Dystrophia myotonica type 1 presenting with dysarthria: A case report and literature review

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Abstract. Dystrophia myotonica (DM) type 1 is an autosomal dominant disorder, caused by a trinucleotide CTG repeat expansion in the 3' untranslated region of the dystrophia myotonica protein kinase *(DMPK)* gene (chromosome 19q13.3). The disorder affects different organ systems, including the skeletal muscles, ocular lens, lungs, heart and gastrointestinal tract, as well as the endocrine and central nervous systems. The skeletal muscles are most frequently involved, whereby the disorder manifests as myotonia, muscle weakness and amyotrophy. However, DM type 1 presenting with dysarthria is rare. The current study presents a case of a 28-year-old male with DM type 1 presenting with dysarthria and associated multifocal hyperintense lesions in the white matter. Although electromyogram measurements identified myotonic discharges in all extremities, a muscle biopsy failed to detect the characteristic pathological features of DM type 1. A lack of a positive family history for DM type 1 also obscured diagnosis. However, genetic analysis detected a single allele in the P12 segment of the *DMPK* gene that included a CTG expansion of 13 repeats and a three-base gradient fragment in the P134 segment that included a CTG expansion of >600 repeats. According to the characteristics of dysarthria, multifocal hyperintense lesions in the white matter, electromyogram measurement results and genetic testing results, a diagnosis of DM type 1 was confirmed.

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Introduction

Dystrophiamyotonica (DM) is a systemic autosomal dominant disorder and follows a progressive, chronic course (1,2). Incidence rates of DM range from 1 in 500 to 3 per 100,000, depending on the population (3). DM affects the skeletal muscles, ocular lens, lungs, heart and gastrointestinal tract, as well as the endocrine and central nervous systems (1,2,4). The clinical manifestations of DM vary, however typical symptoms include myotonia, weakness and atrophy of the skeletal muscles (5,6). Poor sleep quality, fatigue and excessive daytime sleepiness have an important effect on the quality of life of DM patients. Mathieu *et al* (7) proposed that DM mortality rate was 7.3 times higher than that of the normal population, and the average age of death was 53 years old in one 10-year follow-up study. Seventy percent of cases of mortality in DM are associated with cardiorespiratory disorders and there is solid evidence that timely intervention and active monitoring significantly reduces morbidity and mortality, although there is no curative therapy (8).

DM belongs to the RNA-dominant disorders of the family and are autosomal dominant neuromuscular diseases caused by microsatellite expansions (9). Based on the mutations that occur within the DM protein kinase *(DMPK)* gene, DM is categorized as two distinct types: Types 1 and 2 (5). DM type 1 is caused by expansion of CTG triplet repeat in the 3' untranslated region of the *DMPK* gene on chromosome 19q13.3 (5). DM type 2 is caused by the progressive expansion of a CCTG tetramer repeat in *ZNF9*. To date, only a small number of cases of white matter lesions in patients with DM1 have been reported. The current study presents the case of a 28-year-old male diagnosed with DM type 1, who also presented with dysarthria and associated multifocal hyperintense lesions in the white matter. Diagnosis of DM type 1 was confirmed by genetic analysis.

Case report

A 28-year-old man presented with a 6-year history of progressive dysarthria and 2-year history of bilateral hand weakness. The patient was admitted to the Department of Neurology in the First Teaching Hospital of Jilin University (Changchun, China) in December 2014. On admission, the patient underwent

physical examination that revealed exiguous hair, dysarthria, limited movement of the eyes, facial muscle weakness, glossal amyotrophy, bilateral sternocleidomastoid atrophy and left major-thenar amyotrophy. Muscle strength in the hands and muscle tone of all four limbs was decreased and a lack of tendon reflexes was observed in the extremities. Furthermore, bilateral mammary gland hyperplasia was detected. Magnetic resonance imaging (MRI) scans of the brain identified multifocal hyperintense lesions in the white matter of the bilateral parietal and frontal lobes, which were suggestive of demyelination (Fig. 1). The patient complained of a 4-year history of intermittent diarrhea. The patient denied any relevant family history of DM-associated pathologies. Written informed consent was provided by the patient prior to the current study.

Laboratory tests identified elevated levels of progesterone [0.30 nmol/l (normal range, 0.138-2.671 nmol/l)] and luteinizing hormone [9.518 mIU/ml (normal range 1.24-8.62 mIU/ml)], as well as reduced levels of vitamin B12 [107.59 pmol/l (normal range 133-675 pmol/l)]. Creatinase levels, blood routine examination, conventional coagulation parameters, liver and kidney function, pituitary endocrine examination, hypersensitive C-reactive protein level, cortisol urine levels and glycosylated hemoglobin levels were all normal. An electrocardiogram detected first-degree atrioventricular block and ST segment elevation in leads II, III and avf. Electromyography (EMG) identified myotonic discharges in all extremities.

Biopsy of the right bicep muscle was performed according to routine surgical aseptic operation under local infiltration anesthetic. A dose of 5-20 ml of 1% lidocaine (Shanghai Zhaohui Pharmaceutical Co., Ltd.) was used (10). Fresh muscle specimens were placed in tragacanth on a piece of cork and inverted into liquid nitrogen cooled isopentane, shaken gently and removed after 20-30 sec. The muscle was then placed in a cryostat and cut into 6-μm sections at -25˚C. In general, based on the differential expression of isoforms of myosin heavy chains, skeletal muscle consists of four types of muscle fiber: Types I, IIA, IIB and IIX (11). Type I is a slow aerobic metabolism muscle fiber, which contains relatively more mitochondria and cytochromes and has low glycogen content (11). Subsequent hematoxylin stainig at 60˚C for 30-60 sec and eosin staining at room temperature for 1-3 min identified muscle fibers of variable sizes (primarily type I) and some atrophic fibers with an angular shape, observed by electron microscopy (Fig. 2). In addition, necrotic and regenerated fibers were identified, however, there was no evidence of sarcoplasmic reticulum or inflammatory cell infiltration. Enzymatic activity of nicotinamide adenine dinucleotide (NADH) and succinic dehydrogenase (SDH) was assayed by placing the slides in NADH and SDH incubating solution, containing NADH or SDH as a substrate and nitroblue tetrazolium for visualization of reaction for 1 h at 37˚C. NADH staining exhibited small type I fibers and reduced activity of NADH, observed by electron microscopy (Fig. 3).

Glutamyltranspeptidase staining was also performed. Fresh muscle specimens were placed in liquid nitrogen cooled isopentane to be frozen. Muscle tissue specimens were then placed at room temperature (25˚C), relative humidity 70%. The dried frozen sections (6 μm) were stained with hematoxylin for 10-20 min, then rinsed with tap water for 5 min and dried with filter paper. The sections were then placed into a vat dye of Gomori trichrome stain for 10 min at room temperature (25˚C). The sections were differentiated using 0.2% acetic acid for 2 min at room temperature (25˚C). Sections were dehydrated in ascending alcohol solutions. The sections were cleared with xylene and mounted. The results did not reveal ragged red fibers by electron microscopy. In addition, no abnormalities were observed following staining with cytochrome oxidase, Periodic acid-Schiff or Oil red O (staining protocol as described for Gomori trichome stain).

The patient's genetic testing was performed using the fluorescent dye primer polymerase chain reaction (PCR) technique combined with the triple repeat primed PCR (TP-PCR) technique (12). Normal chromosome 19q13 was amplified by routine PCR. PCR products were detected by capillary electrophoresis. Abnormal chromosome 19q13 containing a mutation in the *DMPK* gene was amplified into a series of bands on the gel by TP-PCR, due to presence of the PCR primer sequence within the mutant CTG repeat region (Fig. 4). Genetic analysis detected a single allele in the P12 segment of the *DMPK* gene that included a CTG expansion of 13 repeats (Fig. 5), as well as a three-base gradient fragment in the P134 segment including a CTG expansion of >600 repeats (0-50 repeats; Fig. 6). The results of the genetic analysis were consistent with the pathological characteristics of DM type 1. Thus, the patient was diagnosed with DM type 1 and orally treated with vitamin B1 10 mg, vitamin B12 500 μg and folic acid 5 mg three times a day. The patient was discharged after 4 days of hospitalization. Over a 5-month follow-up period, the patient experienced a marked improvement in muscular function and was able to perform daily activities.

Discussion

DM type 1 is one of the most prevalent hereditary neuromuscular disorders and follows a pattern of autosomal dominant inheritance. It typically affects skeletal and smooth muscle, as well as the endocrine and central nervous systems (5,6,13). The disorder is characterized by progressive myopathy, myotonia and the involvement of multiple organs. Although the pathogenesis of DM type 1 is not fully understood, it is associated with a trinucleotide CTG repeat expansion in the 3'untranslated region of the *DMPK* gene (chromosome 19q13) (13,14).

Previous studies have focused on determining the pathogenetic mechanisms underlying the effects of the trinucleotide CTG repeat expansion on multi-systemic dysfunction (15,16). The CTG triplet repeat expansion in the *DMPK* gene may cause nuclear localization of mutant mRNA. The mutant mRNA may then form RNA foci and sequestration of interacting RNA-binding proteins (15) Toxic repeat RNA sequences may potentially alter the regular expression of genes and the splicing process and may induce the abnormal expression of neuromuscular proteins, resulting in systemic manifestations including myotonia, muscle wasting, weakness and histopathology, cardiac conduction defects, cataracts and insulin resistance (17,18).

DM type 1 is categorized into four distinct clinical forms: Adult-onset, congenital, childhood-onset and late-onset oligosymptomatic (19). The prognosis of DM type 1 is associated with the age of onset (20). Patients with childhood-onset DM typically experience poorer outcomes and have higher mortality

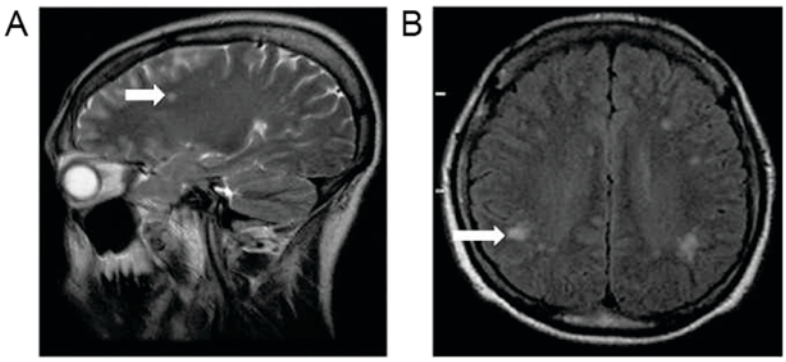

Figure 1. MRI scan of the patient. (A) T2-weighted image and (B) fluid attenuated inversion recovery MRI scan of the brain exhibiting bilateral, multifocal hyperintense lesions (white arrows) in the white-matter of the frontal (left) and parietal (right) lobes. MRI, magnetic resonance imaging.

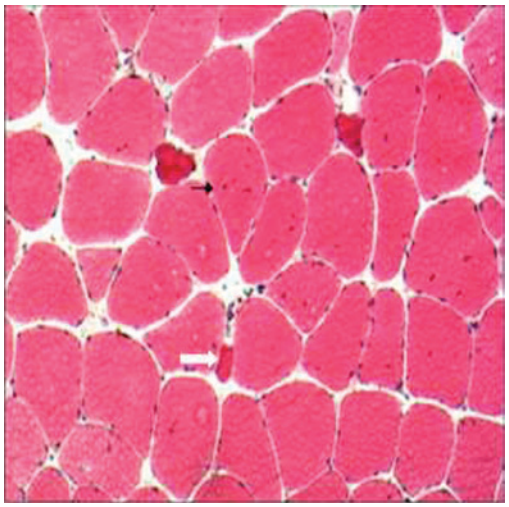

Figure 2. Image of stained right bicep tissue exhibiting muscular fibers of variable sizes and some atrophic fibers with an angular shape (white arrow). Larger internal nuclei of necrotic and regenerated fibers are also visible (indicated by the black arrow). Fibers lack sarcoplasmic reticulum or inflammatory cell infiltration. Magnification, x400. Hematoxylin and eosin staining.

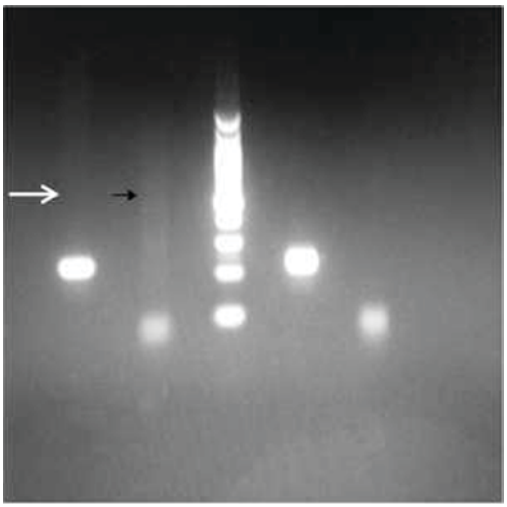

Figure 4. Electropherogram detection of PCR products. Normal chromosome 19q13 was amplified by routine PCR (D1: the products of PCR, white arrow). Abnormal chromosome 19q13 containing a mutation in the dystrophia myotonica protein kinase gene was amplified into a series of bands on the gel by tri-primer-PCR (D2: the products of TP-PCR, black arrow), due to presence of the PCR primer sequence within the mutant CTG repeat region. PCR, polymerase chain reaction.

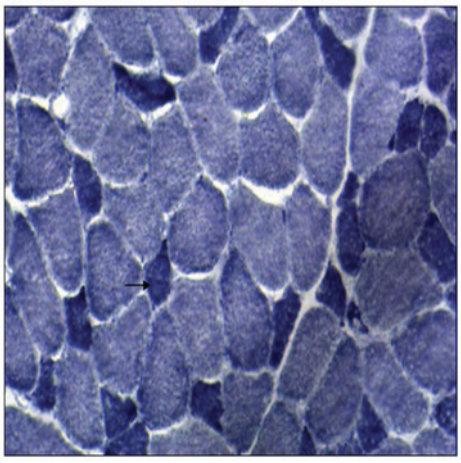

Figure 3. Dihydronicotinamide-adenine dinucleotide staining of the right bicep tissue. Image of stained right bicep tissue exhibiting small type I fibers (black arrow). Magnification, x400.

rates, whereas patients with adult-onset DM generally exhibit a more favorable prognosis (20). Adult-onset DM type 1, as documented in the present report, is the most prevalent form of the disorder (21). The primary clinical manifestations of DM type 1 are myotonia, muscle weakness and amyotrophy of the skeletal muscles. Myotonia is the most frequent symptom and typically manifests as difficulty in actively relaxing the thumb and/or fingers following contraction and may cause hypoventilation in some cases, due to stiffness of the respiratory or throat muscles. Amyotrophy initially affects the hand and forearm muscles but typically progresses to involve the head and facial muscles, and myotonia may present concomitantly with amyotrophy or precede it by a few years (22). The involvement of multiple organ systems may also complicate the pathophysiology of DM type 1 (23). For example, peristalsis in the gastrointestinal tract may become abnormal and potentially lead to abnormal rectum peristalsis, spasmodic colic and delayed emptying of the gallbladder, which ultimately results in cholelithiasis (17). Furthermore, endocrinal involvement in DM type 1 may lead to alopecia, impaired glucose tolerance, genital hypoplasia, sexual dysfunction and menstrual disorders (24). Central nervous system abnormalities observed in

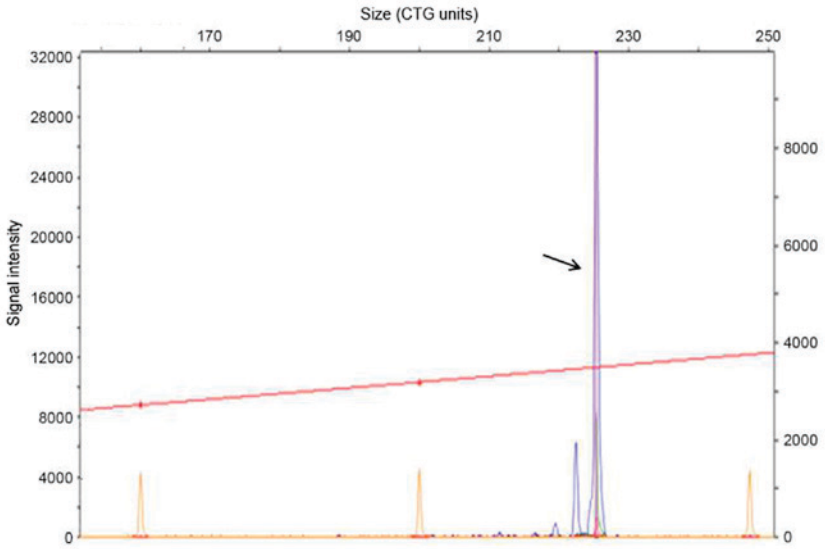

Figure 5. Genetic analysis of the P12 segment. Genetic testing identified a single allele in the P12 segment of the dystrophia myotonica protein kinase gene containing a CTG expansion of 13 repeats (black arrow).

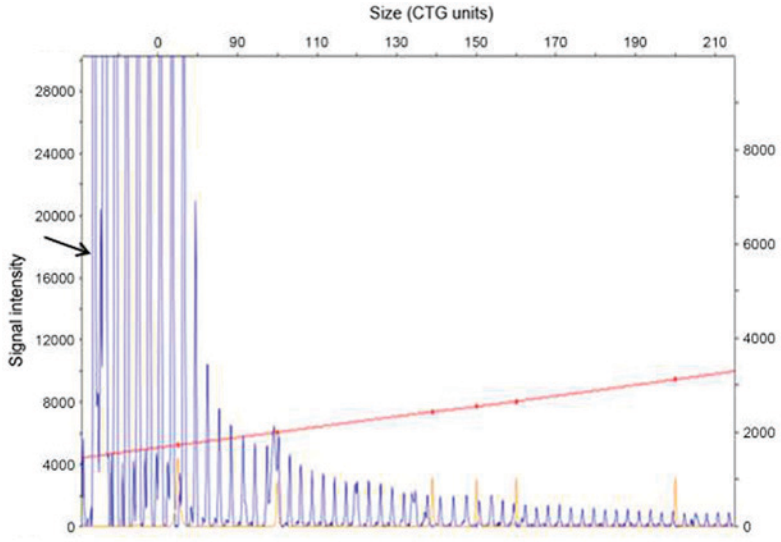

Figure 6. Genetic analysis of the P134 segment. Genetic testing identified a three-base gradient fragment in the P134 segment of the dystrophia myotonica protein kinase gene containing a CTG expansion of >600 repeats (black arrow).

patients with DM type 1 are structural and functional; patients typically present with hypophrenia and somnolence, and brain MRI scans indicate a thickened skull, narrowed sella, encephalatrophy and regional or diffuse white-matter changes (25). In addition, patients with DM type 1 are predisposed to develop cataracts and/or undergo retinal degenerative changes (21).

Diagnosis of DM type 1 is based on a combination of clinical manifestations, family history, EMG results, muscle histopathology and genetic testing. In the present case, the patient presented with chronic, progressive dysarthria, which initially obscured diagnosis. However a few years later, symptoms of myotonia, muscle weakness and amyotrophy became evident. No relevant family history of DM-associated pathologies was noted. A brain MRI scan identified multifocal hyperintense lesions in the white matter of the bilateral parietal and frontal lobes, suggestive of demyelination. As cases of DM type 1 with lesions in the white matter are rare (26), this was an unexpected result. It is not yet universally accepted that there is an association between white matter lesions and the severity of cognitive impairment (27). However, the present results suggest that conducting routine brain MRI scans in all patients with DM type 1 may be useful in diagnosing this disease, even in the absence of clear neurological manifestations.

It is important to differentiate DM type 1 from congenital myotonia (also known as myotonia congenital). There are two forms of congenital myotonia caused by mutations in the chloride voltage gated channel 1 gene located on chromosome 7q35, which encodes the skeletal muscle chloride channel CIC-1 (28). The clinical presentation of congenital myotonia differs from that of DM type 1 in that it is typically accompanied by hypermyotrophy and systemic involvement other than that of the skeletal muscles is uncommon (29).

In the present case report, the patient presented with multiple organ system involvement. Endocrinal involvement manifested as exiguous hair and bilateral mammary gland hyperplasia, whereas smooth muscle involvement was indicated by a 4-year history of intermittent diarrhea, potentially related to decreased gastrointestinal peristalsis and emptying. The ECG also identified a first-degree atrioventricular block and the brain MRI scan confirmed the presence of multifocal white matter lesions. The clinical symptoms in the present case were atypical. Although EMG identified myotonic discharges in all the extremities, a muscle biopsy failed to identify the characteristic pathologies of DM type 1. The absence of a family history of DM type 1 further inhibited the diagnosis. However, genetic analysis ultimately confirmed the diagnosis of DM type 1, indicating the value of genetic analysis as a diagnostic tool.

There are limited therapeutic options available for patients with DM type 1. Previous studies have indicated that membrane-depressant drugs, including phenytoin sodium and carbamazepine, may alleviate the symptoms of myotonia by promoting the activity of sodium pumps, leading to a reduction in intramembranous sodium concentration and an increase in resting membrane potential (30,31). In addition, physical training may aid the maintenance of normal muscle functions (22). Cardiac arrhythmia is a primary cause of mortality in patients with DM type 1 and thus requires stringent monitoring during treatment. Cataracts associated with DM type 1 may be treated using conventional surgical strategies. In patients that exhibit endocrinal involvement, lifestyle changes, such as diet and exercise (8), are generally adequate to relieve symptoms. Recent progress in the understanding of the underlying molecular mechanisms involved in myotonic dystrophy have generated new approaches for DM type 1. Thus, future therapeutic strategies may employ gene therapy to treat genetic disorders such as DM.

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