A CASE REPORT ON MYOTONIC DYSTROPHY AND LITERATURE REVIEW

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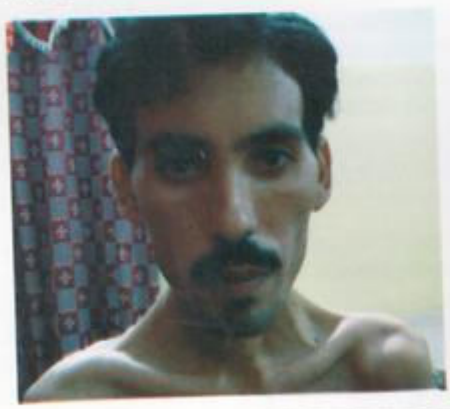
INTRODUCTION

Myotonic dystrophy (MD) was first diagnosed by Steinert in 1909. It is also known as myotonia dystrophica, Steinert's syndrome or Curschmann-Steinert's disease. MD is a severe dominant autosomic multi systemic disorder, and the most common and serious form of myotonic dystrophy afflicting adults. MD has an incidence of 1/8000 newborns and a prevalence of 2.1-14.3/100000 habitants[1-4]. The clinical manifestations of MD can range from a late onset presented after 50 years of cataracts, to an extremely severe, often fatal congenital myopathy. DM's heredity is characterized by the existence of anticipation, so that successive generations show the earliest and severest appearances of the illness.

CASE REPORT

A 28 years old young man from Bannu presented to the out patients department with the chief complaints of progressive weakness of both the lower limbs for the last 1 year, and difficulty in releasing his grip of objects which he holds and some degree of dysphagia at times. His past history was insignificant and he was recently married .On general physical examination he was a thin tall young man with wasting of the facial as well as all the limbs muscles. His vitals were stable. Examination of the nervous system showed that he has weakness of the limbs (lower more than upper), reflexes were diminished and plantar was down going. The sensory system was intact. Ophthalmological examination showed early faint cortical opacities.

His FBC, Renal functions, ESR, Liver function tests, serum Electrolytes, ECG and Echocardiography were normal. EMG study showed electrophysiological evidence which were consistent with the diagnosis of Dystrophia Myotonica. He was counseled about the nature of the illness and advised family screening.



DISCUSSION

Myotonic dystrophy (DM) is a clinically and genetically heterogeneous disorder. There are two major forms:

- DM1, for a century known as Steinert's disease
- DM2, recognized in 1994 as a milder version of DM1.

The prevalence of DM is 1 in 8000 in the general population, but the proportions of myotonic dystrophy caused by DM1 and DM2 are unknown. These autosomal dominant conditions are among the most common forms of adult-onset muscular dystrophy. However, DM is more than simply a muscular dystrophy per se, since affected individuals may show cataracts, cardiac conduction abnormalities, infertility, and insulin resistance. Furthermore, there is a severe congenital form of DM1 with marked developmental disability. One consequence of the multi systemic nature of this disorder is that individuals affected by DM1 or DM2 may first present to internists, cardiologists, ophthalmologists, endocrinologists, and pediatricians (in the case of DM1), before they see a neurologist.

GENETICS

The genetic heterogeneity of myotonic dystrophy was apparent by 1992, when genetic testing became available for myotonic dystrophy type 1 (DM1). This has turned out to be the most common form of the disorder[1-5].

- DM results from an expansion of a CTG trinucleotide repeat in the 3'-untranslated region of the Dystrophia Myotonica protein kinase gene (DMPK gene) on chromosome 19q 13.3[1-5].
- Individuals with repeat size between 35 and 49, designated premutation status or mutable normal, are asymptomatic.
- Longer repeats, in the range of 100 to 1000, are seen in individuals with the classic myotonic dystrophy phenotype (onset between 12 and 30 years of age) with muscle wasting and weakness, myotonia, cataracts, baldness, and cardiac conduction defects. In these patients, average lifespan is reduced.
- With CTG repeat length in the range of 500 to 2700, myotonic dystrophy may manifest at birth with infantile hypotonia, – so-called congenital myotonic dystrophy. Most patients with congenital DM1 have >1000 CTG repeats

PATHOPHYSIOLOGY

Myotonic dystrophy provides an example of a novel mechanism of disease.

- In myotonic dystrophy type 1 (DM1), the expanded trinucleotide repeat is located in the 3'-untranslated region of the DMPK gene, and also happens to be located within the promoter region of another gene, Six5.
- In myotonic dystrophy type 2 (DM2), the expanded tetranucleotide repeat is located within the first intron of the ZNF9 gene.

Current understanding of the pathophysiology of this disease posits what is known as a "trans" effect, in which the repeat expansions exert a dominant toxic effect on other genes not localized to either the DM1 or DM2 loci. This effect is mediated by two RNA-binding protein families[6,7].

- Muscleblind-like (MBNL)
- CUG-BP- and ETR-3-like-factors (CELF)

CLINICAL FEATURES

Myotonic dystrophy type 1 (DM1) and type 2 (DM2) are similar in that both are multisystem disorders characterized by skeletal muscle weakness and myotonia, cardiac conduction abnormalities, cataracts, testicular failure, hypogammaglobulinemia, and insulin resistance.

However, DM2 is generally a less severe disease than DM1. In addition, there are congenital, juvenile, and adult onset forms of DM1, whereas adult onset (typically in the fourth decade) is the most common presentation for DM2[8]. Nevertheless, there is a wide range of symptom onset in DM2 for myotonia (range 13 to 67 years, median 30) and weakness (range 18 to 66 years, median 41)[9].

Skeletal muscle weakness — In DM1, weakness occurs most frequently in facial muscles, levator palpebrae superficialis, temporalis, sternocleidomastoids, distal muscles of the forearm, hand intrinsic muscles (leading to compromised finger dexterity), and ankle dorsiflexors (causing bilateral foot drop). Less commonly, weakness occurs in the quadriceps, respiratory muscles, palatal and pharyngeal muscles, tongue, and extraocular muscles. Muscles of the pelvic girdle, the hamstrings, and ankle plantar flexors are relatively spared in most cases of DM1[10,11]. Weakness of thigh, hip flexor, and extensor muscles frequently impairs the ability to arise from a squat, arise from a chair, or climb stairs[8]. Facial weakness may occur in DM2, generally in later stages of the disease, involving approximately 13 percent of patients over age 50 in one study[9]. However, facial weakness is not as prominent in DM2 as it is in DM1.

Muscle pain

Muscle pain is a very common symptom in DM1. It does not clearly parallel myotonia, and in fact is more common in the legs, where myotonia cannot be demonstrated[12].

The muscle pain and stiffness of DM2 have been likened to those of fibromyalgia. In one study of 63 randomly selected patients diagnosed with fibromyalgia, the DM2 mutation was identified in two (3 percent)[13].

Myotonia

Myotonia is a slowed relaxation following a normal muscle contraction. Most patients with myotonic dystrophy do not describe symptoms referable to the myotonia (unlike patients with myotonia congenita), and those who do often refer to it as muscle stiffness.

Myotonia is most prominent in the early stages of the illness, is aggravated by cold and stress, and is seen most consistently in facial, jaw, tongue, and hand intrinsic muscles[12]. Myotonia is universally present in DM1, whereas myotonia is found in 75 percent of patients with DM2[9]. Myotonia is also more pronounced and relatively more constant in severity in DM1 than DM2. Myotonia varies in DM2, with patients reporting being free of symptoms for days or weeks[8]. As a clinical sign, myotonia is often best appreciated in the hand and fingers.

Gastrointestinal tract involvement

In DM1, smooth muscle involvement is more common than in other muscular dystrophies and manifests particularly with gastrointestinal (GI) symptoms such as colicky abdominal pain, constipation, diarrhea, and pseudo-obstruction[14]. Irritable bowel-like symptoms (abdominal pain, bloating, and changes in bowel habits) are common in DM1. Upper GI tract involvement is seen in most patients with classic DM1 and leads to dysphagia with resulting aspiration pneumonia, an important cause of morbidity and mortality in DM1.

Cardiac abnormalities

DM1 and DM2 are associated with both cardiac conduction disturbances and structural heart abnormalities, which are potential causes of early mortality. While there is some risk of sudden death from cardiac arrhythmias in DM1[15-18] and DM2[19], the magnitude of this risk is not easily quantified based on the available data, which consists mainly of small observational studies. A comprehensive review of DM1 found that atrial flutter and fibrillation were the most common arrhythmias; ventricular arrhythmias were less common but represented major management problems[20].

Conduction disturbances

Electrocardiographic (ECG) abnormalities are common in patients with DM1[15-19] Atrioventricular and intraventricular conduction disturbances are the most frequent abnormalities, indicating that the His-Purkinje system bears the brunt of the disease, with consequent prolongation of the PR interval and QRS complex[20].

- First degree atrioventricular block in 20 to 30 percent
- Bundle branch block in 10 to 15 percent
- Atrial flutter and atrial fibrillation in 2 to 11 percent, with a smaller proportion experiencing ventricular and supraventricular tachycardia

Respiratory function and sleep abnormalities

Respiratory complications are common in DM1, and stem from pharyngoesophageal weakness, weakness and myotonia of respiratory muscles, and a cerebral abnormality of control of respiration[10], suggesting an alteration of central respiratory drive. Weakness of respiratory muscles leads to a diminution in vital capacity and causes alveolar hypoventilation. Respiratory failure may occur, sometimes precipitated by general anesthesia because of heightened sensitivity to sedatives, anesthetics, and neuromuscular blocking agents[21].

Endocrine abnormalities

Primary hypogonadism (low-serum testosterone, elevated serum FSH concentration, oligospermia, and infertility), testicular atrophy, and associated oligospermia or azoospermia with infertility are common problems in DM1[22] and less common in DM2[8].

Insulin hypersecretion is another common finding in patients with DM.

Hyperhidrosis of the hands and trunk is prominent in most individuals with DM2[8]. Premature, male-pattern frontal balding is seen in both DM1 and DM2.

Peripheral and cranial neuropathy

Several reports suggest that patients with myotonic dystrophy can develop an axonal sensorimotor polyneuropathy[23,24], and that this manifestation is independent of underlying glucose intolerance[25].

Congenital myotonic dystrophy

The congenital form of myotonic dystrophy, which is only seen as part of DM1, is characterized by profound hypotonia, facial diplegia, poor feeding, arthrogryposis (especially of the legs), and respiratory failure. Affected infants have a characteristic "V" shape of the upper lip that results from facial diplegia. Myotonia is not usually present in the first year of life, and electrical myotonia is rare. Respiratory involvement is common and is the leading cause of death in the neonatal period. Mechanical ventilation is required for 80 percent or more of patients[26]. With intensive support, most infants survive the neonatal period, but the overall mortality rate is approximately 15 to 20 percent, and approaches 40 percent in severely affected infants[26]. It is not uncommon for an adult (typically the mother) to be diagnosed with myotonic dystrophy only after giving birth to an affected neonate, underscoring the potential for subclinical presentation of this disorder.

Juvenile myotonic dystrophy

The symptoms of this childhood form of DM1, with onset of symptoms before the age of 12, typically reflect the involvement of systems and organs other than skeletal muscle; these include cognitive deficiency, difficulty with speech (dysarthria) and hearing, poor coordination, and rarely, postoperative apnea[27]. Serious cardiac rhythm disturbances may occur in asymptomatic adolescents with no or only subtle signs of myotonic dystrophy. Sports and physical exercise precipitate arrhythmias in over one-half of these patients. Fewer than 10 percent of patients have clinical evidence of a cardiomyopathy and heart failure.

Cognitive impairment

Neonates with DM1 myotonic dystrophy develop cognitive dysfunction in a pattern consistent with mental retardation[28].

DIAGNOSIS

The diagnostic process begins with the clinical impression that myotonic dystrophy might account for the presenting symptoms and signs. The clinical diagnosis of one of the myotonic dystrophies can be readily established when there is muscle weakness and clinical myotonia in the setting of a positive family history.

Genetic testing — Specific genetic testing to demonstrate the presence of an expanded CTG repeat in the DMPK gene is the gold standard for the diagnosis of DM1. It is appropriate to begin the confirmatory laboratory testing with genetic analysis and omit electrodiagnostic studies when there is a strong clinical suspicion for the diagnosis of DM1.

Electromyography — Electromyography (EMG) is an important test in the evaluation of patients suspected of having a myopathic disorder and specifically, one of the myotonic dystrophies. It is useful for demonstrating the presence of myotonia. Electrical myotonia may also be encountered in non-dystrophic myopathies[29]. These include:

- Myotonia congenita
- Hyperkalemic periodic paralysis
- Paramyotonia
- Adult onset acid maltase deficiency

Muscle biopsy

Muscle biopsy in DM1 and DM2 is notable for pathologic alterations, including a marked increase of internalized nuclei (arrayed in chains in longitudinal section

Other investigations

- Electrocardiography (ECG) is critically important, not only to provide support for the diagnosis of myotonic dystrophies, but for the recognition and characterization of asymptomatic cardiac conduction defects.
- Creatine kinase concentration may be mildly to moderately elevated in both DM1 and DM2, and g-glutamyltransferase level is often increased in DM2, but these tests do not have a definitive role in the diagnostic process other than raising the index of suspicion that a myopathic disorder may be present.
- Slit lamp examination may reveal the characteristic posterior subcapsular cataracts, which are detectable as red and green iridescent opacities.
- Serum immunoglobulin studies will typically disclose IgG and IgM hypogammaglobulinemia in both DM1 and DM2[12]. As evidence of male hypogonadism, follicle-stimulating hormone (FSH) is elevated while testosterone levels may be low-normal or decreased.

TREATMENT

Only symptomatic treatment can be provided. Whatever symptomatic improvement can be achieved for the patient's dysphagia and respiratory difficulties will substantially.

Improve his or her quality of life. Cardiac arrhythmias may necessitate Pacemaker placement. Orthopedic procedures to correct abnormal postures should be resorted to sparingly, as they generally do not improve function. The myotonia itself can be very disturbing in the early stage of the disease. It can often be ameliorated With antiepileptic and antiarrhythmic drugs such as phenytoin 100mg t.i.d., quinidine sulfate 1–1.5 g/day, or procainamide 0.5–1.0 g q.i.d. These medications can be dangerous, as they may worsen an intracardiac conduction abnormality.

SUMMARY AND RECOMMENDATIONS

- Myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) are multisystem disorders characterized by skeletal muscle weakness and myotonia, cardiac conduction abnormalities, cataracts, testicular failure, hypogammaglobulinemia, and insulin resistance. Although estimates vary, excessive daytime sleepiness is found in about one-third of patients with DM1.
- Patients with DM2 have symptoms due to proximal muscle weakness, particularly of the hip girdle muscles. In general, DM2 is a less severe disease than DM1. There are congenital, juvenile, and adult onset forms of DM1, whereas only an adult onset form of DM2 is recognized.
- The congenital form of myotonic dystrophy, which is only seen as part of DM1, is characterized by hypotonia, poor feeding, and respiratory failure.
- The symptoms of the juvenile form of myotonic dystrophy (DM1) typically reflect the involvement of systems and organs other than skeletal muscle. The nonskeletal muscle manifestations of DM1 include cognitive deficiency, difficulty with speech (dysarthria) and hearing, poor coordination, or rarely, postoperative apnea.
- DM1 results from an expansion of a CTG trinucleotide repeat in the 3'-untranslated region of the DMPK gene. DM2 is caused by an expanded CCTG tetranucleotide repeat expansion located in intron 1 of the ZNF9 gene.
- The pathophysiology of myotonic dystrophy is incompletely understood, but the leading theory is that the CUG and CCUG RNA repeat expansions mediate a dominant effect on other genes not localized to either the DM1 or DM2 loci by altering RNA binding protein activity. This in turn results in altered splicing and abnormal function of several genes, including the skeletal muscle chloride channel, the insulin receptor, and cardiac troponin T. Skeletal muscle chloride channel dysfunction is responsible for the myotonia.
- The diagnosis of myotonic dystrophy can usually be made clinically in a patient with the characteristic presentation and a positive family history. Genetic testing for an expanded CTG repeat in the DMPK gene is the gold standard for confirming the diagnosis of DM1. Testing for the CCTG repeat in the ZNF9 gene is appropriate if DM1 testing is negative. Electromyography will usually demonstrate the presence of myotonia if this has not been found clinically or if uncertainty persists regarding its presence or absence on examination.
- There is no disease-modifying therapy available for the treatment of myotonic dystrophy. Treatment is symptomatic.

PROGNOSIS

Among patients who develop symptoms in young adulthood, more than half will become disabled from work at a young age. Most die between the ages of 45 and 50. The course of the disease, however, is highly variable. Persons with mild forms may attain old

age with no more serious problem than a cataract. Patients and their relatives should undergo genetic counseling, whenever possible, before they marry and have children.

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