INVITED REVIEW

ABSTRACT: Myotonic dystrophy types 1 (DM1) and 2 (DM2) are similar yet distinct autosomal-dominant disorders characterized by muscle weakness, myotonia, cataracts, and multiple organ involvement, including the brain. One key difference between DM1 and DM2 is that a congenital form has been described for DM1 only. Expression of RNA transcripts containing pathogenic repeat lengths produces defects in alternative splicing of multiple RNAs, sequesters specific repeat-binding proteins, and ultimately leads to developmentally inappropriate splice products for a particular tissue. Whether brain pathology in its entirety in adult DM1 and DM2 is caused by interference in RNA processing remains to be determined. This review focuses on the similarities and differences between DM1 and DM2 with respect to neuropsychological, neuropathological, and neuroimaging data relating to cerebral involvement, with special emphasis on the clinical relevance and social consequences of such involvement.

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CEREBRAL INVOLVEMENT IN MYOTONIC DYSTROPHIES

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Myotonic dystrophies, the most common type of adult-onset muscular dystrophy, are dominantly inherited disorders characterized by muscle weakness and atrophy, myotonia, and cataracts, together with involvement of a number of different organs, including the brain.[4,41] Myotonic dystrophy type 1 (DM1) is caused by an expanded (CTG)n repeat (from 37 to several thousands) within the noncoding 3′ untranslated region of the myotonic dystrophy protein kinase (*DMPK*) gene[9,35,61] on chromosome 19q35. Myotonic dystrophy type 2 (DM2) is caused by an expanded CCTG repeat (from 75 to 11,000 repeats) in the first intron of the zinc finger protein 9 (*ZNF9*) gene on chromosome 3q21.[25,60,95,96]

Fascinating aspects of the myotonic dystrophies are the multisystem involvement and the way that two unrelated genes cause strikingly similar yet distinct phenotypes. Both DM1 and DM2 manifest signs of myotonia, muscle weakness, and early-onset cataracts. In addition, there is often testicular atrophy, frontal balding, insulin resistance, and cardiac conduction defects, as well as occasionally dilated cardiomyopathy.[41,70,97] There is, however, one key clinical difference between DM1 and DM2: the degree of cognitive impairment. The DM1 locus presents a severe congenital form of mental retardation, which is not present in DM2. In addition, whereas personality changes, visual-spatial defects, and behavioral problems have been described mainly in the juvenile and adult-onset forms of DM1, it is only in the last few years that there have been reports of cognitive and behavioral deficits in DM2, and these may be captured only by specific neuropsychological tests. Considering these results and the absence of a congenital form, there is still controversy as to the clinical significance of the cognitive and behavioral abnormalities reported in patients with DM2.

Recent advances in molecular genetics in vitro and using mouse models have shed light on the pathophysiology of myotonic dystrophies.[8,17,44,54,59,63,64,66,83,89,94,116–119] The current model is that expression of RNA transcripts containing pathogenic repeat lengths produces defects in alternative splicing of multiple RNAs by sequestering repeat-binding proteins, ultimately leading to the expression of splice products that are developmentally inappropriate for a particular tissue. This provides a fascinating rationale for many of the multisystem features of DM1 and

Abbreviations: CNS, central nervous system; CTG, cytosine, thymine, guanine; CCTG, cytosine, cytosine, thymine, guanine; DM1, myotonic dystrophy type 1; DM2, myotonic dystrophy type 2; DMPK, myotonic dystrophy protein kinase; IQ, intelligence quotient; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; WAIS, Wechsler Adult Intelligence Scale; ZNF9, zinc finger protein 9

Key words: brain; myotonic dystrophy type 1; myotonic dystrophy type 2; neuroimaging; neuropsychological tests

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DM2, including cerebral symptoms, but in-depth studies are still lacking. Caution is required when interpreting the results of such studies. There are still a number of open issues regarding DM1, and particularly DM2, concerning brain involvement. (1) Although likely, an abnormality in the alternative splicing of tau, amyloid precursor protein (APP), and the like in DM2 brains is yet to be demonstrated. Whether brain involvement in adult DM1 and DM2 is caused entirely by interference in RNA processing remains to be determined. Convincing evidence on a molecular level is still missing, although there are suggestions that a number of genes are probably affected by spliceopathy in DM1, including tau, amyloid precursor protein (APP), and N-methyl-D-aspartate receptor 1 (NMDAR1).[83] In addition, other genes such as the dystrophia myotonica-containing WD repeat motif (DMWD) clustered in the DMPK gene region may also be implicated in brain-related symptoms,[129] and this too requires further investigation. (2) The existence of a juvenile form of DM2 is yet to be described. (3) There are unique features at the DM1 locus that account for the congenital form, irrespective of repeat size.

In this review we focus on the similarities and differences in brain involvement between DM1 and DM2, with particular emphasis on the central nervous system (CNS) characteristics of the adult forms and on therapeutic and management problems.

EVIDENCE FOR BRAIN INVOLVEMENT IN DM1

Clinical Evidence. The occurrence of mental retardation in the congenital form and behavioral abnormalities in the juvenile form is unquestionable. In such patients the brain is undoubtedly involved primarily in the disease process.

Congenital DM1. Congenital DM1 is associated with (CTG)n expansions greater than 1,000. It occurs in the offspring of mothers affected with myotonic dystrophy.[120] Congenital myotonic dystrophy is the most severe presentation of DM1, not only from a muscle and respiratory perspective, but also because of the degree of cognitive involvement. In contrast with the classic adult form, neuromuscular involvement and arrhythmias are not a major concern. Myotonia is not even present at birth and cardiovascular involvement is not a common problem.[41]

Onset is in the prenatal period. In almost half of the pregnancies reported, fetal movements are reduced and polyhydramnios occurs.[41] A small percentage of premature births occur. After birth, one prominent sign is delay in motor milestones. Hypotonia results in a floppy baby and immobility. Failure to thrive is due to an inability to suck that affects almost all patients as a result of bilateral facial and jaw muscle weakness.[41,107] This is typically present at birth, giving rise to a characteristic facial appearance: the newborn baby keeps the mouth open with a tented upper lip and a high-arched palate. Respiratory distress may be the presenting symptom in up to 50% of patients.[40,41] This is the result of different factors including intercostal and diaphragmatic muscle weakness, pulmonary immaturity, aspiration pneumonia, and failure of respiratory control.[103] In nearly half of the reported cases talipes is present, most often bilateral and in the equinovarus position. Contractures may be present and athrogryposis multiplex may be an associated finding.[41,107] Other dysmorphic features and organ malformations may be present. There is no clinical or electromyographic (EMG) myotonia. Tendon reflexes are usually absent.

As time passes muscle symptoms improve but the delayed motor development becomes prominent, closely paralleling the degree of hypotonia. In those patients who survive the early weeks of life the prognosis is one of steady improvement throughout early childhood. Almost all children eventually become able to walk independently.

Mental retardation is observed in a number of patients and does not parallel motor retardation. Intelligence quotient (IQ) levels varying between 40 and 80 are present in 50%–90% of patients. Regardless, patients are able to take care of themselves throughout adult life with no evidence of a gross deterioration in intellectual function.[41] Speech development is delayed because of hypotonia and the weakness of facial and jaw muscles as well as by delayed psychomotor learning abilities. Behavioral abnormalities such as hyperactivity attention deficit, autistic behavior, and difficulty in social relationships with peers and family members are frequently reported in the preschool age group.[113] Neuroimaging studies in these patients reveal ventricular dilatation in more than 50% of patients, which is present at birth, thus supporting a prenatal origin for the mental retardation.[53]

The congenital form differs from the classic form not only clinically, but also from a biomolecular view. Specifically, there are several distinct features in congenital DM. The first is aberrant methylation at the DM1 locus.[30,112] Dinucleotide CpGs in the region of the CTG repeat are aberrantly methylated only in congenital DM.[112] The second is that increased levels of DMPK transcripts have been found

in the congenital form, whereas in the adult form these levels are typically decreased.[34,104] Congenital myotonic dystrophy is only transmitted by affected mothers and there is a suggestion of maternal imprinting; paternally transmitted cases do not occur even if the CTG repeats are similar in size.[13]

Childhood and Juvenile Onset. In DM1 a childhood or juvenile onset implies a different clinical presentation than in the classic adult form. In the juvenile form, CNS symptoms predominate over muscle symptoms.

Unlike the congenital form, transmission is maternal or paternal. Symptoms are present in childhood before the age of 10, and there are usually no prenatal signs. Motor symptoms are typically mild, and motor development is usually normal or delayed only slightly. There may be some degree of distal weakness and atrophy as in the classic adult form, as well as mild signs of clinical myotonia.[40,41] The major features, however, are behavioral and there is usually a paucity of neuromuscular or cardiorespiratory symptoms. Learning disabilities and difficulties in relationships with peers generally become evident during school age. Cognitive impairment has been reported with IQ below normal for age.[41,113,125] Children may require teacher assistance and manifest autistic behavior, lack of interest, and inhibition that link to the adult-onset dysexecutive syndrome. Attentional deficit hyperactive disorder is frequent and is often diagnosed in preschool children, before evolving into anxiety disorders in childhood and young adulthood. Excessive daytime sleepiness and fatigue may be present in this form as in the classic adult form,[93,113] suggesting that complaints of fatigue and somnolence should be investigated by polysomnography to look for sleep apnea syndrome and periodic limb movements.

Conventional neuroimaging is often normal but quantitative studies on a large number of patients are lacking. There may be ventricular dilatation and sulcal enlargement but, unlike the congenital form, these are not prominent. The white matter hyperintense lesions that are seen in the adult form are infrequent.[27,41]

Adult-Onset DM1. More than 50% of patients with classic DM1 are referred because of excessive daytime sleepiness[55,90,102] or fatigue.[49] Patients usually minimize their symptoms, do not keep outpatient appointments, and seem unconcerned about their health. The general clinical impression in most cases is one of apathy, decreased emotional participation, and psychomotor delay.

The result of neuropsychological tests provides some evidence for this. Neuropathology and neuroimaging studies provide further support for the clinical impression of brain involvement in the classic adult form of DM1 (Table 1).

Neuropsychological Evidence. ***Global Intelligence.*** Patients may give the impression of having reduced overall intelligence because of the delay in motor responses related to muscle impairment, the facial expression resulting from bilateral ptosis and facial muscle weakness, and the lack of initiative that may predominate during an examination. Scores on overall IQ as measured by the Wechsler Adult Intelligence Scale (WAIS) are within the normal range in patients with DM1,[11,15,20,87,91,122,132,134] although lower than age- and education-matched controls. In a subset of patients with moderately severe DM1 (CTG range 500–700), we have found reduced IQ values in one-third of patients irrespective of the degree of muscle disability.

On Mini Mental State Examination (MMSE), scores are also within the normal range, although lower than age- and education-matched controls.[71,72,78]

These studies, although interesting, are limited by methodological restrictions and especially by the variability in disability range and the molecular status of the patients considered. Whether measurements of global intelligence correlate with CTG size is a controversial issue. Some authors have concluded that CTG size correlates with IQ or MMSE scores and thus may be of predictive value,[23,47,65,88,101,122] but others have not found any correlation.[71,72,78]

Visual-Spatial Deficits. Visual-spatial impairment is appreciated when patients with DM1 are asked to perform everyday tasks requiring the assembly of elements (e.g., dice, puzzles, or similar things), to draw two-dimensional (2D) or three-dimensional (3D) figures, or to make a spontaneous drawing of a single figure. Patients may then admit to having decreased ability to draw 2D or 3D shapes and figures or to join up elements of a figure to form a complete figure. There may be impairment in spatial orientation as shown by map reading, target reaching on a specific trajectory through the quickest route, or constructional ability. Solving maze-like problems may constitute a limitation. In the workplace, visual-spatial impairment may translate into a certain difficulty in aligning numbers in the correct rows and putting items in appropriate columns. From a neuropsychological perspective, visual-spatial deficits are detected when patients are asked to copy a complex figure while maintaining its correct intersections and angles (Rey copy and recall). There is

general agreement that patients with DM1 present deficits in visual-spatial performance[14,37,71,125] because their scores on neuropsychological tests are significantly lower than in age- and education-matched controls. Modoni et al.[78] strengthened this conclusion in a recent study performed on a larger sample of patients stratified by CTG size and demonstrated that, despite small expansions, visual-spatial deficits characterize the neuropsychological profile of adult patients with DM1 in contrast with the more general intellectual impairment of patients with congenital forms.

Attentional Deficits. Several investigators have described attention deficits assessed by neuropsychological test scores as below the normal range compared to normal controls.[78,133] In our experience, a significant difference was observed in test scores for attention ability between patients with moderately severe DM1 and controls.[72]

Verbal Fluency. Weakness of facial, jaw, and palatal muscles, often in combination, results in a speech disturbance that may be a concern for the patients and family owing to the resulting difficulties in communication. Additional factors may also aggravate speech production, such as tongue and jaw muscle myotonia and structural malformations such as jaw subluxation and malocclusion, which are present more frequently than in the general population. Despite these peripheral causes of speech dysfunction, language function seems to be normal in patients with adult DM1. Normal performance on verbal function tests in patients with DM1 using the Token Test and the Controlled Association Letters and Categories Test has been described.[71,72]

Behavior. ***Dysexecutive Syndrome.*** Reduced initiative and inactivity are to be expected in any chronic muscle disease. However, clinical experience suggests that this is a prominent and consistent finding in patients with DM1 as compared to patients with other muscular dystrophies and similar or even worse muscle weakness and functional limitations. Frontal lobe motor areas and the prefrontal cortex are involved in strategic planning tasks. Earlier reports had documented a significant impairment of frontal lobe function,[14,24] as is typical of a dysexecutive syndrome. Several authors tried to correlate neuropsychological and neuroimaging findings.[6,24,27,28,45,62,101] Meola et al.[71,72] confirmed a selective impairment on tests of frontal lobe function in DM1 and suggested that this type of deficit does not correlate with cortical atrophy and white matter hyperintense lesions, but might be associated with fronto-temporal lobe hypoperfusion on PET studies. Although interesting, these studies were limited by the lack of quantitative magnetic resonance imaging (MRI) studies. Other studies have confirmed a selective involvement of frontal lobe function.[13,36]

Apathy. Apathetic temperaments are often reported by family members of patients with DM1. It is another aspect of the frontal dysexecutive syndrome reported above. Rubinsztein et al.[102] applied a specific rating scale for apathy and demonstrated that apathy was significantly greater in patients with DM1 than in normal controls or patients with Charcot–Marie–Tooth disease. This was not related to the degree of muscle impairment or the duration of illness.

Anxiety. There are conflicting data as to the occurrence of anxiety in DM1,[10,20,22] although there are suggestions that DSM-IVR Axis I disorders are frequent in DM1 as in the general population.[41] Meola et al.[71] demonstrated that anxiety was not a feature of a subset of patients with DM1 subjected to a battery of neuropsychological tests and psychiatric interviews. They concluded that the abnormal performance found after specific tests for frontal lobe function could not be attributed to anxiety or similar affective disturbances.

Depression. Depression does not seem to be increased in patients with myotonic dystrophy compared to other patients with muscular dystrophies,[29] although some reports describe a higher frequency in DM1.[22] Meola et al.[71] investigated patients with DM1 and did not find a higher frequency of depression.

Personality Patterns. Whether patients with DM1 have specific personality patterns is debatable.[7,12,26,33,72] It is common clinical experience that patients with DM1 have characteristic personalities: they tend to be either obsessive in their health-related care, continuously consulting their referring physician, or avoidant and passive in their attitudes toward health care. In an initial study by Bird et al.,[7] one third of a small series of patients had prominent abnormalities, but these were considered to be the natural consequence of their motor and cognitive impairment. In a later study, Delaporte[26] described a specific personality pattern in patients with DM1. Obsessive-compulsive, avoidant, and passive-aggressive behavior were prominent in these patients. More recently, Meola et al.[71] confirmed these results and suggested that there may be a homogeneous avoidant personality profile in patients with DM1. In a minority of patients tested by Delaporte[26] but in none of those tested by Meola et al.,[71] the scores reached a pathological level for personality disorder. Winblad et al.[133] applied the Temperament and

Table 1. Summary of cognitive, behavioral, and neuropsychological evidence for brain involvement in DM1 and DM2.

	DM1	DM2	References
Clinical presentations			
Congenital onset	+	−	27, 40, 41, 103, 107, 113, 120,
Juvenile onset	+	−	40, 93, 113, 125
Adult onset	+	+	17, 41, 83, 94, 116, 117
Signs and symptoms of CNS involvement			
Cognition			
General intelligence			
IQ	−	−	11, 15, 20, 87, 91, 122, 132, 134
MMSE	−	−	71, 72, 78
Visual spatial deficits	++	+	14, 37, 71, 78, 125
Attentional deficits	++	+	72, 78, 133
Verbal fluency	+/−	−	71, 72
Behavior			
Dysexecutive syndrome	++	+	6, 14, 24, 27, 28, 45, 62, 101
Apathy	++	+	102
Anxiety	−	+/−	20, 22, 41, 71
Depression	−	−	22, 29, 71
Personality patterns			
Avoidant	++	+	26, 71
Obsessive-compulsive	+	−	26, 33
Passive-aggressive	+	−	26, 33
Dependent	+	−	12
Emotion			
Facial emotion recognition deficit	+	?	131
Excessive daytime sleepiness	++	+	10, 18, 19, 55, 56, 90,102, 124
Fatiguability	+	+/−	49

Character Inventory to patients with DM1 and compared the results with those of patients with other neuromuscular disorders, again emphasizing that their DM1 patients had a deviant personality regarding temperament and character; signs of personality disorder were found in 20% of patients. In all of these studies the personality profile did not correlate with the degree of muscle impairment or CTG expansion size.

Emotion. Winblad et al.[131] demonstrated that facial emotion recognition is also impaired in patients with DM1, the findings correlating with CTG size. This impairment correlated only mildly with scores on tests of frontal lobe function, suggesting that mechanisms other than cognitive ability are involved.

Somnolence. Excessive daytime sleepiness is a prominent complaint made by partners and relatives of patients with DM1,[55,90,102] but the patients seem to minimize the problem for unclear reasons that may relate to their global cognitive and behavioral profile. This attitude may explain why the Epworth Sleep Scale often underestimates excessive daytime sleepiness in patients with DM1.[56] In patients with end-stage disease, degeneration of oropharyngeal, intercostals, and diaphragm muscles may lead to obstructive sleep apnea and nocturnal alveolar hypoventilation.[18,19] There is evidence that excessive daytime sleepiness in DM1 is not the result of sleep apnea[124] but may result from direct involvement of bulbar neurons in the reticular formation of the brainstem.[81,82] Broughton et al.[10] concluded that cognitive impairment cannot be attributed to a secondary effect of nocturnal sleep apnea or sleep disturbance in patients with DM1, but probably represents a direct effect of CNS lesions. It is interesting to consider that hereditary canine narcolepsy is caused by mutations in the hypocretin receptor 2 (*HcrtR2*) gene that induces aberrant splicing of the HcrtR2 pre-mRNA, resulting in a truncated receptor.[58] Recent reports have demonstrated low levels of Hcrt1 in some patients with DM1[68] but how these findings and whether receptor abnormalities relate to excessive daytime sleepiness in DM1 is still unclear.

Fatigue. Fatigue is a prominent complaint in patients with DM1. The degree of inactivity in patients with DM1 may go beyond the degree of objective muscle weakness. Kalkman et al.[49] assessed the prevalence of fatigue in patients with DM1 as compared to patients affected by muscular dystrophies with a similar degree of muscle impairment but no cognitive involvement (such as facioscapular muscular dystrophy and hereditary motor and sensory neuropathy type I). They concluded that patients with

myotonic dystrophy had significantly higher scores of severe fatigue, reported more problems with concentration, and had more difficulty in initiating and planning than the other two groups. Factors related to cognitive abnormalities may play a more prominent role in patients with DM1.

Neuropathological Evidence. ***Cell Loss.*** Ono et al.[81] reported cell loss in specific areas of the brain at postmortem of patients with DM1, such as in the dorsal raphe nucleus, superior central nucleus, dorsal and ventral medullary nuclei, and subtrigeminal medullary nucleus. Cell loss was more prominent in patients suffering from excessive daytime sleepiness and hypoventilation so that primary degeneration of specific brainstem nuclei was considered a possible neuropathological correlate of the clinical findings. Other authors[77] have also reported neuronal loss in the superficial layer of the frontal, parietal, and occipital cortex as well as in the substantia nigra and locus ceruleus. The patient described by Mizukami et al.[77] had extrapyramidal traits as well as behavioral abnormalities such as hallucinations, indifference, mental slowness, and visual cognitive impairment, so that in this case also the neuropathological changes correlate with the clinical findings. These and other observations[81,99] suggest that, in the brains of patients with DM1, cell loss of specific areas may occur and contribute to the cognitive and behavioral abnormalities observed.

Neuronal Intranuclear Inclusions. Neuronal eosinophilic inclusion bodies have been described in early studies[80] in a relatively large proportion of the thalamic nuclei (up to 30%) of patients with DM1, similar to findings in primary progressive neurodegenerative disorders. These observations were confirmed by other authors,[86] although their clinical significance is still unclear. Not only the thalamus but also the substantia nigra[80] and caudate nucleus[86] may be involved. More recently, immunostaining of the inclusions has demonstrated that they are composed of ubiquitin and microtubule-associated proteins, thus creating the neuropathological substrate for including myotonic dystrophies amongst the neurodegenerative disorders.

Strong support for the hypothesis of neurodegeneration has come from the work of Thornton and colleagues,[48] who demonstrated in postmortem brain slices from patients with DM1 that mutant RNA accumulates as nuclear foci in specific brain areas where muscleblind proteins are also sequestered, leading to deregulated alternative splicing in neurons of specific gene proteins including tau (exons 2 and 10), amyloid precursor protein, APP (exon 7), and N-methyl-D-aspartate receptor 1, NMDAR1 (exon 5). The distribution of ribonuclear inclusions was wide, involving all sectors of the hippocampus, dentate gyrus, thalamus, substantia nigra, and the brainstem tegmentum. The only exception was the cerebellar cortex, where localization was minimal. RNA foci were also detected in the subcortical white matter and the corpus callosum. Whereas in other neurodegenerative disorders characterized by inclusion bodies the significance of these is still uncertain, the fact that ribonuclear inclusions in muscle are directly involved in disease pathogenesis raises the possibility that CNS symptoms may also be the result of alternative splicing of specific brain protein mRNAs.

Neurofibrillary tangles of the type seen in Alzheimer's disease and other neurodegenerative disorders have been demonstrated in DM1.[85,126,135] The main constituent of neurofibrillary tangles is pathologic tau proteins, which are usually hyperphosphorylated and insoluble, phosphatase-resistant, and aggregated. Vermersch et al.[126] have demonstrated specific tau variants in the brains of patients with DM1 in the hippocampus, entorhinal cortex, and most of the temporal areas. In contrast to the situation in Alzheimer's disease, tau precipitates are not linked to amyloid deposits. In light of the abnormal posttranscriptional control of tau protein demonstrated in recent studies of postmortem brain slices from patients with DM1, and in vitro studies on transgenic mice,[48,83,109,110] it is conceivable that abnormal splicing gives rise to abnormal tau variants that precipitate in specific brain areas and constitute the neurofibrillary tangles described. In vitro studies have demonstrated that expanded CUG repeats disturb tau phosphorylation in a specific cell line.[42] Whether splicing alteration of tau transcripts involves various factors needs further investigation.[57] Whether the effects of this spliceopathy on tau transcripts alone account for the neurodegenerative aspects of patients with DM1 requires further in-depth molecular evidence.

Cerebrospinal Fluid Findings. No specific cerebrospinal fluid findings have been reported in patients with DM1. One report documented abnormal protein content in a subset of patients with DM1,[43] the significance of which is unclear. More recently, Martinez-Rodriguez et al.[68] reported decreased orexin-A levels in the cerebrospinal fluid of 3 of 9 patients with DM1 affected by excessive daytime sleepiness, thus suggesting analogies with the mechanisms involved in narcolepsy.

Neuroimaging Evidence. ***CT Scans.*** The most frequent finding is hyperostosis frontalis interna together with a more diffuse hyperostosis in the calvarium. Avrahami et al.[5] found significant hyperostosis in 17 of 24 patients studied and concluded that this was independent of endocrine abnormalities such as increased growth hormone secretion or abnormal calcium metabolism, but rather might be the result of brain atrophy; endocrine abnormalities have not been excluded by other authors.[98]

Conventional MRI Studies. Several reports have documented cortical atrophy and white matter hyperintense lesions[15,24,27,28,45,52,72,76,79] in patients with DM1. Fiorelli et al.[31] documented an increased frequency of subarachnoid cysts in DM1. Cortical atrophy is generally more prominent in the frontal and temporal lobes, and white matter hyperintense lesions are usually diffuse in both hemispheres, single or confluent, and often asymmetric in appearance. There has been inconsistency in interpreting these white matter hyperintense lesions and no general agreement as to their clinical relevance. Some authors do not find a clinical correlate to the neuroimaging profile,[14] whereas others find a correlation between neuropsychological data and the distribution and severity of white matter abnormalities.[24,45,111] We found no correlation between the degree of cerebral involvement on traditional MRI studies and cognitive and behavioral profiles.[72] Other authors suggest an evolution of white matter abnormalities during the disease.[28]

Quantitative MRI Studies. Kassubek et al.[51] confirmed and extended the initial reports with traditional MRI, demonstrating that cortical brain atrophy occurs in both diseases but to a minor degree in DM2 compared to DM1. Voxel-based morphometry has been used by several authors to map cortical and subcortical gray matter atrophy in DM1 even where there were no or minimal abnormalities on traditional MRI studies.[2,38,84] These studies confirm that regional neuronal loss occurs in the parietal and frontal lobes and demonstrate that atrophy extends to the superior and middle temporal gyrus and the occipital lobes. Ota et al.[84] demonstrated that large CTG expansions correlated with small brain volumes. The exact distribution of neuronal loss may facilitate clinical and functional correlations with the cognitive and behavioral changes observed in DM1.

Qualitative MRI Studies. Several authors have demonstrated with diffusion tensor imaging that there are diffuse microstructural changes even in normal-appearing white matter on traditional MRI studies, suggesting that these abnormalities play a role in the wide range of CNS symptoms described in DM1.[36,114] Ota et al.[84] demonstrated microstructural changes in fractional anisotropy and diffusivity in the corpus callosum subregions connecting to cortical areas, especially motor ones.

PET Studies. PET studies[72] have demonstrated hypoperfusion of frontal and temporal lobes in patients with DM1 and to a minor degree in patients with DM2. This regional hypoperfusion correlated with the frontal dysexecutive syndrome demonstrated on neuropsychological testing. Fiorelli et al.[32] demonstrated that cortical glucose utilization decreased in 20% of patients with DM1 using ^{18}F-labeled 2-fluoro-2-deoxy-D glucose (FDG) and dynamic PET.

Brain MR Spectroscopy. Neurochemical alterations observed with proton magnetic spectroscopy have been documented in patients with DM1[16] and these were correlated with CTG size.

BRAIN INVOLVEMENT IN DM2

The adult presentation of DM2 usually occurs in the 3rd to 6th decade, later than the classic adult form of DM1. There is remarkable clinical heterogeneity in DM2 and high serum CK levels may be the sole manifestation of the disease,[70,74] but, in general, two main clinical pictures of DM2 emerge. Homozygosity for the DM2 expansion does not seem to alter the disease phenotype as compared with the heterozygous state.[108] There is the proximal myotonic myopathy (PROMM) phenotype[73,97] characterized by onset in the 3rd or 4th decade, proximal muscle weakness (usually mild to moderate), mostly affecting the pelvic girdle with little or no muscle atrophy, and normal or increased deep tendon reflexes associated with mild clinical myotonia. Early-onset iridescent posterior lens cataracts are usually present. In addition to this classic form, there may be a distinct clinical presentation of DM2, the proximal myotonic dystrophy phenotype (PDM), first described by Udd et al.[123] In this form, onset occurs at a later age and is characterized by remarkable proximal muscle atrophy and weakness, often mimicking progressive spinal muscular atrophy.[100] Clinical myotonia may be absent and early-onset cataracts are not as frequent as in PROMM.[70] In both presentations, brain symptoms are not prominent. However, there is some evidence from neuropsychological test scores, psychiatric interviews, and neuroimaging data that brain involvement may be present in DM2 as in the adult form of DM1, although to a minor degree.

Neuropsychological Evidence. ***Cognition.*** The main neuropsychological evidence of cognitive impair-

ment in DM2 comes from the studies of Meola et al.,[71,72] although these are limited by small numbers of patients. In general, IQ and MMSE scores were in the normal range, whereas neuropsychological scores were below normal for age- and education-matched controls on tests for visual-spatial performance and attention, a situation similar to that in DM1 patients, but milder. Regarding verbal fluency, patients with DM2, like those with DM1, do not display lexical impairment on clinical examination and, in agreement with the clinical impression, have normal verbal fluency.[71,72] This is in contrast with findings of Gaul et al.[37] that DM1 and DM2 patients scored lower than controls with respect to lexical verbal fluency.

Behavior. Evidence for some degree of behavioral abnormalities in DM2, similar to those described in DM1, comes from studies on a small number of patients.[71,72] As in patients with DM1, the main clinical finding suggesting behavioral abnormalities comes from tests of frontal lobe function, suggesting a dysexecutive syndrome. As in DM1, abnormal scores on tests of frontal lobe function did not correlate with cortical atrophy and white matter hyperintense lesions but rather were associated with fronto-temporal lobe hypoperfusion as documented by PET studies. These studies were limited by the lack of quantitative MRI studies. There was no evidence in these studies that anxiety or depression were a characteristic finding of patients with DM2. Meola et al.[71] found a homogeneous avoidant personality profile in patients with DM2 as in DM1.

Somnolence. The degree of this complaint and frequency in DM2 has not been investigated in detail. In our experience, there is a subset of patients in whom this complaint is prominent and cases of central sleep apnea have been demonstrated, but less frequently in DM2 than DM1.

Fatigue. There are no reports on the prevalence and relevance of fatigue in patients with DM2, but this does not seem to be a prominent feature in these patients except for those with severe lower-limb muscle weakness or muscle pain and locking.

Neuropathological Evidence. There is limited neuropathological data for DM2. Maurage et al.[69] suggested that a similar brain tau pathology is found in DM2 as in DM1, but further studies and evidence at a molecular level are needed.

Neuroimaging Evidence. ***Conventional and Quantitative MRI Studies.*** The first reports of CNS involvement on neuroimaging in DM2 came from Hund et al.[46] using conventional MRI studies. They described a subset of patients with diffuse and confluent white matter hyperintense lesions similar to those found in CADASIL. There was no apparent link to neuropsychological abnormalities, but these were not explored in detail in the initial description. Other studies[52,71,72] followed, demonstrating that brain atrophy and white matter hyperintense lesions are found in DM2 just as in DM1, but the severity of white matter involvement described by Hund et al. remained an isolated finding. These initial studies were limited by the lack of quantitative MRI studies. More recently, Kassubek et al.[51] confirmed and extended the initial reports with traditional MRI in DM2,[72] demonstrating that cortical brain atrophy occurs in both diseases but to a lesser degree in DM2 than DM1.

Brain MR Spectroscopy. Recent studies[127] suggest that, although structural abnormalities may occur in patients with DM1 and DM2, changes in cerebral metabolites can differentiate these disease groups. Further studies are needed to clarify whether this difference accounts for involvement of different neuropathological pathways in the two disorders.

PET Studies. PET studies[72] have demonstrated mild hypoperfusion of the frontal and temporal lobes in patients with DM2 as in patients with DM1. Sansone et al.[105] studied one DM2 patient with camptocormia using PET. Mesotemporal glucose was reduced but the DOPA pathway was normal, suggesting that the extrapyramidal signs encountered in this patient involved different pathways and pathomechanisms than those of Parkinson's disease, and emphasize the clinical heterogeneity of DM2.

MULTIORGAN INVOLVEMENT AND COGNITIVE FUNCTION

Cardiac conduction arrhythmias and cardiomyopathy together with respiratory insufficiency frequently present in these patients and contribute to the general hypoperfusion and hypoxia of brain structures, aggravating the cognitive and behavioral features described.

Insulin resistance may play a role in aggravating brain function. Brain metabolism accounts for 50% of total body glucose utilization. The brain depends on glucose as an energy substrate, with most brain insulin coming from the pancreas, whence it is taken up by the brain via a receptor-based carrier similar to those demonstrated in muscle. Animal models of type 2 diabetes associated with insulin resistance show reduced insulin brain uptake and content. There are suggestions that brain insulin receptors may become less sensitive to insulin, and this could

reduce synaptic plasticity.[75] In addition, there is some indication from animal models that reduced sensitivity to insulin in the brain, as observed in aging, decreases the clearance of abeta amyloid, thus increasing amyloid toxicity. These fascinating observations are limited to animal models of type 2 diabetes, and caution is needed in interpreting these findings; however, these preliminary suggestions may provide some indirect speculative evidence that glucose metabolism abnormalities such as those observed in DM might influence brain symptoms.

CLINICAL RELEVANCE OF BRAIN INVOLVEMENT IN DM

Although cognition in terms of overall intelligence may not be impaired, lack of initiative, inactivity, and apathetic attitudes constituting the cardinal feature of the dysexecutive syndrome are all characteristic of DM patients. In clinical practice this represents a limitation because patients may be passive in their health-related care, may miss outpatient visits, and may not attach any importance to certain symptoms. Family members, relatives, and possibly even employers need to be aware of these aspects because inactivity may be related to CNS dysfunction rather than muscle disability.

Excessive daytime sleepiness is a prominent feature that may interfere with daily and work-related activities. This is often underestimated by patients and should be sought by asking family members and relatives. Deviant personalities are another characteristic of patients with DM1 and DM2. Obsessive-compulsive, passive, or avoidant traits may dominate the clinical picture and limit patients' relationships and everyday activities. This knowledge is important to clinicians and relatives in order to improve the approach to these patients, who may require more time and persuasion if they are to overcome their obsessive, passive, or avoidant personality traits.

Although no specific therapeutic agents are currently available to influence CNS symptoms,[1,115] and while awaiting drugs that may revert abnormal splicing of brain gene proteins or replace MBNL depletion,[21,50] awareness of the frequent occurrence of CNS symptoms even in the adult form of myotonic dystrophy is helpful. It may help physicians, family members, and employers to understand why, despite mild muscle disability, patients with DM may not function as well as expected by their muscle strength and status. These aspects should be taken into account when planning a clinical trial. Measures of cognitive and behavioral involvement should be included to assess the efficacy of treatment. If the target is muscle, strength may improve, but if inactivity related to the dysexecutive syndrome is unaffected the results of a treatment may be underestimated.

As to the psychosocial aspects, Prevost et al.[92] have said that predictive testing for DM1 was perceived as a change for the worse by many DM1 carriers, suggesting that despite the apparently apathic attitudes and reduced ability to capture emotion by facial expression, the disease represents an emotional burden for these patients.

In general, patients and relatives should be reassured about the degree of brain involvement. If patients with the congenital form survive the initial phases of respiratory distress, the outcome in general is one of gradual improvement, especially with adequate family and psychosocial support.

There are suggestions[3] that health-related quality of life assessed by short form 36 item health status survey (SF-36) is severely impaired in patients with DM1 and that it is negatively influenced by the severity and duration of the disease as well as by specific cognitive deficits such as visual-spatial and verbal-abstract reasoning. Emphasis on these findings may target therapeutic strategies that could improve the quality of life for these patients.

There are limited studies on the progression of cognitive decline over time[121,130] and whether the brain abnormalities described so far in patients with DM1, and to a lesser degree in patients with DM2, culminate in a dementia syndrome is yet to be demonstrated. We have followed a small group of patients with DM1 and DM2 over a mean follow-up period of about 8 years, and observed that there was worsening of neuropsychological test scores over time, but no extension to additional areas of cognition or interference with everyday activities.[106] These observations, although they relate to only a small group of patients, may have important prognostic implications.

Finally, we can conclude that signs of CNS involvement (inactivity, decreased initiative, memory deficits, and visual-spatial abnormalities) together with multiple organ degeneration contribute, at least in part, to premature aging in patients with myotonic dystrophies so that DM1 has, in fact, been considered a possible segmental progeroid syndrome.[128] The exact mechanisms of premature aging in DM1, at least, may in part be related to increasing (CTG)n repeat lengths with age.[39] Future treatments that revert abnormal brain gene protein splicing may maintain proper protein processing and folding, thus representing a partial antidote to

premature aging in DM1 through genetic modulation.[67]

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