult life and has variable manifestations, such as early-onset cataracts (younger than 50 years), varying grip myotonia, thigh muscle stiffness, and muscle pain, as well as weakness [6,13,29–32]. These complaints often appear between 20 and 70 years of age, and patients as well as their care providers ascribe them to overuse of muscles, “pinched nerves,” “sciatica,” arthritis, fibromyalgia, or statin use [33]. Early in the presentation of DM2 there is only a mild weakness of hip extension, thigh flexion, and finger flexion. The myotonia of grip and thigh muscle stiffness varies from minimal to moderate severity over days to weeks. Myotonia is often less apparent in DM2 compared with patients with DM1. It is more difficult to elicit myotonia on standard EMG testing in DM2 compared to DM1 except for proximal muscles such as the tensor fascia lata and vastus lateralis muscles. In cases of late-onset DM2, myotonia may only appear on electromyographic testing after examination of several muscles [30]. The cataracts in DM2 have an appearance identical to that observed in DM1 and develop before 50 years of age as iridescent, posterior capsular opacities on slit-lamp. Cardiac problems appear to be less severe and frequent in patients with DM2 than in patients with DM1 [34–36]. In DM2, cardiac conduction alterations are primarily limited to first-degree atrio-ventricular and bundle branch block. However, sudden death, pacemaker implantation, and severe cardiac arrhythmias have been described in small numbers of patients [31,36,37].

Central nervous system involvement represents one of the big issue and neglected aspect in DM [24]. Although retarded DM2 individuals have been reported, these occurrences may be either accidental or an infrequent disease consequence [13,29]. The type of cognitive impairment that occurs in DM2 is similar to but less severe than that of DM1. Other manifestations, such as hypogonadism, glucose intolerance, excessive sweating, and dysphagia, may also occur and worsen over time in DM2 [6,13,32,38–42]. PDM patients show many features similar to those found in PROMM, including proximal muscle weakness, cataracts, and electrophysiologically detectable myotonia. Unlike PROMM patients, however, they do not report myalgias, symptomatic myotonia, or muscle stiffness. Instead they present traits not present in PROMM, such as pronounced dystrophic–atrophic changes in the proximal muscles and late-onset progressive deafness [8].

3. Genetics

In patients affected by DM1 the repeat size range is from 50 to 4.000 (150–12.000 bp) and is 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 of up to 500 who are asymptomatic into middle age. Healthy individuals have between 5 and 37 CTG repeats. Repeat lengths of 38–50 are considered premutation alleles, whereas 51–100 repeats are protomutations, both of which show increased instability toward expansion. Patients with premutations or protomutations are asymptomatic or present few mild symptoms, such as cataracts, but are at risk of having children with larger, pathologically expanded repeats [6]. The DM1 mutation length >2.000 repeats causes the congenital form of the disease [11,43].

In DM1, repeat mutations are dynamic gene defects and show instability with variation in different tissue and cell types causing somatic mosaicism [44,45]. The size of the CTG repeat appears to increase over time in the same individual and across generation. Children may inherit repeat lengths considerably longer than those present in the transmitting parent. This phenomenon is known as genetic anticipation in which disease severity increases and/or age of onset of disease decreases from one generation to the next. A child with congenital DM1 almost always inherits the expanded mutant *DMPK* allele from their mother. However anticipation may be seen in patients with DM1 who inherit a smaller expanded CTG repeat from their father [46,47]. Germ-cell instability is possibly the major determining factor underlying the pronounced anticipation in DM1 [48]. However, the CTG repeat size does not always increase in successive generations of DM families. Intergenerational contraction of CTG repeats, a decrease in the CTG repeat size during transmission from parents to child, can also occur in about 6.4% of transmissions, most frequently during paternal transmissions (10%) [49,50].

In DM1, repeat expansion length is predictive of clinical severity and age of onset, however, due to somatic mosaicism, CTG repeat size correlates more significantly with age of onset and disease severity below 400 CTG repeats [51]. The correlation between CTG repeat size and the severity of the disease can be observed in blood but not in other organs (eg, muscle). In DM1 the repeat lengths in muscle are shown to be larger [52] and there is no correlation between the size of the CTG repeats in muscle and the degree of weakness. It should be noted that in clinical practice, the CTG expansion is measured in blood and there is no additional clinical advantage of measuring repeat size in muscle.

Recently, DM1 families with expanded alleles with variant repeats (eg, (CCG)n and (GGC)n repeats, part of the overall (CTG)n repeat array) have been described [53–56] and in patients with variant repeats the symptoms are generally less severe than those observed in classical DM1 [54]. The presence of variant repeats has a dramatic stabilizing effect on expansion reducing the rate of expansion in affected tissues leading directly to a delay in the onset and slowing of the progression of the DM1 symptoms [55]. These observations suggest that interruptions in the primary structure of the CTG expansion could modulate the clinical phenotype, either by increasing DNA strand stability during cell divisions, or by producing conformational changes of the variant RNA species with effects on their toxic gain-of-function. However, Santoro et al. [56] report that characteristic ribonuclear inclusion colocalizing with MBNL1 positive foci and splicing defects is observable

in muscle tissue from variant DM1 patients suggesting that CCG interruptions do not considerably affect the toxic gain of function of expanded RNAs.

Such variation has been found in up to 4% of unrelated individuals with DM1 [55] but might have gone undetected in patients presenting with atypical manifestations. Indeed, variant repeats with extreme GC contents yield false negatives in both repeat primed PCR and standard PCR based approaches to diagnostics. For this reason bidirectional triplet primed PCR (TP-PCR) should be included in the routine diagnostic protocol used for DM1 testing since it is very sensitive to detect DM1 expansions presenting variant repeats [57].

DM1 is most common in populations of European descent, is present in Japan at about half the frequency, and is rarer still in India [58–60]. To date only one kindred from sub-Saharan Africa has been described [61].

In contrast to the (CTG)n repeat in DM1, in myotonic dystrophy type 2 the (CCTG)n repeat is a part of the complex repetitive motif (TG)n(TCTG)n(CCTG)n. In contrast to the DM1 associated (CTG)n repeat, the DM2 associated (CCTG)n repeat tract is generally interrupted in healthy range alleles by one or more GCTG, TCTG or ACTG motifs, while it is typically uninterrupted in the expanded alleles [10,62,63]. The size of the (CCTG)n repeat is below 30 repeats in normal individuals while the range of expansion sizes in DM2 patients is huge [63]. The smallest reported mutations vary between 55 and 75 CCTG [10,63] and the largest expansions have been measured to be up about 11.000 repeats [10]. The expanded DM2 alleles show marked somatic instability, with significant increases in length over time [10,13] thus the threshold size of the disease-causing mutation remains to be determined. Somatic instability, present in both DM1 and DM2, gives rise to intra-tissue, inter-tissue, and cell-type variability and somatic mosaicism over a patient's lifetime [10,62,64,65]. In DM2 the mutation usually contracts in the next generation being shorter in the children [13]. This may explain some distinct features of DM2 such as the missing of a congenital form, the lack of anticipation and the later onset [27]. The size of CCTG repeat expansion in leukocyte DNA in DM2 seems to be related in large part to the age of the patient and not necessarily to the severity of symptoms or manifestations. This complicates attempts to correlate the size of the repeat with earlier clinical onset of more severe symptoms as it occurs in patients with DM1.

Evidence that a large proportion of DM2 patients may be undiagnosed came from recent studies which indicate that the co-segregation of heterozygous recessive CLCN1 mutations in DM2 patients is higher than expected and modifies the DM2 phenotype [66,67]. The mutations of *CLCN1* gene, codifying for a skeletal muscle chloride channel (CLC-1), are responsible of myotonia congenita (recessive Becker disease OMIM no. 255700; dominant Thomsen disease OMIM no. 160800) and a slight effect on biophysical proprieties of the chloride channel has been demonstrated in heterozygous recessive mutation [68]. Generally, DM2 affected carriers showed more severe muscle stiffness and more severe clinical EMG than those having exclusively the CNBP expansion. More recently, Meola and collaborators (manuscript in preparation) have identified the first case of a DM2 patient with a concomitant mutation on *SCN4A* gene. SCN4A codes for Nav1.4 a voltage gate sodium channel (VGSC) expressed in muscle [69] and is another gene implicated in myotonic disorders (Myotonia, Potassium-aggravated OMIM no. 608390). This DM2 patient presented an atypical phenotype characterized by early and severe myotonia however no mutation on *CLCN1* gene has been found. Moreover, in this study a novel functional missense mutation (P72L) on SCN4A gene has been identified affecting the cytoplasmic N terminus domain of Nav1.4. Also in this case the additive effect of the two mutations may create the atypical severe phenotype observed in this patient. Thus the *CLCN1* or *SCN4A* mutations may contribute to exaggerating the DM2 phenotype and these patients could be more easily identified and diagnosed than DM2 patients without the modifier allele. Consequently the majority of DM2 patients remain undiagnosed even in clinical centers with considerable experience with DM2.

To date, DM2 mutations have been identified predominantly in European Caucasians and most patients are of northern and eastern European descent [62,70]. Single kindred of Afghan [32,70] and Japanese [71] origin have been identified. It is supposed that both mutations have occurred after migration out of Africa, between 120 000 and 60 000 years ago [58,72]. Haplotype analysis indicates that the European DM2 mutations originate from a single founder, between approximately 4000 and 11,000 years ago [62].

4. Molecular pathomechanism

As described above, the two types of the disease are associated with two different loci: DM1 is caused by the expansion of an unstable CTG trinucleotide repeat in the 3′ UTR of the *DMPK* gene [2–4] while DM2 mutation consists in the expansion of an unstable CCTG tetranucleotide within the first intron of *CNBP* [10]. Although genetically distinct, DM1 and DM2 share a common pathogenic mechanism. Experimental evidence supports an RNA gain-of-function mechanism in which expanded CUG/CCUG-containing transcripts accumulate in the cell nuclei as foci, also called ribonuclear inclusions, and are responsible for the pathologic features common to both disorders. The mutant RNAs form imperfect double-stranded structure which lead to the deregulation of several RNA binding factors, including the muscleblind-like proteins (MBNLs), CUGBP1, hnRNP H and Staufen1 proteins [73–79]. The MBNL proteins appear to play a prominent role in DM pathogenesis since each of the three MBNL isoforms (MBNL1, MBNL2 and MBNL3) are sequestered by CUG RNAs in the cell nuclei [75,80]. MBNL1 is the most abundant MBNL protein in adult skeletal muscle and plays the predominant role in alternative splicing regulation in skeletal and cardiac muscle while MBNL2, which muscle levels decrease during postnatal development, serves a related function in the central nervous system [81–83]. Support for the MBNL loss-of-function model comes from Mbnl1 ($Mbnl1^{\Delta E3/\Delta E3}$) and Mbnl2 ($Mbnl2^{\Delta E2/\Delta E2}$) isoform knockout mice which recapitulate multiple features of adult-onset DM [76,84]. While Mbnl1 knockout mice develop the muscle, eye, and RNA splicing abnormalities that are characteristic of DM1 disease and show modest effects on alternative splicing regulation in the brain [76,85], the loss of Mbnl2 leads to widespread changes in postnatal splicing patterns in the brain, many of which are similarly dysregulated in the human DM1 brain, but not in skeletal muscle [82]. Nothing is known about the functions of MBNL3 in vivo, although this protein is also sequestered by toxic CUG exp RNAs [80]. In vitro studies show that MBNL3 acts as an antagonist of myogenesis possibly by maintaining myoblasts in a proliferative state [86–88]. Mbnl3 isoform knockout mice show age-dependent impairment of adult muscle regeneration suggesting that Mbnl3 inhibition by toxic RNA expression may be a contributing factor to the progressive skeletal muscle weakness and wasting characteristic of DM [88].

CUGBP1, a member of the family of CELF (CUGBP, Elav-like family) proteins, is a regulator of alternative splicing and of mRNA translation and stability [89–93]. CUGBP1 does not colocalize with ribonuclear foci in DM1 cells [75,80,94], however this protein was identified through its capacity to bind CUG RNA repeats in vitro [95]. CUGBP1 may have a role in the pathogenesis of splicing abnormalities because it is overexpressed in DM1 myoblasts, skeletal muscle and heart tissues [40,96,97] due to PKC-mediated hyperphosphorylation and subsequent protein stabilization and upregulation [98]. While it is clear that MBNL1 is depleted from nucleoplasm through recruitment into ribonuclear inclusions both in DM1 and DM2 even when clinical symptoms and muscle alterations are very mild [67,99–102], CUGBP1 overexpression has been clearly demonstrated in DM1 but not in DM2 muscle biopsies. In a recent work on the expression of CUGBP1 in human skeletal muscle from DM1 and DM2 patients, Cardani et al. [103] demonstrate that this protein is overexpressed in muscle biopsies from patients affected by the adult classical form of DM1 but not in muscle from DM2 patients suggesting that sequestration of MBNL1 evidently has a central role in splicing misregulation in both types of DM while in DM1 CUGBP1

overexpression might be an additional pathogenic mechanism not shared by DM2. Besides its nuclear role in splicing, CUGBP1 also has other functions in the cytoplasm where it regulates mRNA translation and stability [89,92,93]. The alterations of protein [92] and mRNA [104] levels occur in DM1 consistent with the idea that the perturbation of CUGBP1 cytoplasmic functions contributes to DM1 pathogenesis. CUGBP1 cellular localization depends on its phosphorylation status [91]. The activation of the Akt pathway increases CUGBP1 phosphorylation at Ser-28 altering the transition from proliferating myoblasts to differentiated myotubes in DM1 [105]. On the other hand, DM1 cells show decreased activity of cyclin D3-cdk4, another kinase that phosphorylates CUGBP1. This renders higher levels of unphosphorylated CUGBP1, which forms inactive complexes with eIF2a (CUGBP1-eIF2a) affecting translation of mRNAs required for myoblast differentiation. These inactive complexes containing CUGBP1 accumulate in the cytoplasm of DM1 cells in stress granules [91]. CUGBP1-eIF2a complex has been found also in the cytoplasm of DM2 myoblasts [106].

Other splicing factors involved in early phases of pre-mRNA processing, beside MBNLs and CUGBP1 proteins, have been found to be altered in DM pathologies. An elevation of the steady-state level of hnRNP H has been observed in DM1 myoblasts while recent data demonstrate that MBNL1-containing foci in DM2 cells also sequester snRNPs and hnRNPs. These data strengthen the hypothesis that a general alteration of pre-mRNA post-transcriptional pathway could be at the basis of the multifactorial phenotype of DM patients [78,107,108]. Staufen1 is another regulator of alternative splicing that has been involved in DM1 pathology [79]. As CUGBP1, this protein is not sequestered by nuclear foci of CUGexp mRNAs but it has been found to be markedly and specifically increased in skeletal muscle from DM1 mouse models and patients. Interesting, Staufen1 up-regulation might have a protective role in the DM1 pathology since it appears that the increase in Staufen1 may indeed be a compensatory mechanism used by muscle fibers to reduce and/or delay the detrimental effects caused by MBNL1 sequestration and CUGBP1 up-regulation [79].

Thus, the misregulation of alternative splicing caused by the deregulation of several splicing regulators clearly plays a central role in the development of important DM symptoms [109,110]. Among the symptoms of DM, myotonia, insulin resistance and cardiac problems are correlated with the disruption of the alternative splicing of the muscle chloride channel ClC-1, of the insulin receptor (IR) and of the cardiac troponin T (TNNT3), respectively [40,42,74,111,112]. More recently, muscle weakness has been associated with bridging integrator 1 (BIN1) missplicing both in DM1 and DM2. BIN1 is a lipid-binding protein that is involved in the biogenesis of the T tubule network in muscle and in the regulation of the excitation–contraction coupling [113]. However, there is no direct evidence of a cause–effect relationship between symptoms and missplicing and it is now clear that spliceopathy may not fully explain the multisystemic disease spectrum. Bachinski and collaborators [114] performed global array-based expression and splicing profiling on a large number of DM and non-DM neuromuscular patients and found that DM1 and DM2 skeletal muscles were essentially identical to each other for both expression and splicing. Moreover, most expression and splicing changes were shared between multiple muscular dystrophies, as previously reported [115,116]. This suggests that splicing changes may be a much more general phenomenon of muscle disease and can be secondary to muscle regeneration [115,116].

Studies performed on different DM animal models suggest that splicing, RNA foci, and muscle pathology are separable events [76, 117–119] and strongly suggest that DM molecular pathogenesis may be vastly more complex involving changes in gene expression and translation efficiency, non-conventional translation and micro-RNA (miRNA) deregulation.

Various studies reported the effects of repeat expansion on gene expression in DM1 and DM2 muscle biopsies indicating common profiles, suggestive of a mutual pathophysiology [120–123]. Altered gene expression may also result from a direct effect of the repeat expansion on transcription factors. The binding of mutant RNA in DM1 causes inappropriate redistribution (leaching) of various transcription factors, such as Sp1 and RARγ, reducing their availability and the expression of target transcripts [124]. Changes to the levels of a panel of RNAs involved in muscle development and function that are downregulated in DM1 have been associated to aberrant localization in the cytoplasm of DM1 myoblasts of the transcription factor SHARP (SMART/HDAC1-associated repressor protein) [125].

A novel molecular mechanism that may contribute to the pathogenesis of several diseases including myotonic dystrophies has been described in a recent paper by Ranum's group [126]. RNA transcripts containing expanded CAG repeats can be translated in the absence of a starting ATG and this non-canonical translation, called Repeat Associated Non-ATG translation (RAN-translation) occurs across expanded CAG repeats in all reading frames (CAG, AGC, and GCA) to produce homopolymeric proteins of long polyglutamine, polyserine, and polyalanine tracts [126]. RAN translation across human spinocerebellar ataxia type 8 (SCA8) and myotonic dystrophy type 1 (DM1) CAG expansion transcripts results in the accumulation of SCA8 polyalanine and DM1 polyglutamine expansion proteins in previously established SCA8 and DM1 mouse models and human tissue [126]. Antibodies developed specifically against DM1 polyGln proteins, detect polyGln nuclear aggregates in DM1 mouse tissues and DM1 patient cardiac myocytes, leukocytes, and myoblasts not detectable in control tissues. RAN-translation products appear to be toxic to cells and may contribute to DM1 pathology. More recently RAN translation has been found to occur across intronic DM2 CCUG transcripts and that these transcripts produce a tetra-repeat expansion protein with a repeating Leu-Pro-Ala-Cys (LPAC) motif. Moreover an LPAC antibody shows strong immunostaining in human DM2 autopsy brain but not controls. Immunostaining has been observed in neurons, astrocytes and glia in frontal cortex, hippocampus and basal ganglia. These data suggest that RAN translation may be common to both DM1 and DM2 and that RAN proteins may be responsible for some of the CNS features of DM [127].

miRNAs are small non-coding RNA modulating gene expression at posttranscriptional level and their expression and intracellular distribution are deregulated in many human diseases, including muscular dystrophies [128–132]. Both in DM1 and DM2 it has been demonstrated that the highly regulated pathways of miRNA is altered in skeletal muscle potentially contributing to DM pathogenetic mechanisms [130–132]. The misregulation of miR-1 observed in the hearts of people with DM1 and DM2 may contribute to the cardiac dysfunctions observed in affected persons [133]. The significant reduction of miR-1 in DM cardiac muscle appears to be caused by the expression of expanded CUG repeats and subsequent MBNL1 nuclear sequestration [133]. Interestingly, Perfetti et al. [134] identify a signature of miRNA deregulated in peripheral blood plasma from DM1 patients. In particular one specific miRNA, miR-133a, clearly correlates with muscle strength measurement and increased in patients with higher MIRS score, potentially reflecting disease severity [134]. This work is particularly significant since the identification of minimally invasive analytical biomarkers for DM1 and the established potential of circulating miRNAs as prognostic and diagnostic biomarkers are important to monitor DM1 progression and the effectiveness of new drug treatments.

Another open question in the field of DM is to clarify the pathomechanisms underlying the phenotypic differences between DM1 and DM2. Clinical signs in DM1 and DM2 are similar, but there are some distinguishing features: DM2 is generally less severe and lacks a prevalent congenital form. This suggests that other cellular and molecular pathways are involved besides the shared toxic-RNA gain of function hypothesized. Disease-specific manifestations may result from differences in spatial and temporal expression patterns of *DMPK* and *CNBP* genes. Similarly, changes in the expression of neighboring genes may define disease-specific manifestations. Importantly, the role of CUGBP1 in DM2 is particularly intriguing with contradictory

results being reported [100,103,106,135]. Another possible explanation for the clinical differences between the two DM forms is the reduction of DMPK or ZNF9 protein levels in DM1 and DM2 respectively [3,91,103, 136,137] However *Dmpk* knockout young mice do not develop a multisystemic phenotype mimicking myotonic dystrophy [138–140]. On the contrary reduction of *CNBP* levels is sufficient to produce multiorgan symptoms resembling those of DM as observed in heterozygous Cnbp +/− knockout mice [141]. Moreover the reduction of *CNBP* expression has been reported in DM2 compared with non-DM2 individuals, including patients with DM1 thus explaining some of the phenotypic disparities between both types of DM [103,135,137].

5. Pathology

The histological features of skeletal muscle biopsy in DM1 and DM2 are very similar, and sufficiently characteristic that a diagnosis of DM can be suggested based on muscle biopsy alone [1,13,142]. In both diseases, affected muscles show a high number of central nuclei and a markedly increased variation in fiber diameter that commonly ranges from less than 10 μm to greater than 100 μm. Basophilic regenerating fibers, splitting fibers, fibrosis and adipose deposition occur in both diseases to a variable degree depending on the extent of muscle involvement. Ring finger fibers and sarcoplasmic masses are generally more frequent in DM1 muscle biopsy. However the comparison of muscle biopsy findings in classic DM1 with those in DM2 has indicated that specific features are present in DM2 muscle biopsy helping the diagnosis of DM2. Severely atrophic fibers with pyknotic nuclear clumps similar in appearance to the severely atrophic fibers in neurogenic atrophy are frequently found in DM2 biopsy also before the occurrence of muscle weakness. In DM1, nuclear clumps are present in end-stage muscle biopsy [122] (Fig. 1A,B). A predominant type 2 fiber atrophy in contrast to the type 1 atrophy observed in DM1, has been described in DM2 [142–145] (Fig. 1C,D). Moreover, in DM2 muscle biopsy central nucleation selectively affects type 2 fibers and the atrophic nuclear clumps express fast myosin isoform (type 2 fiber) indicating that DM2 is predominantly a disease of type 2 myofibers [144] (Fig. 1D).

To date there are no definitive explanation for the histopathological alterations observed in DM skeletal muscle. However, it has been demonstrated that the combined effects of misregulated splicing of several genes involved in calcium regulation and EC coupling, such as RyR1, SERCA and CaV1.1, may contribute to the muscle degeneration in DM [146–148].

Classically DM has been considered as neuromuscular diseases and for many years research on DM has been principally focused on muscular aspects. However the interest in the neurological aspects of DM has increased in the last several years since central nervous system (CNS) dysfunction is one of the major issue affecting quality of life in DM patients. Recently several workshops of these studies have been organized to increase our understanding of CNS pathophysiology [24,149].

Cognitive impairment in DM1 has been clearly established. DM1 patients exhibit changes in personality traits and/or mood disorders [41,150–153]. Brain involvement in DM2 shows similar cognitive and behavioral dysfunctions as in DM1, with milder manifestations compared with DM1 [41,154]. In contrast to DM1, DM2 has not been associated with developmental abnormalities thus explaining why no mental retardation similar to that reported in congenital and juvenile forms of DM1 has been described in DM2 patients.

Brain involvement in myotonic dystrophy types 1 and 2 has been demonstrated in vivo using different neuroimaging techniques. MRI studies revealed white matter lesions and diffuse brain atrophy in myotonic dystrophy types 1 and 2. White matter lesions located within anterior temporal lobes represent a characteristic feature in myotonic dystrophy type 1 [155–158]. A recent comparative study on brain involvement in myotonic dystrophies reveals a frontal white matter most prominently affected in both disorders, and temporal lesions restricted to myotonic dystrophy type 1. Voxel-based morphometry analyses demonstrated extensive white matter involvement in all cerebral lobes, brainstem and corpus callosum in myotonic dystrophy types 1 and 2, while gray matter decrease (cortical areas, thalamus, putamen) was restricted to myotonic dystrophy type 1. Accordingly, we found more prominent white matter affection in myotonic dystrophy type 1 than myotonic dystrophy type 2 by diffusion tensor imaging [159]. In myotonic dystrophy type 1, gray matter reductions have been described in various cortical regions and recently also in hippocampi and thalami using voxel-based morphometry (VBM) [154,160]. In DM2 patients gray matter reduction was present in several cortical regions, including hippocampi, hypothalami and thalami [154,161].

As observed in skeletal muscle, ribonuclear inclusions of CUG-containing RNA colocalizing with MBNL1 and MBNL2 proteins have also been detected in human DM1 brains, particularly in the neuronal cells of the cerebral cortex, hippocampus, dentate gyrus, thalamus, substantia nigra, and brain stem tegmentum [99]. Interestingly, focus formation has also been observed in the brains of transgenic DMSXL mice bearing more than 1000 CTG repeats [162]. These observations strongly suggest that a pathomechanism involving RNA gain-of-function and spliceopathy also occurs in DM brain. Indeed missplicing of Tau exons 2, 3, 6 and 10 has been reported in DM1 brains [99,163, 164]. Jiang et al. [99] reported, defective splicing of other two important genes in DM1 brain, amyloid-β precursor protein (APP) gene and N-methyl-D-aspartate receptor 1 (NMDA-R1) gene. In a recent study Charizanis and collaborators [82] reported that the major pathological changes in the DM brain are attributable to MBNL2 more than MBNL1 sequestration by C(C)UGexp RNAs. Indeed while Mbnl2 knockout mice did not display pronounced muscle pathology, the loss of Mbnl2 resulted in widespread splicing abnormalities in the brain. On the contrary Mbnl1 knockout mice show modest effects on alternative splicing regulation in the brain [85].

In addition to these changes, DM1 brains show neurofibrillary degeneration (NFD) made of the intraneuronal aggregation of hyperphosphorylated Tau proteins [163,165]. A similar tau pathology in the CNS has been reported in DM2 suggesting a similar physiopathologic process that may contribute to common neurologic features in patients with DM [166].

Cardiac arrhythmias are a major cause of mortality in DM1 and DM2, cardiac deaths occur with low frequency [36,37,167,168], however, the molecular mechanisms underlying the cardiac defects, are unclear. The misregulation of miR-1 in heart samples from people with DM1 and DM2 has been recently reported and it may contribute to the cardiac dysfunctions observed in affected persons. The significant reduction in the expression of miR-1 in DM heart samples leads to a deregulation of two important mir-1 targets, GJA1 (connexion 43) and CACNA1C (cardiac L-type calcium channel). Importantly, the down regulation of miR-1 in cardiac muscle is caused by MBNL1 nuclear sequestration since MBNL1 is a cytoplasmic regulator of the biogenesis of pre-miR-1 [133].

More recently, an association between DM1 or DM2 and Brugada ECG pattern has been reported potential role of Brugada syndrome in ventricular tachyarrhythmias and sudden death in DM1 patients [169, 170]. Ventricular myocardial specimen analysis displayed a splicing switch of *SCN5A* adult exon 6B toward fetal exon 6A [170,171]. Electro-physiological experiments demonstrate that SCN5A channel containing exon 6A (the DM isoform) presents a slower cardiac conduction compared to the control SCN5A containing exon 6B [171].

6. Animal models

Several important mouse models of myotonic dystrophies have been generated to clarify the disease mechanisms however no one model completely recapitulates all aspects of the multisystemic phenotype in type 1 or type 2 disease. Here we reviewed the most significant mouse models resulting from the inactivation of genes in the DM1 or

DM2 loci, the overexpression of toxic CTG repeats or abnormal splicing regulation through *Mbnl* inactivation or *CUGBP1* overexpression.

To test if the reduction of cytoplasmic *DMPK* transcripts observed in DM1 had a role in disease pathomechanism, *Dmpk* or *Cnbp/Znf9* knockout mice were generated. However *Dmpk*−/− mice failed to reproduce the complex and multisystemic DM1 phenotype [138,139], suggesting that haploinsufficiency of the gene in the *DM1* locus is not the primary mechanism of disease. On the contrary, *Zfn9*+/− mice exhibited myotonia, muscle wasting, defective walking, cardiac conduction defects and ocular cataracts without the alteration of alternative splicing suggesting a role for *CNBP* haploinsufficiency in DM2 pathology [141]. To further investigate the role of CNBP in DM2, a *Cnbp*−/− mice model has been recently developed. This model shows some features consistent with DM2, including mild myopathy and muscle weakness and no missplicing thus strengthening the role for *CNBP* in disease pathogenesis. Further the characterization of *Cnbp* −/− mice as a model for DM2 is under way [172].

The toxicity of expanded transcripts was studied with the generation of transgenic mice overexpressing untranslated CUG repeats in the skeletal muscle. HSA^{LR} (long repeat length) model is a transgenic mouse based on the human skeletal actin (HSA) gene that includes approximately 250 untranslated CUG repeats [173]. These animals show MBNL1 sequestration in nuclear foci and the alteration of alternative splicing of several genes (e.g. *Clcn1*, *Atp2a1*/*Serca1*, *Mbnl1*, *Ldb3*/*Cypher*).

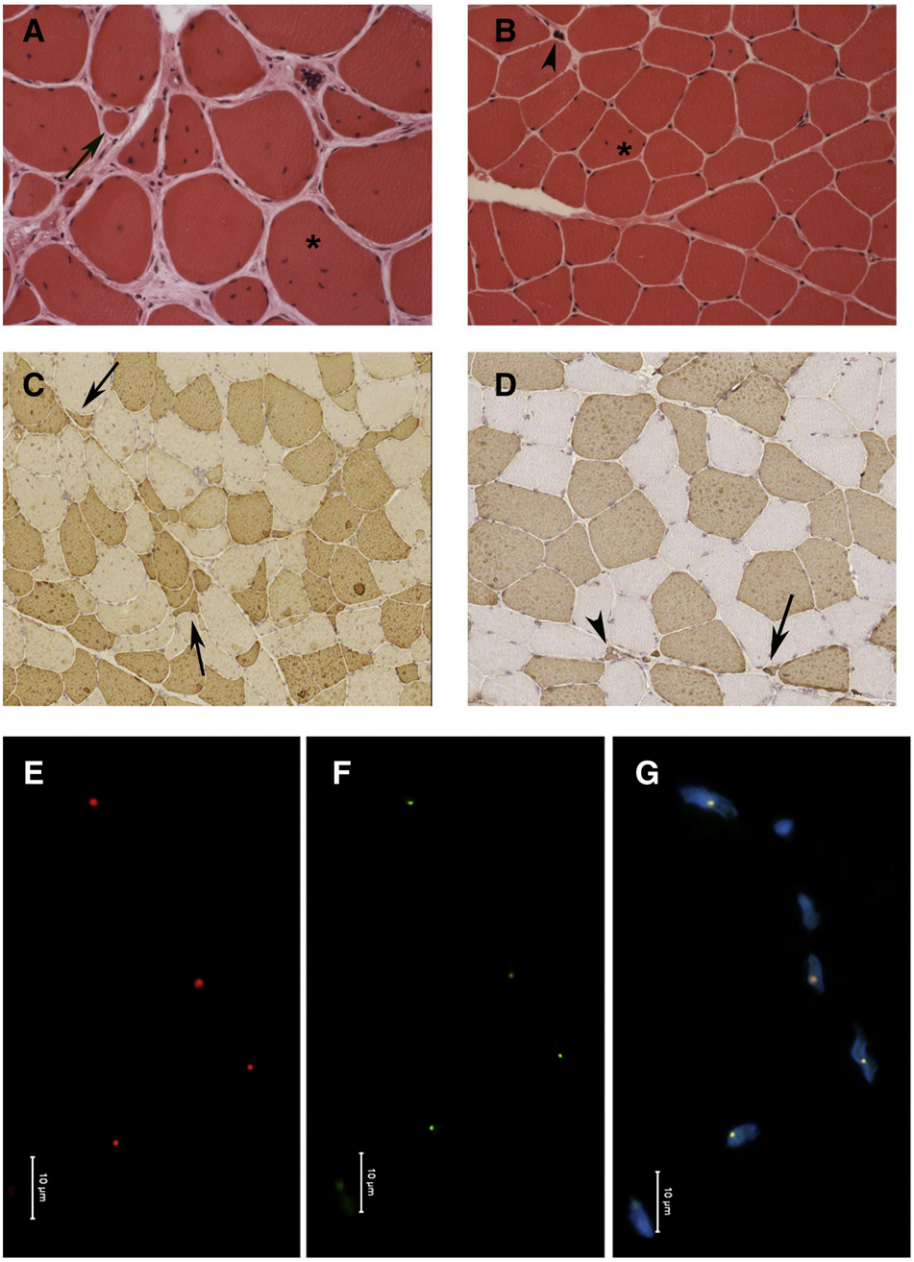

Fig. 1. A–D. Panel showing muscle histology in DM1 and DM2. A. Hematoxylin & Eosin stained transversal sections of DM1 muscle biopsy presenting a severe fibrosis. Fiber size variation is present with numerous atrophic fibers (arrow) and central nuclei (asterisk). Original magnification, 200×. B. Hematoxylin & Eosin stained transversal sections of DM2 muscle biopsy. Fiber size variation and central nuclei (asterisk) are present. Arrowhead indicates a nuclear clump. Original magnification, 200×. C. Slow myosin (MHCslow) stained section of DM1 muscle biopsy. The population of atrophic fibers (dark brown) is preferentially type 1 fibers (arrows). Original magnification, 200×. D. Fast myosin (MHCFast) stained section of DM2 muscle biopsy. Type 2 fibers (dark brown) are predominantly affected in DM2 muscle: type 2 fast positive nuclear clumps (arrowhead) and type 2 atrophic fibers (arrow) are present. Original magnification, 200×. E–G. Fluorescence in situ hybridization (FISH) in combination with MBNL1-immunofluorescence on DM2 muscle biopsy. E. Visualization of (CCUG)-containing RNA on muscle section by FISH using $(CAGG)_5$ specific probe. Red spots represent ribonuclear inclusions. F. Visualization of nuclear foci of MBNL1 (green spots). G. Visualization of ribonuclear inclusions colocalizing with MBNL1 foci in myonuclei (blue, DAPI).

CUGBP1 is not upregulated. They have been reported to be myotonic and their myotonia claimed to be sufficiently explained by significant reductions in the ClC-1 current. Moreover, these mice present histological signs of myopathy but no muscle weakness or wasting and to date represent the most suitable mouse model to investigate the adult skeletal muscle pathology.

DM300 mice carrying a large (CTG) 300–600 expansion in the context of the human DM1 locus [174] showed ribonuclear foci in multiple tissues (e.g. skeletal muscle, heart and CNS), muscle histopathology, myotonia, progressive muscle weakness, defects in glucose metabolism due to *INSR* splicing alteration, growth retardation and high mortality [175–177]. The intergenerational instability of DM300 led to DMSXL mice carrying 1000–1800 CTG repeats which exhibit a more severe phenotype and could represent a model of congenital DM1 [178].

Mice models have been generated to characterize the molecular and physiological effects of MBNLs inactivation and CUGBP1 upregulation and to demonstrate the central role of these two families of splicing regulators in DM1 pathogenesis.

In *Mbnl1*$^{\Delta 3/\Delta 3}$ mice disruption of *MBNL1* exon 3 eliminates CUG-binding isoforms and mimics the MBNL1 sequestration and inactivation observed in DM1 [76]. These mice exhibit overt myotonia associated with abnormal *CLCN1* splicing and develop cataracts and myopathy but no signs of muscle degeneration [76,100,179]. Recently Suenaga and collaborators [85] have found three novel splicing events (Sorbs1 exon 25 (exon 26 in human), Dclk1 exon 19 and Camk2d exons 14–16 (exons 14–15 in human)), altered both in DM1 and in Mbnl1-knockout brains.

To elucidate the role of MBNL2, two knockout lines were generated however contradictory results were obtained on skeletal muscle. While myopathy and myotonia associated with *CLCN1* splicing alteration were detected in one line [180], the other line appeared to be overtly normal [100]. To address this inconsistency, a Mbnl2$^{\Delta E2/\Delta E2}$ knockout mouse has been generated in which, as Mbnl1 exon 3, Mbnl2 exon 2 encodes the initiation codon for the full-length Mbnl2 protein [82]. These mice do not display pronounced muscle pathology and myotonia is absent, however the loss of Mbnl2 results in widespread splicing abnormalities in the brain.

Mbnl1 and Mbnl2 isoform knockout mice recapitulate multiple features of adult-onset DM supporting the toxic RNA pathogenetic model. Moreover, it appears that while MBNL1 regulates alternative splicing during postnatal development prevalently in muscle, MBNL2 exerts its function in the brain.

Mbnl3$^{\Delta E2/\Delta E2}$ isoform knockout mice have been recently generated using a homologous recombination strategy previously described for *Mbnl1*$^{\Delta 3/\Delta 3}$ and Mbnl2$^{\Delta E2/\Delta E2}$. MBNL3 is an unusual member of the Mbnl family because it is expressed during the embryonic period and MBNL3 RNA is either absent or detectable only at low levels in adult tissues [84] indicating that it may not be essential in adults but may be required during embryogenesis and its sequestration by toxic C(C)UG-RNAs during embryogenesis might influence tissue development in DM1 and DM2. Mbnl3 mice fail to develop overt mutant muscle or CNS phenotypes during postnatal development but instead show a late-onset and age-associated impairment of muscle regeneration following injury. These findings indicate that MBNL3 expression is important for normal adult muscle satellite cell activation and/or myoblast function [88].

Two CUGBP1-overexpressing lines have been generated to investigate the contribution of CUGBP1 upregulation to DM1 pathogenesis. The CUGBP1-TR line showed growth retardation, delayed myogenesis, and histological and molecular abnormalities [118] while the MCKCUGBP1 mice had normally sized stillborn pups showing histological abnormalities and missplicing in skeletal muscle [181]. However, both lines were characterized by high mortality and breeding difficulties. Subsequently, tissue-specific CUGBP1 overexpression in either skeletal muscle or heart of adult mice induced DM1-characteristic phenotypes indicating that CUGBP1 upregulation is sufficient to reproduce alternative splicing deregulation, myopathy and cardiomyopathy) [182,183].

7. Diagnosis

As for all genetic diseases with identified mutation, the typical DM1 and DM2 diagnostic method is mutation verification by genetic tests. In the case of DM1, symptoms and family history are often clear and distinctive enough to make a clinical diagnosis, and the mutation can be confirmed by PCR and Southern Blot analysis. PCR analysis is used to detect repeat lengths less than 100 and Southern blot analysis to detect larger expansions. Predictive testing in asymptomatic relatives as well as prenatal and preimplantation diagnosis can also be performed. Recently, a molecular diagnostic kit, Myotonic Dystrophy SB kit, has been developed and validated. The advantage of this assay is that all reagents are pre-packaged and ready to use. The analytical results, evaluated on a total of 113 DNA samples, in terms of sensitivity, specificity and accuracy were very high (>99%), and both prospective and retrospective analyses gave no false positives or false negatives [184].

Triplet-repeat primed PCR (TP-PCR) [185] has come into routine diagnostic procedure since it represents a robust and reliable PCR method that can rapidly identify the presence of expanded alleles for any disorder caused by repeat expansions. Although it can distinguish between healthy homozygous and affected heterozygous samples with no length restriction, it is not able to determine the exact size of the repeats over a certain threshold. Thus the association of two molecular methods as a Long-PCR and Southern transfer, together with TP-PCR [186,187], is strongly recommended because they should be able to detect a wide range of mutations. Critically, recent evidence has shown that TP-PCR can lead to false negative results in 3%–5% of DM-1 cases due to sequence interruptions (comprising CCG, CTG, and GGC sequences) that lie within the 3′ end of an expanded CTG repeat tract [55]. In order to address this problem, Radvansky et al. [188] has described a bidirectionally labeled TP-PCR method in which amplification products are anchored at the 3′ end of a CTG repeat expansion rather than the 5′ end. The effect of this redesign is that it overcomes the failure in detecting expansion-positive patients carrying repeat interruptions.

On the contrary, the wide clinical spectrum DM2 phenotype makes the clinical diagnosis more difficult. Moreover conventional PCR and Southern blot analysis are not adequate for a definitive molecular diagnosis in DM2 due to the extremely large size and somatic instability of the expansion mutation [10,62]. The copy number of DM2 CCTG is below 30 in phenotypically normal individuals and up 11.000 in patients [189]. A complex genotyping diagnostic procedure is now commonly used consisting of a three step molecular protocol [13,27]: (1) a conventional PCR assay across the mutation locus using probes binding to mutation flanking sequences can be used for mutation exclusion. In all DM2 patients, a single PCR product representing the normal allele can be identified because the DNA polymerase fail to amplify the mutant allele due to length and stable secondary structure. All individuals showing two alleles for the marker are excluded from having the DM2 mutation. However, identical allele size on two normal alleles occurs in 12% of the population; (2) all patients appearing to have one allele need further molecular analysis to determine whether or not they carry a DM2 expansion. Because of the incomplete sensitivity of Southern analysis, a DM2 repeat assay (RP-PCR) was developed; (3) the RP-PCR method involves amplifying the CCTG repeat by PCR, and probing the resultant product with an internal probe to assure specificity. The combined use of these methods allows 99% sensitivity and specificity for known expansions. Several alternative and highly sensitive methods have been developed for DM2 mutation verification including long-range PCR [190] and a tetraplet-primed PCR [187]. A modified Southern method using field-inversion electrophoresis (FIGE) is particularly efficient in determining the mutation length [62]. However, these methods are still too long and complicated to be part of routine laboratory

diagnostics. Nevertheless ribonuclear foci and splicing changes are present before any histological abnormality manifestations [42,191]. This could be important for an early diagnosis before the spectrum of clinical signs of muscle disease appears. So a more practical tool to obtain a definitive DM2 diagnosis in few hours is represented by in situ hybridization (ISH) which is a method that allows the direct visualization of the mutant RNA on muscle biopsy [192,193]. By using specific probes for CCUG expansions, it permits a differential diagnosis between DM2 and DM1. Therefore it may be a simple approach for DM2 diagnosis, which can be performed in a rapid and sensitive manner in any pathology laboratory. ISH with CAGG probe should be considered as a routine laboratory procedure to confirm or refute the clinical suspicion of DM2. It should also be applied routinely to screen patients with myotonic disorders [192,193]. This approach makes muscle biopsy an essential tool for DM2 diagnosis (Fig. 1E). Moreover, since MBNL1 is sequestered by mutant RNA foci, it is possible to visualize the nuclear accumulation of MBNL1 by immunofluorescence on muscle sections (Fig. 1E–G). However, although MBNL1 represents a histopathological marker of DM, it does not allow to distinguish between DM1 and DM2 [194].

8. Management

Even though there is currently no cure for myotonic dystrophies, the active management of patients involves monitoring expected complications of the disease. The management of DM2 is similar to that of DM1 and there are very few specific treatments that are distinct for DM2. Especially for DM1, physiatrists can help affected individuals regarding the need for ankle–foot orthoses, wheelchairs, or other assistive devices as the disease progresses. Cataracts require monitoring and can be removed if patients complain impaired vision [23]. Cardiorespiratory disorders are responsible for 70% of the mortality in DM1 and many of these patients could have been treated by active monitoring and a lower threshold for input. Cardiac problems appear to be less severe and frequent in patients with DM2 than in patients with DM1 [34–36], however, sudden death, pacemaker implantation, and severe cardiac arrhythmias have been described in small numbers of patients [31,36,37]. Careful cardiac evaluation is recommended in DM2 patient population to identify patients at risk for potential major cardiac arrhythmias [36]. Patients with DM1 frequently report complaints of daytime sleepiness and/or fatigue that impinge significantly on their quality of life. Early recognition and treatment of sleep-related disordered breathing with nocturnal non-invasive mechanical ventilation are first mandatory. However, daytime sleepiness often persists and may require a psychostimulant but no consensus has been yet established [195]. Hypogonadism and insulin resistance need monitoring in both diseases. Insulin resistance is common in people with DM1 and is thought to affect approximately 20% of those with DM2. The phenomenon should be monitored by a physician and if it becomes problematic, insulin or other medications that lower blood sugar can be prescribed. Myotonia tends to be less marked and less troublesome in DM2, but in specific circumstances antimyotonia therapy is helpful, especially if muscle stiffness is frequent and persistent or if pain is prominent [196]. Some individuals have responded to mexiletine or carbamazepine. Logigian et al. [197] found mexiletine of 150–200 mg TID to be effective and safe for treating myotonia. Cognitive difficulties also occur in DM2 as in DM1 but have manifested in adult life and appear to be associated with decreased cerebral blood flow to frontal and anterior temporal lobes [38,153] and decreased brain volume [198,199]. The changes are less severe in DM2 than in DM1. Their etiology is unknown but may relate to the toxic effect of intranuclear accumulations of abnormally expanded RNA. The management of these brain symptoms is similar in DM1 and DM2. Pain in the skeletal muscles is a common feature of DM2 and is less common in DM1 [28,33]. The exact mechanism underlying the pain is unknown, and there is no well-established, effective treatment. The pain does not appear to be related to myotonia or to exercise, however cold temperatures make it worse. Painful stiffness can occur, particularly in the legs. Pain management can be an important part of DM treatment. Different medications and combinations of medications work for some individuals, although none has been routinely effective; medications that have been used include mexiletine, gabapentin, nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose thyroid replacement, low-dose steroids, and tricyclic antidepressants.

9. Conclusions

Currently myotonic dystrophies have to be considered also as a brain disorder in addition to their classic categorization as a muscle disease. The knowledge of underlying molecular pathomechanism in muscle and CNS dysfunction in myotonic dystrophies will be necessary to identify suitable targets and evaluate therapeutic benefit of current and future drug candidates.

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