Myotonic Dystrophies

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Myotonic dystrophies or dystrophia myotonica (DM) is a clinical syndrome that includes myotonic dystrophy type 1 (DM1), myotonic dystrophy type 2 (DM2), myotonic dystrophy type 3 (DM3), and so forth. The terminology was recommended by the new nomenclature for myotonic dystrophies of an International Panel for Consensus. Previous studies have shown that DM1 is caused by the expansion of a cytosine-thymine-guanine (CTG) repeat in the DM protein kinase gene on chromosome 19, and DM2 is caused by an expansion of a cytosine-cytosine-thymine-guanine (CCTG) repeat in the zinc finger protein 9 (ZNF9) gene on chromosome 3. Because DM1 and DM2 have very similar clinical presentations, the diagnosis of these two disorders needs to be confirmed by molecular genetic analysis. Recently, DM3 was reported to include a multisystem myotonic disorder with frontotemporal dementia, and a linkage to chromosome 15q21-24. Although the age at onset, disease severity, and cerebral abnormality on a brain magnetic resonance spectrometry may correlate with the number of triplet repeats in the blood cells of DM1, it is too early to reach a conclusion. In Taiwan, the prevalence of DM1 is much lower than in Western countries. Previous studies have shown that the central nervous system symptomatology is correlated mainly with the white matter lesions in the brain MRI, but the CNS manifestations seem unrelated to the numbers of CTG triplet repeats in the blood cells. The inverse correlation between age at onset and CTG repeat length is significant only in patients with small expansions of about 100-250 triplet repeats. Transmission contraction of the repeat size is likely to occur in alleles with large repeats and is associated with paternal transmission. In congenital DM1, individual variability of muscle differentiation does occur, in spite of the same number of CTG repeats in the leukocytes. *(Chang Gung Med J 2005;28:517-26)*

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Myotonic dystrophies, also known as dystrophia myotonica, are a group of autosomal-dominant multi-systemic disorders with highly variable phenotypes.[1] DM can be regarded as a clinical syndrome that includes several subtypes designated as myotonic dystrophy type 1, myotonic dystrophy type 2, myotonic dystrophy type 3, and so forth by the International Myotonic Dystrophy Consortium.[2]

DM is characterized by myotonia of the skeletal muscles, progressive myopathy, cataracts, cardiac

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conduction defects, gonadal dysfunction, and neuropsychological impairments.[1] In late 1991, DM1 was proven to be an unstable expansion of cytosine-thymine-guanine repeats in the 3' untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19.[3-5] In 1994, another form of autosomal-dominant myotonic disorder with a predominant proximal muscle weakness, but without a CTG repeat expansion at the DMPK gene, was reported.[6] Subsequently, several similar families were noted and this became known as proximal myotonic myopathy (PROMM).[7-10] In 1998, a new disease locus was proved in a 10 cm region of chromosome 3q in a 5-generation family with PROMM.[11] The mutation that caused DM2 was then discovered to be an expansion of CCTG repeats in the zinc finger protein 9 (ZNF9) gene on chromosome 3.[12-14] Although DM2 has a relatively mild symptomatology, the DM2 CCTG expansion can be larger than the DM1 CTG expansion.[15] Both of these DNA expansion mutations are highly unstable in the length of the repeat in successive generations and in the somatic cells of an individual. Furthermore, some families with a DM-like disorder have neither a DM1 nor a DM2 mutation indicating the existence of DM type 3. Recently another DM gene locus was reported in a large kindred with proximal muscle weakness, myotonia, cataracts, and fronto-temporal dementia.[16] Linkage analysis suggested a DM3 locus to chromosome 15q21-24. DM is one of the most common adult forms of muscular dystrophy, with a prevalence of 2.1 to 14.3 per 100,000 in Western Europe and North America,[1] and even 189 per 100,000 in the Saquenay-Lac-Saint-Jean region of Quebec, Canada;[17] its prevalence in Japan is 1 in 20,000.[18] DM occurs much less frequently in Africa, Southeast Asia,[19] and Taiwan.[20] In this review, we summarize the available genetic and clinical information about DM and related disorders, and emphasize the data from Taiwan.

Myotonic dystrophy type 1 (DM1)

DM1 is an autosomal-dominant disorder with variable clinical manifestations. The severity of DM ranges from mildest to classic and severe congenital disorders. The numbers of CTG repeats in leucocytes vary from 50-80 in minimal DM, 100~1000 in classic DM, and even more than one thousand in congenital DM.[21-23] However, the age at onset shows a significant overlap for individuals who have 100-1000 CTG repeats.[21]

A significant inverse correlation is noted between ages at onset and numbers of repeats, and there is a general correlation between the degree of expansion and the severity of clinical manifestations.[21,24] In DM1 families, a phenomenon of genetic anticipation is noted, that is, the clinical symptoms appear earlier and the clinical severity increases with transmission to successive generations.[25] Interestingly, the tremendous increase of the repeat sizes of the CTG expansions is more frequently associated with female than male transmission.[26,27] In the normal population, the numbers of CTG repeats at the DMPK gene are between 4 and 37.[3,28] Healthy persons who carry a "small normal" allele (4-18 repeats) and a large normal allele (19-37 repeats) may transmit the large allele to their offspring preferentially,[29] a phenomenon known as segregation distortion. Occasionally, transition mutations may occur, with a transition from a large normal allele to small expanded repeats ($\geqq$50 repeats).[30] If the repeat exceeds the disease-causing threshold (about 50), small expansions (50-70 repeats) may be transmitted to the next several generations without major changes.[31,32] If the expansion exceeds 80 repeats, significant genetic anticipation with intergenerational enlargement may develop. Occasionally, intergenerational contraction will occur, and the affected parents may transmit a smaller contracted CTG repeat.[33]

Peripheral nervous manifestations in DM1

In DM1 patients, muscle weakness and wasting are common in some specific areas such as the facial and temporal muscles. In the extremities, muscle weakness and wasting are more prominent in the distal limbs.[34] The primary involvement of the peripheral nerves is still debated; some authors deny the presence of polyneuropathy,[35,36] but some suggest that muscular weakness and dystrophy is a consequence of polyneuropathy.[34] In our previous study,[37] polyneuropathy with sensory and motor involvement was found in approximately 40% of DM patients, using the standard electrophysiological methods. In addition, sural nerve biopsy studies showed a decrease of nerve fiber density with a predominant loss of large myelinated fibers. Electronmicroscopic findings also confirmed primarily axonal damage and secondary disruption of the myelin.

Central nervous system manifestations and neurobehavioral changes in DM1

Strong evidence suggests that obsessive-compulsive, passive-aggressive, and dependent-avoidant personalities, increased apathy and depression are common manifestations in DM1 patients.[38] The changes in personality, motivation, and affection may result in social isolation. In addition, excessive daytime sleepiness or hypersomnia is very common in these patients.[39] Recently, an aging-related decline of the frontal and temporal cognitive function was noted.[40] There is no correlation between cognitive impairment and CTG repeats in leucocytes or severity of muscle involvement.[41,42] The data supported the notion of an abnormal tau-protein expression in the brain tissues and neurofibrillary tangles in the frontal and temporal lobes.[43] Brain magnetic resonance images demonstrated cerebral cortical atrophy, subcortical white matter lesions, and ventricular dilatation.[44-46] The subcortical white matter lesions were frequently found in the frontal, parietal and temporal lobes.[43-49] In addition, the severity of involvement in subcortical white matter lesions might correlate with the degree of cognitive dysfunction.[46-49]

Although the age at onset and cerebral abnormalities on brain MRI spectrometry may correlate with the number of triplet repeats in the blood cells, caution is necessary before reaching a conclusion.[45] The correlation among clinical manifestation, brain MRI, and molecular genetic studies remains unclear. In Taiwan, the clinical manifestations, brain MRI, and molecular genetic analyses were reported in 10 patients with DM1.[50] Clinical manifestations included hypersomnia, memory impairment and mental deterioration. Neuropsychological examinations revealed impairments of performance IQ and verbal IQ, particularly impairment of attention, and difficulties in visual space and construction, reasoning, and calculation. Brain MRI showed ventricular dilatation, diffuse cortical atrophy and WML. The WML tended to involve the frontal and then temporal or parietal lobes, and finally the insular subcortical area. Molecular genetic study confirmed an increased number of CTG triplet repeats ranging between 230 and 1000 in the leucocytes. The CNS symptomatology was correlated with the WML in the brain MRI, but seemed unrelated to the numbers of CTG triplet repeats in the blood cells. In addition to the above brain MRI findings, arachnoid cysts in the supratentorial areas, posterior fossa cyst lesion, and even posterior fossa tumors, such as Schwannomas, have also been reported.[51,52]

Molecular genetic studies in Taiwan

In 1999, Hsiao et al.[53] first established a protocol with a simple and reliable method, which required only 10 nucleate cells to determine the CTG repeat number of normal and DM1 alleles. The method could be useful in the clinical and prenatal diagnosis of DM1. In addition, with the same method, Jou et al.[54] also found that oral mucosa cells could serve as an alternative to leucocytes in the evaluation of the number of CTG repeats of the DMPK gene.

In the normal population, at the DM1 locus, the number of CTG repeats varies from 5 to 37. In DM1 patients, the number of CTG repeats is greater than 50. Persons with premutation alleles containing 40-50 repeats have no clinically detectable manifestation. However, persons carrying permutation alleles may have a high risk of having symptomatic offspring within several generations.[55] The phenomenon indicates that premutation alleles are unstable during meiosis. The prevalence of DM1 is closely associated with the frequency of large normal CTG alleles. In Taiwan, the allelic frequency of large normal CTG repeats[18~37] is much lower than that in Europe and Japan.[20] In China, the frequencies of large normal alleles are close to those in Taiwan (1.0% vs 1.4%).[56]

The Prevalence of DM1 in Taiwan

The prevalence of DM1 was studied in Taiwan, and revealed a low prevalence of 0.46 per 100,000.[20] The prevalence of DM1 might be underestimated because of the hospital-based data, and that most of the index patients were referred to neurologists after having serious neurological symptoms. Clinical anticipation was frequently observed in the affected families, but occasionally transmission contraction of the CTG repeat size was noted in some families with large repeats. In addition, most of the transmission contractions were associated with paternal transmission. Male DM1 patients tend to have a decreased sperm function and have a selection against extreme expansion in the sperm.[57,58] The correlation of the expansion size in lymphocytes and the age at onset has shown a negative linear correlation in several

previous studies.[22,59,60] However, in our study, the inverse correlation between age at onset and the CTG repeat length was noted only in patients with small expansions of about 100-250 triplet repeats.[20] In addition, a DM1 carrier with a childhood-onset son was found to have CTG length heterogeneity in the range of 40-50, indicating that premutation alleles could be very unstable.[20]

Congenital myotonic dystrophy

Congenital DM is characterized by hypotonia, feeding difficulties, and respiratory failure present from birth.[61] More than 75% of children with congenital DM have mild to moderate mental retardation.[62] Myotonia is usually absent in infants with congenital DM, but it may develop by the age of 10. The biopsied muscle pathologies showed small fibers with central nuclei and poor fiber type differentiation, suggesting delayed muscle fiber maturation. Congenital DM is usually inherited from an affected mother. The likelihood of congenital DM is higher if the mother has more than 500 CTG repeats or if a previous baby had congenital DM. The hypotonia in infants with congenital DM1 may improve if they survive the neonatal period. However progressive myopathy with contracture and talipes may occur.

In order to understand the involvement of specific muscles and the development of contracture in the limb muscles in children with congenital myotonic dystrophy, the genetic effects on various tissues were studied in 2 siblings with congenital DM1.[63] Clinically, they had facial diplegia, tented mouth, and muscle wasting of the distal legs with talipes. The distal leg muscles were more severely involved than the thigh muscles, and the skeletal muscle MRI also confirmed the findings. Muscle biopsies showed a significant difference in the fiber type distribution between these two congenital DM1 patients. One revealed a predominance of type 2 fibers in all muscle specimens, and dystrophic changes were observed in the peroneus longus muscle. Another revealed a prominent involvement of the tibialis anterior muscle with a predominance of type 1 fibers, similar to those muscle fiber distributions in adult DM1 patients. Molecular genetic analysis of DMPK showed an elongation of CTG triplet repeats between 850 and 1400 in the leukocytes, skin, fat, tendon, and muscles. The severity of muscle involvement in the MRI and histopathology was not well correlated with the sizes of the expanded trinucleotide repeats in various muscles. The data indicated that despite nearly the same number of CTG repeats in the leukocytes, a high variability of muscle differentiation may occur. The above data also confirmed a delay in the differentiation and maturation of the skeletal muscles.

Brain MRI in congenital myotonic dystrophy

The CNS involvement differs between the classic and congenital forms of DM1. Recent studies have suggested that the brain MRI abnormalities are developmental in congenital DM1, and degenerative in adult DM1.[64,65] We evaluated the brain MRI findings and intellectual functions of 2 patients with congenital DM1, and compared them with 4 classic DM1 patients in the same family[66] These 2 patients with congenital DM1 had severe mental retardation and the characteristic feature of hyperintensity of the white matter at the posterior-superior trigone (HWMPST), in addition to ventricular dilatation on T2-weighted images (T2WI) of the brain MRI. In classic DM1 patients, the brain MRI showed hyperintensity lesions in the bilateral frontal and temporal regions on T2WI, which were absent in congenital DM1. The data suggest that in congenital DM1, the HWMPST in the brain MRI is a characteristic finding.

Molecular mechanisms of DM1

The fundamental nature of the disease process of DM1 is still debated. The protein kinase encoded by DMPK can be expressed in the brain and muscles, but its function is not clear. The expansion mutation in the 3' untranslated region of the DMPK gene does not cause the production of altered DMPK protein, but it may cause effects on the other genes at the DM1 locus, including the SIX5 gene which may contribute to the development of cataracts in DM1.[67-69] In addition, recent studies have suggested that a reduced expression of DMPK might contribute to cardiac disease.[70,71] However, animal studies showed that knocking out the DMPK gene in mice does not lead to myotonia or muscle degeneration.[72,73] Recently, a mediated disease mechanism appeared, in which the RNA produced from the mutant DMPK gene has a toxic effect on muscle cells. A transgenetic mouse model, in which expanded CUG repeats were expressed at a high level in skeletal muscles,

developed ribonuclear inclusion, myotonia, and histological changes in the muscles, similar to human DM1.[74] Seznec et al.[75] reported another transgenetic model of DM1 which developed abnormalities of the tau protein in the brain, suggesting that a toxic gain-of-function by mutant RNA may occur in the brain RNA binding proteins, as well as abnormal regulation of alternative splicing. It is not clear whether the toxic effect is caused by RNA in the ribonuclear inclusions or is a function of the mutant RNA that remains free in the nucleoplasm.

The DM1 and DM2 genes are transcribed into aberrant RNAs, with expanded CUG and CCUG respectively, which aggregate in nuclear foci and sequester RNA-binding protein in the muscleblind family.[76,77] Recent studies in DM1 and DM2 point to the abnormal regulation of the alternative splicing of various transcripts, including insulin receptor, CIC1 chloride channel, myotubularin, troponin I and microtubule-associated protein (MAP) tau.[43,78-81] The common underlying mechanism of a toxic gain-of-function by the expanded RNAs might explain the phenotypic similarities between DM1 and DM2.

Myotonic dystrophy type 2 (DM2)

In 1994, an autosomal-dominant DM-like disorder was reported, but the CTG triplet repeat expansion was absent at the DMPK gene.[6] Subsequently, Ricker et al.[7] also described a new autosomal-dominant disorder with proximal myotonic myopathy, myotonia and cataracts. In the following few years, several families with proximal myotonic myopathy (PROMM) were reported with characteristic findings of proximal muscle weakness, relatively mild manifestations, less severe mental changes, and a higher frequency of peripheral neuropathy and mitral valve prolapse.[8-11,82,83] In 1998, Ranum et al.[12] first established a linkage to chromosome 3q21.3 in a large kindred, and subsequently, kindreds with proximal muscle weakness were linked to the same DM2 locus. The mutation of DM2 (PROMM) was discovered to be an expansion of CCTG repeats in the ZNF 9 gene of chromosome 3.[14]

DM2 patients[7-11,15,82-85] occasionally have weakness of the distal muscle groups, but the predominant weakness in most individuals is in the proximal limb muscles and neck flexors. In addition, the facial and respiratory muscles are relatively spared. Although cataracts and hypogonadism in DM2 are indistinguishable from those in DM1, effects on the cardiac conduction system are less common. Therefore, the overall prognosis is favorable. In DM2, the symptoms often appear in patients aged 30-40 years. There is no congenital form of DM2 comparable with DM1, although central nervous system involvement has been reported.[83] Like DM1, the DM2 repeat is transcribed, and the mutant RNA may form intranuclear inclusions that titrate muscleblind proteins.[76,77] The ribonuclear inclusions are larger and more intense in DM2 than that in DM1. Although observations have supported the notion that RNA gain-of-function is responsible for both the muscle and non-muscle manifestations in DM2, the results of research into the disease mechanisms in DM2 remain unclear.

Myotonic dystrophy type 3 (DM3)

Ricker et al.[13] have demonstrated that some kindreds with PROMM are linked to chromosome 3, whereas other kindreds are not linked to either chromosome 3 or 19. Recently, the third gene that produces a multisystem myotonic disorder with frontotemporal dementia has been reported.[16] The clinical features included proximal muscle weakness, characteristic myotonia, early bilateral cataracts and early onset dementia. Subsequently, muscle weakness and atrophy in the proximal, distal and neck extensor muscles, and severe fronto-temporal dementia, were noted. The mean age at onset was 46.7 ± 12.6 years. Cortical atrophy was noted in the brain MRI, but subcortical white matter lesions were not observed. Pathological studies of the brain showed prominent fronto-temporal spongiosis, neuronal loss, and rare neuronal and glial tau inclusions. A genome-wide linkage analysis suggested a linkage to chromosome 15q21-24.

Diagnosis of DM

Percussion myotonia and weakness of the facial and temporal muscles are the early characteristic findings in DM. With these characteristics, diagnosis of DM can be made. In most patients with classic DM1, the myotonia can also be demonstrated by electromyography (EMG), with a characteristic “dive bomber” discharge. In order to determine the conduction defects, an electrocadiogram (ECG) is warranted. In addition, an examination of family members is valuable, particularly in a floppy baby with

congenital DM. When a patient is suspected to have DM, a genetic DNA test for either the expanded CTG, CCTG repeats, or a linkage analysis is required. Genetic testing is reliable and sensitive. Other diagnostic procedures such as EMG or muscle biopsy can also be used. Genetic counseling is also important for persons who consider a testing before development of symptoms. However, ordering this test requires informed consent.

Treatment

No treatment has been shown to cure, or reverse the progression of myopathy in DM1, DM2, or DM3, but some symptoms of DM can be effectively modified by drugs. The myotonia of DM has a good response to treatment with phenytoin or mexiletine.[86] Periodic ECGs are important to monitor the development of any cardiac conduction defects. A cardiac pacemaker is indicated in DM patients with a third-degree heart conduction block. Excessive daytime sleepiness is very common in DM1. Modafinil can regulate the sleep-wake cycle and many patients had a major improvement in daytime sleepiness without serious side effects.[87-89] Troglitazone was reported to reduce insulin resistance and improve myotonia in DM1 patients, but further large, double blind, and control studies are necessary.[90]

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肌強直性肌肉失養症

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肌強直性肌肉失養症是一種臨床症候群包括第一型、第二型、第三型和其他型肌強直性肌肉失養症。肌強直性肌肉失養症的分類是經由國際專家審查會議一致同意而命名。第一型肌強直性肌肉失養症是位於第 19 對染色體長臂上的肌強直性肌肉失養症蛋白激動酶基因的 CTG 三聯核苷酸重複序列倍增突變，而第二型肌強直性肌肉失養症是位於第 3 對染色體長臂手指蛋白 9 基因的 CCTG 四聯核苷酸重複序列倍增突變所致。二型肌強直性肌肉失養症臨床症狀類似，所以有時須靠分子基因檢測才可確定診斷。最近第三型肌強直性肌肉失養症被報告合併有多系統症狀和額、顳葉痴呆，而且基因異常位於 15q21-24 處。文獻報告發現第一型肌強直性肌肉失養症的發病年齡、疾病嚴重度和腦部病變特別是腦部核磁共振造影的異常，可能與血中三聯核苷酸重複序列增加程度有關。在台灣肌強直性肌肉失養症盛行率比西方國家低很多。近年台灣對第一型肌強直性肌肉失養症包括流行病學、分子基因研究和臨床表現包括肌肉病理變化及中樞神經異常表現，有相關文獻資料報告。在腦部核磁共振造影的白質病變與血中三聯核苷酸重複序列增加程度似乎無關。分子基因與臨床表現發現，三聯核苷酸重複序列在 100 至 250 之間可能與發病年齡有關。此外發現這類疾病基因遺傳如果來自父系及較大的三聯核苷酸重複序列可能會有基因傳遞收縮現象。在先天型肌強直性肌肉失養症病患的肌肉病理變化方面，年齡及血中三聯核苷酸重複序列相近的個案，其肌肉細胞的分化程度有明顯差異。(長庚醫誌 2005;28:517-26)

關鍵字：肌強直性肌肉失養症，第一型肌強直性肌肉失養症，第二型肌強直性肌肉失養症，第三型肌強直性肌肉失養症，近端肌強直性肌肉病變，肌強直性肌肉失養症蛋白激動酶，流行病學，遺傳病逐代早發。

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