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MYOTONIC DYSTROPHY IN A PAKISTANI FAMILY: A CASE SERIES AND LITERATURE REVIEW

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ABSTRACT:

INTRODUCTION:
Myotonic dystrophy also known as (Steinert's disease) is a clinically and genetically heterogeneous multisystem disorder with a prevalence of 1 in 8000 in the general population. It is inherited as an autosomal dominant trait. It is characterized by myotonia, myopathy of voluntary and involuntary muscles, frontal baldness in men, cardiac conduction abnormalities, cataracts, intellectual deterioration and endocrinopathies. Affected men may have gonadal atrophy and infertility. On the other hand women are generally fertile. We report a case series of three individuals belonging to the same family presenting with characteristic features of myotonic dystrophy. The presentation of these cases depicts that this disease can lead to disability, loss of independence and social isolation especially in the elderly. They warrant adequate work up for diagnosis which may sometimes be extensive. Proper genetic counseling of the family is required regarding nature of the disease and with risks and prognosis.

KEY WORDS: Myotonic dystrophy; Autosomonal dominant; Myotonia

INTRODUCTION: Myotonia is defined clinically as the occurrence of "delayed relaxation of muscle after voluntary contraction or percussion."[1] It may be apparent from the first handshake, presenting with a delayed release of the hand. Myotonic dystrophy is a clinically and genetically heterogeneous multi-system disorder with a prevalence of 1 in 8000 in the general population inherited as an autosomal dominant trait.[1] It is characterized by myotonia, myopathy of voluntary and involuntary muscles, frontal baldness in men, cardiac conduction abnormalities, cataracts, intellectual deterioration and endocrinopathy. Men with this disorder have often gonadal atrophy and infertility. On the other hand women are generally fertile. During pregnancy their myopathy worsens, often causing severe obstetrical complications.[2] Peri-natal mortality rate is 15-16% as compared to 1.9% in the near normal population and mainly accrediting to congenitally grieved fetuses together with complications occurring in pregnancy.[3] Their children may develop congenital form of the disease with signs of myopathy in utero and have great difficulties in maintaining life functions after birth, together with other characteristic signs of this form: bilateral facial weakness, severe hypotonia, feeding difficulties, talipes equinovarus and mental retardation. Electromyography (EMG) findings often becomes a key element in the diagnosis. Myotonic potentials which are waxing and waning in characteristic are commonly recognized on needle EMG. Genetic tests are available for many of these disorders, although in some cases they are only available in specialized laboratories. The goals of treatment is to focus on managing the complications of the disease, particularly those relating to the cardiopulmonary system as these account for 70% of the deaths.[4] Our patients were conservatively managed with Oral Phenytoin 100mg twice daily with physical rehabilitation as the mainstay of management. They are under regular follow up with dose-dependent improvement of symptoms & no apparent drug toxicity at any of the reported dosages.

CASE PRESENTATION

CASE 1: A 48 year old married male with no co-morbidities presents to our neurology department

with progressive muscle stiffness, difficulty in hand gripping and generalized fatigue for three months. His leg muscles appear very stiff at the initiation of walking but stiffness alleviates with continued activity. The effect lasts about five minutes. There is no history of backache, spine trauma, sphincteric involvement, dysphagia, dysarthria, shortness of breath, cyanosis or blurring of vision. He is a shop keeper by occupation with two children. He denies cigarette smoking or alcohol use. Family history is significant for similar complaints in his mother,younger brother and his son (Figure A). On physical examination he has frontal baldness, a narrow and elongated hatchet-shaped face with a transverse smile. There is bilateral ptosis with masseter and temporalis wasting. Diffuse calf muscle hypertrophy is seen in legs. Cranial nerves are normal. Percussion myotonia (on the right abductor pollicis brevis muscle), tongue and grip myotonia is positive. Tone is normal. Muscle power of the Medical Research Council (MRC) grade is 5/5 in both upper and lower limb muscle except bilateral handgrip which is of MRC grade 4/5. Reflexes are absent in upper and lower limbs with a flexor plantar response bilaterally. Sensory system is normal. Gait and coordination is intact. Rest of the systemic examination is unremarkable.

CASE 2: An 11 year old boy was well till the age of five years with normal developmental milestones started to experience difficulty in running and playing at school, difficulty in handgrip and poor intellect. Her teachers complained of him being lazy and having a poor school performance. He is the son of case 1 (Figure A). On physical examination he has frontal baldness, a narrow and elongated hatchet-shaped face with a transverse smile. There is bilateral ptosis with masseter and temporalis wasting. Diffuse calf muscle hypertrophy is seen in legs. Cranial nerves are normal. Percussion myotonia (on the right abductor pollicis brevis muscle), tongue and grip myotonia is positive. Tone is normal. Muscle power of the Medical Research Council (MRC) grade is 5/5 in both upper and lower limb muscle except bilateral handgrip which is of MRC grade 4/5. Reflexes are absent in upper and lower limbs with a flexor plantar response bilaterally. Sensory system is normal. Gait and coordination is intact. Rest of the systemic examination is unremarkable.

CASE 3: A 44 year old un-married male with no co-morbidities presents with muscle stiffness usually beginning in the muscles of the hands, feet, neck and face for two years, which aggravates in cold weather. Whenever he starts to speak his tongue seemed stiff and he had difficulty in pronouncing words but it gets better after sometime. He is the younger brother of case 1 (Figure A). On examination he has frontal baldness, a narrow and elongated hatchet-shaped face with a transverse smile. There is bilateral ptosis with masseter and temporalis wasting. Diffuse calf muscle hypertrophy is seen in legs (Figure B). Cranial nerves are normal. Percussion myotonia (on the right abductor pollicis brevis muscle), tongue and grip myotonia is positive. Tone is normal. Muscle power of the Medical Research Council (MRC) grade is 5/5 in both upper and lower limb muscle except bilateral handgrip which is of MRC grade 4/5. Reflexes are absent in upper and lower limbs with a flexor plantar response bilaterally. Sensory system is normal. Gait and coordination is intact. Rest of the systemic examination is unremarkable. All three cases underwent basic laboratory testing including serum levels of vitamin D, calcium, aldolase, creatine phosphokinase and thyroid hormones, which are normal. Echocardiography is unremarkable. Nerve conduction studies (NCS) is normal. EMG shows myopathic motor units with decrease amplitude and rapid recruitment along with typical 'waxing and waning' pattern consistent with myotonic discharges resembling a dive bomber sound. Muscle biopsy of the left rectus femoris shows fragments of skeletal muscle with focal area of fibrosis.
Genetic testing was not done due to lack of availability and financial constraints.

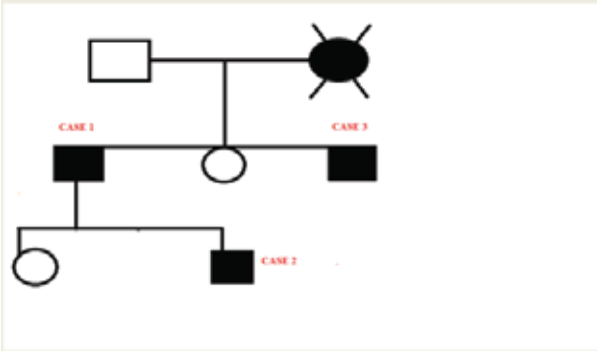

Figure A: Family pedigree showing an 'Autosomal dominant inheritance'

CASE 1
CASE 2
CASE 3

Figure B: Calf Muscle Hypertrophy

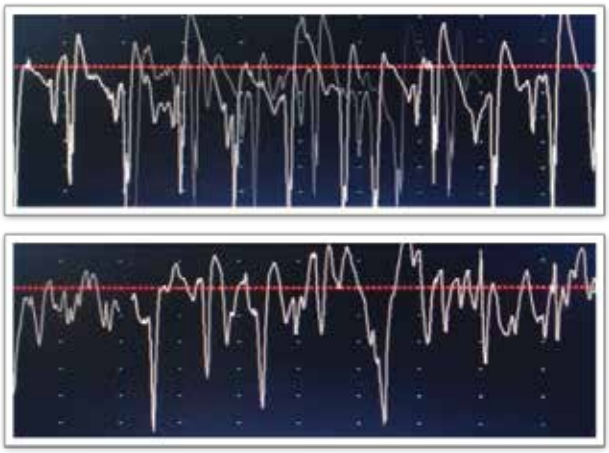

Figure C: Myopathic Motor Units With Myotonic Discharges Showing A Typical Waxing And Waning Pattern On Needle Electromyography

Discussion:

Myotonic dystrophy type 1 is caused by a genetic defect composed of an expansion of cytosine-thymidine-guanine (CTG) repeats, resulting in a defect of the dystrophia myotonica protein kinase (DMPK) gene on chromosome 19 with a reduction of DMPK messenger RNA expression.[5] Individual disorders exhibit distinct phenotypes with identifiable clinical features. Prenatal genetic testing is available for pregnancies at risk by analysis of DNA extracted from fetal cells obtained by amniocentesis at 15 to 18 weeks gestation, or chorionic villus sampling at 10 to 12 weeks gestation.[5] Additional historical detail, a brief physical examination and EMG characteristics are likely to provide the correct diagnosis or to suggest further investigations ruling out other neuromuscular disorders with myotonia e.g muscle channelopathies (paramyotonia congenital, sodium channel myotonia, hyperkalemic periodic paralysis), metabolic myopathies (Acid maltase deficiency, McArdle disease, Debrancher deficiency), toxic myopathies secondary to drugs (chloroquine, hydroxy chloroquine, statins, colchicine), endocrine myopathies (hypothyroidism, vitamin D deficiency) & inflammatory myopathies (polymyositis and dermatomyositis). There is no disease-modifying therapy available for the treatment of myotonic dystrophy. Thus, treatment is symptomatic. The systemic (non-neurological) manifestations can be better treated. Recommendations regarding management are based more on consensus and clinical experience than on evidence from randomized controlled trials. Ankle-foot orthoses are helpful in preventing foot-drop and enhancing gait stability. Muscle pain can be a persistent and troubling symptom. Pharmacologic agents that may be effective for this problem include nonsteroidal anti-inflammatory drugs, gabapentin, tricyclic antidepressants, mexiletine and low-dose glucocorticoids, such as oral prednisone 5 mg on alternate days.[6] The clinical experience of treating myotonia has involved a variety of medications,including phenytoin , mexiletine , procainamide , propafenone , flecainide, and carbamazepine, all of which are sodium channel blockers and share the potential to increase weakness while reducing myotonia.[7] In two small seven-week double-blind randomized controlled trials involving patients with DM1, treatment with mexiletine (at either 450 mg or 600 mg daily, both given in three divided doses) was superior to placebo for improvement in grip relaxation time. Mexiletine was well-tolerated in these trials and was not associated with any serious adverse effects or cardiac conduction abnormalities.[8] Modafinil was evaluated in two trials that included a total of 60 adults which suggested that modafinil was modestly beneficial for the treatment of daytime sleepiness in these patients.[9] When sedation is necessary, use of a short acting agent such as propofol, and avoidance of long-acting sedatives such as the benzodiazepine and short-acting muscle relaxants such as atracurium are preferable to succinylcholine to minimize muscle activation.[10] These patients are particularly susceptible to the respiratory depressant effects of benzodiazepines, barbiturates, anesthetics and opioids, so they should be used with caution. Also, while on statins there should be close monitoring of statin dose, potential myopathic symptoms, and serum creatinine kinase levels. Statin use should be abandoned in favor of another lipid management strategy if an increase in statin-related muscle symptoms and signs develop.[11] It is critical to assess the quality of sleep in such patients probing for whether there is nocturnal restlessness, unexplained awakenings, and loud snoring punctuated by

occasional awakenings and gasping for breath, all of which should suggest the presence of a sleep-related respiratory disorder and lead to further study with a poly somnographic evaluation that will reveal a more specific diagnosis.[12] Noninvasive positive airway pressure ventilation (NIPPV) may be very helpful in correcting sleep apnea, improving hypoventilation, and assisting diaphragm weakness. Bilevel positive airway pressure ventilation (BiPAP) is better tolerated by patients with weakness of the chest wall and diaphragm who cannot overcome expiratory forces. Swallowing assessment is an important part of the management of these patients as dysphagia is a risk factor for aspiration pneumonia and poor nutrition.[13] Assessment by gastroenterology specialists may also be helpful. Intestinal pseudo-obstruction has been reported in patients with myotonic dystrophy[13]; it may be severe enough to require either a temporary or permanent ileostomy. In these patients electrocardiograms at least once a year should be done to screen for cardiac conduction disturbances. When arrhythmias are suspected clinically but are not detected on standard ECG,a 24-hour ambulatory ECG monitoring is suggested. Guidelines from the American College of Cardiology and American Heart Association (ACC/AHA) recommend pacemaker placement for third-degree or advanced second degree atrioventricular (AV) block in patients with myotonic dystrophy.[14] Slit-lamp examination to detect cataracts is appropriate at the time of diagnosis and periodically thereafter, as dictated by symptoms in both DM1 and DM2 patients. In the congenital form of DM1, cataracts are uncommon before the age of ten.[15] We started our patients on Oral Phenytoin 100mg twice daily with physical rehabilitation as the mainstay of management. They are under regular follow up with dose-dependent improvement of symptoms & no apparent drug toxicity has been seen at any of the reported dosages. Although evidence is limited, life expectancy appears to be reduced for patients with DM1 of childhood or adult onset with respiratory and cardiac diseases being the most common causes of death.[16] Younger age of onset, more severe muscle weakness, and cardiac arrhythmia may be associated with an increased risk of death.[17] The complex manifestations of DM1, including neuromuscular, behavioral, emotional, and cognitive disturbances, contribute to suboptimal education levels, employment problems, and diminished income when compared with the general population, and accordingly compromise the daily activities and social roles of these patients.

CONCLUSION

Myotonic dystrophies warrant adequate work up for diagnosis which may sometimes be extensive. Proper genetic counseling of the family is required regarding nature of the disease and with risks and prognosis. Behavioral therapy and physiotherapy is required to prevent social dependence.
to show a significant difference in this regard. It was interesting to note that a multivariate logistic regression model used to assess the simultaneous influence of clinical, radiological and operative variables on the outcomes highlighted the importance of GCS as a critical factor to influence need for post-operative ventilation in these patients.

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Haris Majid Rajput; data collection, data analysis, manuscript writing, manuscript review
Zakir Jan; data analysis, manuscript writing, manuscript review
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