CASE STUDY: MYOTONIC DYSTROPHY

A 49-year-old lady with a sad, lifeless sleepy expression and inability to walk

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CASE PRESENTATION

Madam P, 49-year-old housewife, was admitted to SGH FMCC on 1/3/2008 with a fever of 38 degrees Celsius and left leg swelling for the past 2 days. She did not experience any pain. Clinical features are consistent with cellulitis of the left leg and she was treated with antibiotics.

During the clinical ward round, Madam P was noted to have a hatchet look (sad, lifeless and sleepy expression). She was also unable to walk and was wheelchair bound, without any history of trauma. Further questioning revealed that she had progressive lower limb weakness since her 30s. She was initially investigated in the 1970s at Tan Tock Seng Hospital. She had a muscle biopsy done and she was told that she had "muscle weakness". She subsequently defaulted from follow up. Madam P married at the age of 27-year-old, delivered her first baby at age 31. She underwent a caesarian section at Mount Elizabeth Hospital as she was unable to push out her baby. Since then, over the decades, she noticed progressive lower limb weakness, resulting her being unable to stand from the sitting position for the last 4 years.

SFP 2008; 34(2): 58-61

PAST MEDICAL HISTORY

She had a past medical history of:

- Lower limb swelling and wound debridement for narcotizing fascitis in May 2002 at SGH. On reviewing the anesthesia charts she was noted to have a prolonged recovery period after the anesthesia[8,9].
- Chronic duodenal ulcer diagnosed via oesophago-duodenoscopy (OGD) in 2002. She underwent triple therapy with resolution of symptoms.
- Post RIA hypothyroidism for Grave's Disease in the 1980s.
- Left lower limb deep vein thrombosis in 1989.

CLINICAL EXAMINATIONS

On examination, she had a left lower limb swelling with a fluctuant mass 3x3 cm over the previous old debridement scar, accompanied with surrounding erythema and swelling. Tinea pedis was present in between web space of the left third toe.

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Her cardiovascular, respiratory, and abdominal examination was unremarkable. She had a blood pressure of 110/75 mmHg, pulse rate 90 per min, and respiratory breaths 15 per min. Clinically, she was afebrile and there was no pallor of the conjunctiva. Madam P was orientated to time, place, and person. She was noted to have frontal balding and dysarthria.

Neurologically, her pupils were equal and reactive to light. She had bilateral 7th lower motor neuron lesions accompanied weakness and bilateral ptosis. Her range of eye movement was normal. There were no cerebellar signs. Motor power was 4/5 for her upper limbs and 2/5 for her lower limbs. Her sensation and proprioception were intact. No reflexes were elicited for both her upper and lower limbs including reinforcement. Her jaw jerk was present. There was no winging of her scapular. Plantars were down going for both her lower limbs. Percussion myotonia was present.

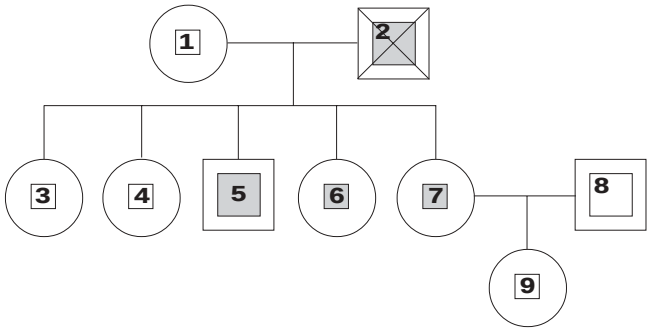
SOCIAL HISTORY

Madam P does not smoke nor drink. She is wheelchair bound. At home, she moves around the floor on a plate with rollers. Madam P is unemployed and currently stays with her disabled brother and sister. Her mother is the main caregiver. She is separated from her husband. Her house has no lift landing and has only squatting toilets.

FAMILY HISTORY

Legend

1: Madam P's mother (asymptomatic) now in her 80's
2: Madam P's late father, died in his 50s (symptomatic but intelligent)
3: Youngest sister, aged 44 years (asymptomatic)
4: Second youngest sister, aged 47 years (asymptomatic)
5: Madam P's brother, aged 53 years (symptomatic and intellectually challenged)
6: Third youngest sister, aged 48 years (symptomatic and intellectually challenged)
7: Madam P, currently aged 49 years (symptomatic but intelligent)
8: Madam P's husband, in good health
9: Madam P's 19-year-old daughter, her genetic destiny = ?



Questions

1. **Based on the above history and clinical examinations, what is the diagnosis?**
   a. **Myotonic dystrophy**
   b. **Becker muscular dystrophy**
   c. **Emery-Driefuss dystrophy**
   d. **Limb-girdle muscular dystrophy**
   e. **Congenital muscular dystrophy.**
2. **What is the pattern of inheritance?**
   a. **Autosomal recessive**
   b. **Mutifactorial**
   c. **Sex-linked recessive**
   d. **Autosomal Dominant**
   e. **Sporadic.**

CASE DISCUSSION

Madam P has Myotonia Dystrophy. This autosomal dominant disorder is among the most common forms of adult onset muscular dystrophy. However, it is more than simply a muscular dystrophy per se, since affected individuals may show cataracts, cardiac conduction abnormalities, infertility, and insulin resistant. As a consequence of its multisystemic nature, affected individuals can be presented to the family physician and different specialists before they are diagnosed.

Madam P was referred to neurologists who suggested nerve conduction study, electromyography and genetic counselling. Nerve conduction study of right upper and lower extremities showed borderline low CMAPs (compound muscle action potential amplitudes). Needle electrode examination of multiple muscles showed abundant myotonic potentials in all muscles tested.

TREATMENT AND MANAGEMENT IN THE WARD

Madam P was treated for left lower limb cellulites with oral antibiotics. The infection started to clear on the 7th day and she was given a total of 14 days of antibiotics. Miconazole cream was applied to her fungal infection in between her toes.

Madam P was referred to the occupational therapist and physiotherapist. She wished to be able to stand and walk again. However, these professionals felt that it may be more realistic and functional to aim for transfer and wheelchair mobilisation. As she had upper limb weakness that impaired her transfers, they felt that she might benefit from rehabilitation at the community hospital for upper and lower limb strengthening and transfer training.

Genetic counselling accompanied with relevant blood investigations was arranged at National Neuroscience Institute (NNI) after counselling was given to patient and her 19-year-old daughter.

The following investigations was done during admission:

Investigations	Results		Normal values
Creatine Kinase	34	U/L	38-164
Aldolase	5.9	U/L	2.0-12.0
Protein	57	G/L	62-82
AST	59	U/L	15-33
ALT	48	U/L	7-36
Albumin	28	G/L	37-51
Bilirubin, Total	12	UMOL/L	3-24
Alkaline Phosphatase	122	U/L	32-103
Hemoglobin	13.0	G/DL	12-16
WBC	9.8 $x10^9$/L		4.0-10.0
Platelets	259 x 10^9/L		140-440
ESR	33	MM/HR	3-15
CRP	106	MU/L	0.2-8.8
Gamma GT	97	U/L	7-39
Glucose fasting	4.9	MMOL/L	3.9-6.0
Free Thyroxine	10.3	PMOL/L	9.6-19.1
TSH	4.14	MU/L	0.36-3.24
Urine protein	Negative		
Blood cultures	Negative		
Electrocardiogram	Normal sinus rhythm		
Chest X-Ray	Normal		

TOPIC DISCUSSION: MYOTONIC DYSTROPHY[1]

Myotonic Dystrophy is also known as Dystrophica Myotonica (DM). The condition is composed of at least two clinical disorders with overlapping phenotypes and distinct clinical molecular genetic defects: Myotonic Dystrophy type 1 (DM1), the classic disease originally described by Steinert, and Myotonic Dystrophy type 2 (DM2), also called Proximal Myotonic Myopathy (PROMM).

Clinical Features

The clinical expression of Myotonic Dystrophy varies widely and involves many systems other than muscle. Affected patients have a typical hatchet faced appearance due to temporalis, masseter and facial muscle atrophy and weakness. Frontal balding is characteristic of men with the disease. Neck muscles, including the flexors and sternocleidomastoids, and distal limb muscles are involved early. Weakness of the wrist extensors, finger extensors, and intrinsic hand muscles impairs function. Ankle dorsiflexor weakness may cause foot drop. Proximal muscles remain stronger throughout the course, although preferential atrophy and weakness of quadriceps muscles occur in many patients. Palatal, pharyngeal, and tongue involvement produce a dysarthric speech, nasal voice and swallowing problems. Some patients have diaphragm and intercostals weakness, resulting in respiratory insufficiency[5,6].

Myotonia, which usually appears by the age of 5, is demonstrable by percussion of the thenar eminence, the tongue and the wrist extensor muscles. Myotonia causes a slow relaxation of the handgrip after a forced voluntary closure. Advanced muscle wasting makes myotonia more difficult to detect[7].

Cardiac disturbances occur commonly in patients with DM1. ECG abnormalities include first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur[5,10]. Congestive heart failure occurs infrequently, but may result from cor-pulmonale secondary to respiratory failure. Mitral valve prolapse also occurs commonly. Other associated features include intellectual impairment, hypersomnia, posterior subscapular cataracts, gonadal atrophy, insulin resistance, decreased esophageal and colonic motility.

Congenital myotonic dystrophy is more severe form of DM1 and occurs in approximately 25% of infants of affected mothers. It is characterised by severe facial and bulbar weakness, transient neonatal respiratory insufficiency, and mental retardation.

DM2, or PROMM, has a distinct pattern of muscle weakness affecting mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur, but are less common, and the hatchet face and frontal baldness are less consistent features. A very striking difference is the failure to identify a congenital form of DM2.

Laboratory Features

The diagnosis of Myotonic Dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present in most cases. Muscle biopsy shows muscle atrophy, which selectively involves type 1 fibers in 50% of the cases. Typically increased numbers of central nuclei can be seen. Necrosis of muscle fibers and increased connective tissue, common in other muscular dystrophies, do not usually occur in myotonic dystrophy.

Genetic Considerations

DM1 and DM2 are both autosomal dominant disorders. New mutations do not appear to contribute to the pool of affected individuals. DM1 is transmitted by an intronic mutation consisting of an unstable expansion of CTG trinucleotide repeats in a serine-threonine protein kinase gene (named DMPK) on chromosome 19q13.3. In general the severity of DM1 type phenotype correlates with the number of CTG repeat size, but there is considerable variability:

- Individuals with repeat size of 35 to 49 are asymptomatic.
- Mutations of 50 to 150 CTG is associated with mild disease, typically characterised by cataracts and mild myotonia[2,3].
- Longer repeats in the range of 100 to 100 are seen in individuals with classical myotonia (onset between the age of 12 to 50) with muscle weakness, wasting, myotonia, cataracts, cardiac conduction defects. The life span of these patients may be reduced.
- With CTG repeat length of 500 to 2,700, the Myotonic Dystrophy will manifest at birth with infantile hypotonia, respiratory distress and mental retardation.

The unstable triplet repeat in Myotonic Dystrophy can be used for prenatal diagnosis. Congenital disease occurs almost exclusively in infants born to affected mothers[4]; it is possible that sperm with greatly expanded triplet repeats do not function well.

DM2 has been linked to chromosome 3q13.3-q24. At this locus, a DNA expansion mutation consists of a CCTG repeat in intron 1 of the *ZNF9* gene. The gene is believed to encode an RNA binding protein expressed in many different tissues, including skeletal and cardiac muscle. In DM2 there is no definite correlation between repeat length and disease severity[2].

How the DNA expansion in DM1 and DM2 impairs function of the muscle and other cells is not well understood. They may alter expression of an adjacent protein kinase gene (DM1), inactivate an important RNA binding protein (DM2), or influence other neighboring genes. In both DM1 and DM2, the mutant RNA appears to form intranuclear inclusions composed of aberrant RNA.

Treatment

The myotonia in Myotonic Dystrophy rarely warrants treatment. There is no disease modifying therapy available, treatment is symptomatic. Phenytoin is the preferred agent for the occasional patient who requires an antimyotonic drug; other agents, particularly quinine and procainamide, may worsen cardiac conduction[7, 11]. Cardiac pacemaker insertion should be considered for patients with unexplained syncope or advanced conduction system abnormalities with evidence of second-degree heart block, or trifascicular conduction disturbances with marked prolongation of the PR interval. Molded ankle-foot orthoses help prevent foot drop in patients with distal lower extremity weakness.

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