Clinical characteristics of 37 Chinese patients with myotonic dystrophy Type 1

Hui Lu, Yun Li, Mordechai Sadowsky, Yuwei Da

Abstract:
OBJECTIVE: This study aims to investigate clinical characteristics of 37 Chinese patients with Myotonic dystrophy Type 1 (DM1).

METHODS: Main clinical features of these cases were analyzed, with a focus on multi-system involvements.

RESULTS: The median age of onset was 21.5 years, with a range from 3 to 45 years. Fourteen patients had a family history positive for DM1, whereas the other 23 were sporadic cases. Twenty-seven of the patients were male. The primary symptoms were myotonia and weakness with varying multi-system involvement including cardiac defects, cataracts, sleep disturbances, cholecystopathy, and peripheral neuropathy.

CONCLUSIONS: This is the first report in China with the diagnosis of DM1 decisively confirmed by CTG expansion testing. Data from our study suggest that Chinese DM1 cases have different clinical characteristics compared with those of Caucasian cases, especially the prevalence of cardiac defects, cataracts, and sleep disturbances.

Key words: Chinese population, clinical characteristics, multi-system involvements, myotonic dystrophy Type 1

Introduction
Myotonic dystrophy is a neuromuscular disorder of autosomal dominant inheritance, which can be divided into two main sub-types: Type 1 (DM1) and Type 2 (DM2).[1] DM1 is caused by a pleiotropic unstable trinucleotide repeat (CTG) expansion located in the 3'-untranslated region of the serine-threonine dystrophia myotonica protein kinase (DMPK) gene on chromosome 19q13.3.[2] A toxic gain-of-function of abnormally stored RNA in the nuclei of affected cells is assumed to be responsible for several clinical features of the disease. The abnormally stored RNA plays a basic role in deregulating RNA binding protein levels and in several mRNA splicing processes of several genes, thus leading to the multi-systemic features typical of DM1.[3] Patients may be categorized by (CTG) n triplet expansion size: E1 = 50–149; E2 = 150–1000; E3 = >1000.[3] It has been observed that patients with small CTG expansions generally have more mild symptoms, and the expansion is generationally unstable with anticipation.[4]

DM1 is the most common form of adult muscular dystrophy, with an overall worldwide prevalence estimated to be approximately 8–12/100,000.[3] A lower prevalence of DM1 and a lower allelic frequency of CTG expansion has been noted in the Chinese population relative to both Caucasian and Japanese populations.[5] However, with a population of 1.3 billion, a relatively low prevalence still indicates a large number of patients suffering from this disease.

The most common presentation of DM1 is an adult-onset multi-system degenerative disorder. The primary characteristics of DM1 are myotonic phenomena and progressive muscular weakness.[6] Along with these core features, patients often report a wide range of symptoms including cataracts, cardiac arrhythmia, digestive dysfunction, respiratory insufficiency, endocrine disturbance, and other developmental and degenerative manifestations.[6]

This work posits that the typical clinical picture of DM1 may be different in Chinese patients than Caucasian patients. In this study, the detailed clinical features, family history, and genetic evidences of 37 DM1 cases in Chinese patients were comparably analyzed.
Materials and Methods

Ethics statement
This surveillance program has been approved by Ethical Review Committee of Xuanwu Hospital, Capital Medical University. All signed informed consents have been collected and stored by Department of Neurology, Xuanwu Hospital.

Thirty-seven DM1 cases were identified and enrolled from our hospital since 2005. Final diagnosis of DM1 was made in accordance with the criteria established by Griggs and Wood as follows: Genomic DNA was extracted from the patients’ peripheral white blood cells. The primers were: P1: 5’-AGAAAGAAATGGCTGTGATCC-3’, P2: 5’-GAAGGTCCCTTGTACCCGG-3’, P3 R: 5’-TACGCATCCCCATTTGAGACGG-3’, and P4 CTG: 5’-TACGCATCCAGTGGGAGACGTGCCTGCGTTGCTGCTGCT-3’. The five prime end of P1 was fluorescently labeled by 5-carboxyfluorescein. Tri-primer polymerase chain reaction (TP-PCR) was used to amplify DNA. ABI PRISM310 sequenator was combined to detect CTG repeats in the 3’-untranslated region of DMPK gene, and the electropherogram of fluorescent compounds was analyzed by ABI 310 GeneMarker software (ABI, US). The standard of positive for the DM1 gene was more than 150 bp of TP-PCR compound in the electropherogram.

Multi-system clinical manifestations were inspected for in each patient, especially muscular involvement, cardiac defects, cataracts, sleep disturbances, cholecystopathy, and peripheral neuropathy. Muscular involvement was evaluated by chief complaint and physical examination. Electrocardiogram, 24-h dynamic electrocardiogram, and echocardiogram were performed to evaluate cardiac defects. Cataracts were diagnosed by slit-lamp examination. Sleep disturbances were found through inquisition. Abdominal ultrasound was performed to detect cholelithiasis and cholestasis. Electromyography (EMG) was performed to differentiate neurogenic and muscular damage.

Results
Since 2005, 37 DM1 cases have been identified in Xuanwu Hospital, with definite genetic confirmation of DMPK gene. All patients were enrolled in this study voluntarily with informed consent. All of the patients were Chinese, 14 of which had a family history consistent with an autosomal dominant mode of inheritance, whereas 23 were identified as sporadic cases. Twenty-seven patients were males and ten females. The median age of onset was 21.5 years old, with a range from 3 to 45 years old. For each patient, the size of the CTG expansion determined by TP-PCR was more than 100 repeats.

Among the primary symptoms present at the onset, myotonia appeared in 23 cases (23/37) and muscle weakness was observed in nine cases (9/37). In addition, eight cases complained of alalia, dysacusis, forehead hair loss, and daytime sleepiness at onset.

With the progression of the disease, other signs and symptoms gradually appeared. Weakness appeared in all 37 cases and lasted the entire clinical course. The weakened muscle groups, listed from most to least common, include: distal limb muscles, facial muscles, sternocleidomastoid, proximal limb muscles, and tongue muscles. In addition to progressive weakness, some of the patients experienced multi-system manifestations of DM1. Forehead hair loss was observed in 18 patients (18/37). Cardiac defects were found in 13 cases (13/37), and include the following: conduction abnormalities of atrioventricular block (3/37) and right bundle branch block (2/37); arrhythmias (6/37); and structural abnormalities revealed by echocardiogram (3/37). Cataracts were present in 12 patients (12/37). Twelve patients complained of daytime sleepiness (12/37). Cholecystopathy including cholecystitis, cholelithiasis, and gallbladder polyps was noticed in seven cases (7/37). Brain magnetic resonance image revealed leukoaraiosis in six patients (6/37) and atrophy in two patients (2/37). A summary of the main clinical features of multi-system involvement is shown in Table 1.

Discussion
The overall worldwide prevalence of DM1 is estimated to be approximately 8–12/100,000. A lower prevalence of the disease has been shown in China relative to Caucasian and Japanese populations. DM1 is an autosomal dominant disease, but only 14 out of our 37 cases had a family history, while the other 23 cases were sporadic. This may be explained by lower reporting or diagnosis of family history, or a higher prevalence of sporadic DM1 cases in China.

Some studies have suggested that CTG expansion size may be correlated with the severity of clinical manifestation. Due to the technical limitations of TP-PCR, this study did not measure patient expansion size above 100 repeats. All patients in our study had more than one hundred repeats.

DM1 is poorly studied in the Chinese population. This work explores differences between Caucasian and Chinese populations with DM1. Key differences between populations were noted in the variability of presenting symptoms. Muscle weakness and myotonia, cardiac abnormalities, cataracts, daytime hypersomnolence, cholecystopathy, and nervous system involvement are discussed below.

The most common presenting clinical features of DM1 are muscle weakness and myotonia. The skeletal muscles of patients with DM1 typically show myotonia, which accompanies weakness and wasting of muscles in distal limbs, face, and neck (sternocleidomastoid muscle). The pattern of muscle Group involvement in our patients is consistent with previous studies.

Abnormalities in the heart are important clinical features of DM1. Conduction defects are often found on electrocardiography in affected adults, including those without cardiac symptoms. In a Danish study, cardiac involvement was found in 71 patients (55%) and included: (1) conduction abnormalities (45.1%), (2) arrhythmias (15.5%), and (3) structural abnormalities (42.3%). In our study, the prevalence of specific cardiac defects was found in 13 patients and included: (1) conduction abnormalities (13.5%), (2) arrhythmias (16.2%),
Table 1: Main clinical features of 37 myotonic dystrophy Type 1 cases

| Case number | Gender | Age at onset | Cardiac defects | Cataracts | Daytime sleepiness | Cholecystopathy | Magnetic resonance image | Neurogenic damage |
|-------------|--------|--------------|-----------------|-----------|-------------------|-----------------|-------------------------|------------------|
| 1           | Male   | 25           | +               | -         | -                 | -               | -                       | -                |
| 2           | Male   | 35           |                | -         | -                 | -               | -                       | -                |
| 3           | Female | 30           | -               | +         | +                 | Cholelithiasis  | Leukoaraiosis           | +                |
| 4           | Male   | 14           | 10              | -         | AVB               | -               | -                       | -                |
| 5           | Male   | 43           | 2               | -         | -                 | -               | -                       | -                |
| 6           | Male   | 14           | 10              | -         | +                 | -               | -                       | -                |
| 7           | Male   | 3            | 20              | -         | -                 | -               | -                       | -                |
| 8           | Male   | 23           | 4               | -         | -                 | -               | -                       | -                |
| 9           | Male   | 29           | 20              | +         | Structural abnormalities | +     | +                     | Galbladder polyps | Leukoaraiosis |
| 10          | Male   | 18           | 30              | +         | -                 | -               | -                       | -                |
| 11          | Male   | 30           | 4               | -         | -                 | -               | -                       | -                |
| 12          | Female | 32           | 10              | +         | -                 | -               | -                       | -                |
| 13          | Female | 11           | 4               | +         | -                 | -               | -                       | -                |
| 14          | Female | 22           | 20              | +         | -                 | -               | -                       | -                |
| 15          | Male   | 43           | 3               | Structural abnormalities | +     | -                     | Choleystitis | Leukoaraiosis |
| 16          | Female | 5            | 50              | AVB arrhythmias | +     | -                     | -               | -                |
| 17          | Female | 19           | 10              | -         | -                 | -               | -                       | -                |
| 18          | Female | 30           | 19              | +         | AVB               | -               | -                       | -                |
| 19          | Female | 17           | 5               | -         | -                 | +               | -                       | -                |
| 20          | Male   | 14           | 11              | -         | -                 | +               | -                       | -                |
| 21          | Male   | 10           | 7               | +         | +                 | -               | -                       | -                |
| 22          | Male   | 21           | 3               | Arhythmias | -     | -                     | -               | -                |
| 23          | Male   | 15           | 16              | -         | Arhythmias        | -               | -                       | -                |
| 24          | Male   | 15           | 16              | -         | RBBB              | -               | -                       | Leukoaraiosis |
| 25          | Male   | 13           | 20              | Arhythmias | -     | -                     | Cholelithiasis | -                |
| 26          | Female | 45           | 3               | Arhythmias | +     | -                     | -               | -                |
| 27          | Male   | 29           | 13              | Structural abnormalities | -     | +                     | -               | -                |
| 28          | Male   | 15           | 6               | -         | -                 | -               | -                       | -                |
| 29          | Male   | 35           | 20              | RBBB      | +     | +                     | -               | atrophy          |
| 30          | Female | 20           | 10              | +         | -                 | -               | -                       | -                |
| 31          | Female | 21           | 5               | -         | -                 | +               | -                       | -                |
| 32          | Female | 12           | 3               | +         | -                 | -               | -                       | -                |
| 33          | Male   | 20           | 10              | Arhythmias | -     | +                     | -               | Leukoaraiosis |
| 34          | Female | 20           | 22              | -         | -                 | -               | -                       | -                |
| 35          | Male   | 8            | 27              | -         | +                 | -               | -                       | -                |
| 36          | Male   | 23           | 10              | -         | -                 | -               | -                       | -                |

+: That the symptom was observed, -: That the symptom was not observed in the corresponding patient. RBBB: Right bundle branch block, AVB: Atrioventricular block.

and (3) structural abnormalities (8.1%). This decreased rate of both conduction and structural abnormalities ($\chi^2 = 4.6, P = 0.03$) may be due to ethnic variation. A study of affected siblings with DM1 showed familial clustering of cardiac involvement, indicating that factors other than CTG repeat expansion length may play a role in the severity and progression of the cardiac muscle disease.$^{[11]}$ These factors may also be distinct between different ethnicities, leading to different probability of cardiac involvement.

Cataracts are the most recognized eye problem in DM1, the prevalence of which is 85% in Caucasian ethnicity.$^{[19]}$ Lens opacities associated with myotonic dystrophy appear to have a complete hereditary penetrance, i.e., are present in close to 100% of dystrophic patients.$^{[21]}$ However, the cataracts were only present in 32.4% of patients in our study. This is the largest discrepancy in prevalence between our sample of Chinese ethnicity and other studies with Caucasian populations ($\chi^2 = 57.9, P < 0.01$). Most of our patients already had a course of more than 10 years before the detection of cataracts, suggesting a possible association between the formation of cataracts and age of onset/course of disease.

Daytime hypersomnolence is frequently noted in DM1, accompanied with short sleep latency, rapid eye movements at sleep onset, and abnormalities in the hypothalamic hypocretin system.$^{[13]}$ This may be partly attributable to sleep apnea. About 80% of DM1 patients in a French study complained of excessive daytime sleepiness through a case–control clinical interview.$^{[14]}$ In our study, 12 patients complained of daytime sleepiness (32.4%), again less than previous research in Caucasian populations ($\chi^2 = 17.8, P < 0.01$). This
phenomenon may be partly explained by less performance of the polysomnogram in Chinese patients before patients complain the symptom of sleep disturbance.

Cholelithiasis and cholestasis are not infrequent problems of adult patients with DM1. It has been reported that 25–50% of DM1 patients in Caucasian ethnicity have abdominal involvement such as cholelithiasis or gallstones. In our study, the ratio of gallbladder involvement is 18.9%, which is almost consistent with other studies. Despite the frequency of cholecystopathy in DM1, little is known about the underlying mechanism. Delayed emptying of gallbladder due to smooth muscle dysfunction has been implicated, and metabolic disturbances in the production of cholesterol and bile acids may contribute to the development of cholelithiasis.

Minor degrees of cerebral atrophy with progressive focal white matter lesions have been found on imaging studies in adults with DM1. In our study, these symptoms were also observed. Involvement of peripheral nerves in DM1 is debated, and if present it is usually subclinical. It has been reported that 20–46% DM1 patients in Caucasian ethnicity have peripheral neuropathy. One study with 97 Caucasian patients found evidence for peripheral neuropathy in 17% with no association with patient age or duration of neuromuscular symptoms. In our study, the prevalence of neurogenic damage revealed by EMG is 16.2%. However, no marked sensory signs or symptoms were noticed. Similar to cataracts, neurogenic damage was only found in our patients with a disease course of more than 10 years, which suggests that there may be an association with patient age or duration of neuromuscular symptoms in contrast to the above mentioned study in Caucasian population. These conflicting conclusions may be the result of unknown environmental factors of varying multifactorial genotype separate from the DMPK gene.

Conclusion
Most of the reported prevalence data that we listed above were estimated in the Caucasian population. By comparing these data with our study in a Chinese population, we have shown that Chinese DM1 cases may have different clinical characteristics compared with that of the Caucasian cases, particularly in the prevalence of cataracts, cardiac defects, and sleep disturbances. We acknowledge the limitations of our small sample size, and look forward to further research on this subject.

Financial support and sponsorship
This work was supported by the grants from the National Science Foundation of China (No. 81071000), the Beijing Natural Science Foundation Program and Scientific Research Key Program of Beijing Municipal Commission of Education (No. KZZ201410025023), the National Science and Technology Pillar Program during the 12th Five-year Plan Period (No. 2013BAI07B01), and Xuanwu Hospital Foundation Program.

Conflicts of interest
There are no conflicts of interest.

References
1. Ranum LP, Day JW. Myotonic dystrophy: clinical and molecular parallels between myotonic dystrophy type 1 and type 2. Curr Neurol Neurosci Rep 2002;2:465-70.
2. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3′ end of a transcript encoding a protein kinase family member. Cell 1992;69:385.
3. Romeo V. Myotonic dystrophy type 1 or Steinert’s disease. Adv Exp Med Biol 2012;724:239-57.
4. Thornton CA. Myotonic dystrophy. Neurol Clin 2014;32:705-19, viii.
5. Sizhong Z, Hui W, Agen P, Cuiying X, Ge Z, Yiping H, et al. Low incidence of myotonic dystrophy in Chinese Hans is associated with a lower number of CTG trinucleotide repeats. Am J Med Genet 2000;96:425-8.
6. Zhao Y, Ishiura S. Current studies in myotonic dystrophy. Brain Nerve 2014;66:259-64.
7. Griggs RC, Wood DS. Criteria for establishing the validity of genetic recombination in myotonic dystrophy. Neurology 1989;39:420-1.
8. Ashizawa T, Harper PS. Myotonic Dystrophies. Emeryand Rimoin’s Principles and Practice of Medical Genetics. 5th ed. Columbia: 2006. p. 3047-71.
9. Sovari AA, Bodine CK, Farokhi F. Cardiovascular manifestations of myotonic dystrophy-1. Cardiol Rev 2007;15:191-4.
10. Petri H, Witting N, Ersbell MK, Sajadieh A, Dunø M, Helweg-Larsen S, et al. High prevalence of cardiac involvement in patients with myotonic dystrophy type 1: a cross-sectional study. Int J Cardiol 2014;174:31-6.
11. Groh WJ, Lowe MR, Simmons Z, Bhakta D, Pascuzzi RM. Familial clustering of muscular and cardiac involvement in myotonic dystrophy type 1. Muscle Nerve 2005;31:719-24.
12. Eshaghian J, March WF, Goossens W, Rafferty NS. Ultrastructure of cataract in myotonic dystrophy. Invest Ophthalmol Vis Sci 1978;17:289-93.
13. Martínez-Rodríguez JE, Lin L, Iranzo A, Genis D, Martí MJ, Santamaria J, et al. Decreased hypocrein-1 (Orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. Sleep 2003;26:287-90.
14. Yu H, Laberge L, Jaussent I, Bayard S, Scholtz M, et al. Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study. Sleep 2011;34:165-70.
15. Schwindt WD, Bernhardt LC, Peters HA. Cholelithiasis and associated complications of myotonia dystrophica. Postgrad Med 1969;46:80-3.
16. Kornblum C, Reul J, Kress W, Grothe C, Amanatidis N, Klockgether T, et al. Cranial magnetic resonance imaging in genetically proven myotonic dystrophy type 1 and 2. J Neurol 2004;251:710-4.
17. Mondelli M, Rossi A, Maldangini A, Della Porta P, Guzzi AC. Axonal motor and sensory neuropathy in myotonic dystrophy. Acta Neurol Scand 1993;88:141-8.
18. Hermans MC, Faber CG, Vanhoutte EK, Bakkers M, De Baets MH, de Die-Smulders CE, et al. Peripheral neuropathy in myotonic dystrophy type 1. J Peripher Nerv Syst 2011;16:24-9.