A Case of Friedreich's Ataxia

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6th year Medicine

INTRODUCTION

M is a sixteen year old girl admitted electively for multidisciplinary review of Friedreich's Ataxia (FA), hypertrophic obstructive cardiomyopathy (HOCM), kyphoscoliosis and peripheral neuropathy. The following history was obtained from M, with collateral information from her father.

HISTORY OF THE PRESENTING COMPLAINT

M's parents and teachers noticed progressive clumsiness and stumbling from the age of six years and a diagnosis of FA was made on the basis of 'nerve tests' in 1994 when she was seven. M was then referred to a Dublin paediatric hospital for confirmation of the diagnosis and further specialist investigation.

M began using a wheelchair when she was eight and has used it full-time since the age of ten. In 2001 M obtained an electric wheelchair, which she now uses most of the time. She cannot stand, walk, or transfer from her wheelchair unaided. M is left-handed but over last two months has begun to find it difficult to feed herself and guide the electric wheelchair due to weakness & loss of co-ordination in her left arm.

Upon referral to Dublin in 1994, M was diagnosed with HOCM and now suffers from periodic 'muscular' chest pain. Although she currently has no chest pain, her last episode was one week prior to admission. She is always breathless on exertion, but never at rest.

M's kyphoscoliosis has been progressive since the age of eleven but does not restrict her breathing.

Both of M's lower limbs are affected by a peripheral sensory neuropathy, the left more so than the right. M has a good foot care regime, assisted by her parents.

PAST MEDICAL HISTORY

M has Type 1 diabetes mellitus (Type 1 DM) which was diagnosed at the age of four years. She currently uses Humalog insulin via subcutaneous pump. M also has hypothyroidism, which was diagnosed at the age of 14 years and is asymptomatic on thyroxine replacement therapy.

M has presented to A&E with diabetic ketoacidosis (DKA) on three occasions , twice in 2002 and once in February 2003. She was subsequently admitted twice for regulation of blood glucose levels. M was also admitted to hospital for three days in early 2003 with chest pain; her parents were told it was 'muscular'.

M has suffered multiple fractures since late childhood, none of which have required admission or surgery. All involved falls due to ataxia.

BIRTH, DEVELOPMENTAL AND SCHOOL HISTORY

M's mother had an uneventful pregnancy and she was born at full term weighing 8lb 6oz (3.78kg). Delivery was by caesarean section due to foetal distress during labour. M was not admitted to the special-care baby unit and went home with her mother after three days.

M walked at thirteen months of age and her father considers her development to have been normal. She progressed normally at preschool and in junior and senior infants, having no gross motor, fine motor or speech and hearing difficulties.

M is now in her fifth year in a mainstream secondary school. Her mother brings her to and collects her from school every day. M is absent from school for approximately 3-4 weeks per term due to illness and hospital admissions. She has many friends at school and socialises with them every weekend.

NUTRITIONAL, IMMUNISATION AND SOCIAL HISTORY

M was breast fed and was introduced to solids at the age of six months. She now eats a diabetic diet but does not use the diabetic exchange method as she has a subcutaneous insulin pump in situ. M's father cannot remember all the immunisations that she received but does not recall any being missed. She remembers receiving the rubella vaccine during her second year at post-primary school.

M's parents are married and live with M and her sister. Her father does not work and her mother is a factory supervisor. Neither parent smokes. The family lives in a bungalow that has been adapted to facilitate M's wheelchair.

M does not smoke. She drinks approximately 4 units of alcohol at the weekend but does not use recreational drugs.

FAMILY HISTORY & GENETICS

Both a maternal and a paternal aunt have Type 1 DM, as does M's younger sister. A paternal aunt has cerebral palsy. All maternal and paternal aunts and uncles underwent chromosomal karyotyping to determine whether they were carriers of the abnormal gene responsible for Friedreich's Ataxia. None were found to carry the

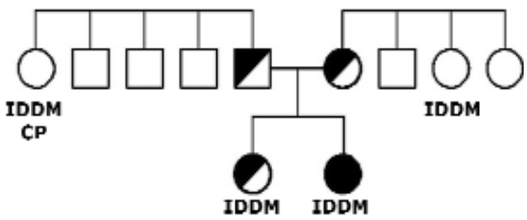

Figure 1: M's Family Pedigree.

gene.

All immediate family members have received extensive genetic counselling and M's sister is aware that if she decides to have children her partner's karyotype should be tested to ascertain whether he too is a carrier of the FA gene. There is no family history of cerebrovascular, cardiac or thyroid disease.

DRUG HISTORY

M is on Humalog insulin that is delivered via a subcutaneous pump system. The line is changed every three days by M and her parents and the dose is adjusted in accordance with dietary intake, exercise and infection. M also takes Eltroxin (thyroxine) 200mg nocte and Brufen (ibuprofen) as required (for pain associated with kyphoscoliosis). She takes no non-prescription drugs and has no known drug allergies.

SYSTEMS REVIEW

At the time of the history M felt well, with a good appetite and no recent weight loss. She had had no recent headaches, faints or double vision and has never had a seizure.

M suffers from periodic chest pain. The latest episode was one week prior to admission, lasted a day and was similar in nature to the pain which prompted her admission to hospital earlier this year. She is always breathless on exertion but not at rest and at the time had no other upper or lower respiratory tract symptoms, dizziness or palpitations.

M stated that her hips click painfully when getting in and out of her wheelchair or her bed. In addition, her kyphoscoliosis causes pain on prolonged sitting. M attends physiotherapy once a week.

Although M is continent of both urine and faeces she requires assistance in getting from her wheelchair to the toilet. She did not complain of abdominal pain, vomiting, diarrhoea or constipation and has no frequency, urgency or dysuria. Her menarche was at the age of thirteen and she now has a regular twenty eight day cycle with bleeding for four days.

EXAMINATION

M measured 170cm in height and weighed 65.2kg. Pulse rate was 73 bpm, respiratory rate was 16, blood pressure was 119/76 mmHg and temperature was 39.6^{o}C. She looked well and was alert, orientated and sitting up in bed. Her upper body movements were ataxic and her speech was dysarthric.

Cranial nerve examination was normal except for bilateral jerky horizontal nystagmus. In the upper limbs there was bilateral pyramidal drift. There was wasting of the small muscles of both hands and of the proximal muscles of the left arm. Tone was normal bilaterally. There was slight weakness of the left arm (grade 3-4 out of 5). Power in the right arm was good (grade 4 out of 5). Light touch sensation was normal in all dermatomes (C4 to T2) with no pain or tingling. Vibration sense was normal and there was normal proprioception at the distal interphalangeal joint of both thumbs. There was marked dysdiadochokinesis and bilateral past-pointing. Upper limb reflexes were absent (biceps C5, supinator C6, triceps C7).

M's feet were cold but colour was normal bilaterally and all pedal pulses were present. There was some wasting of the small muscles of the foot bilaterally, bilateral pes cavus deformity and cocking of the toes. Tone was normal in the lower limbs but power was decreased bilaterally (grade 4 out of 5 – slight weakness). There was loss of light touch sensation on the anterior aspect of the tibia (L4, L5) and lateral aspect of the foot (S1) bilaterally. In addition there was loss of proprioception in the distal interphalangeal joint of the first toe bilaterally. Bilateral lower limb ataxia was present and M was unable to perform the heel-shin test on either side, with eyes either open or closed. Deep tendon reflexes were absent (knee L3,L4; ankle S1, S2) and there was an extensor plantar response bilaterally (L5, S1, S2).

M had a pronounced kyphoscoliosis. However, there was normal chest expansion and good air entry bilaterally. Heart sounds one and two were normal, with no added sounds or murmurs present. A subcutaneous insulin pump was in situ in the left periumbilical region.

SUMMARY

M is a 16 year old girl who was admitted electively for a multidisciplinary review of Friedreich's Ataxia, to include investigation of existing cardiomyopathy, kyphoscoliosis and peripheral neuropathy. Over the last two months her left arm has become increasingly weak, with loss of co-ordination. M also suffers from Type 1 DM and hypothyroidism.

M is unable to walk and uses an electric

wheelchair. Findings of note on neurological examination were dysarthria, nystagmus, small-muscle wasting of hands and feet and wasting of proximal left arm muscles. There was weakness, loss of co-ordination and absence of deep tendon reflexes in all four limbs. There were extensor plantar responses bilaterally. Sensation was diminished in the dermatomes of L4, L5 and S1 bilaterally. There was loss of joint proprioception in both lower limbs.

DIFFERENTIAL DIAGNOSIS

The primary differential diagnosis of monoparesis and loss of coordination of the left arm is of mononeuropathy of the ulnar nerve (C7-T1) due to compression. The ulnar nerve is particularly vulnerable to damage at the elbow.[1] Peripheral neuropathy, possibly with a diabetic component, is clinically present in the patient's lower limbs and probably to a lesser extent in the upper limbs. M is left-handed and as existing neuropathy predisposes to further nerve damage, prolonged amounts of time leaning on the left elbow to control her electric wheelchair could cause M's symptoms.

Progression of ataxia due to increased spinocerebellar degeneration should also be considered in the differential diagnosis. Friedreich's Ataxia is a progressive condition, meaning that continued degeneration of M's spinocerebellar function is expected. However, to date loss of power and co-ordination has been largely symmetrical. In this instance the left side alone is affected.

It is possible that M's symptoms are the result of a focal nerve lesion due to diabetic neuropathy. Diabetic neuropathy is most commonly a symmetrical polyneuropathy but focal neuropathy can occur.[2] M is young to have developed clinical diabetic neuropathy but the risk is higher given her background history of neuromuscular degenerative disease and poor diabetic control. However, M's blood glucose control has been much improved for the last twelve months.

In cases of monoparesis, a stroke should form part of the differential. A lacunar infarct in the middle part of the internal capsule's posterior limb can produce pure motor hemiplegia ('ataxic hemiparesis'). A stroke involving the cerebellum could produce co-ordination loss.[3] Cardiomyopathy may predispose to hypoxic or ischaemic damage to the cerebral cortex although damage is usually mild.[4] As the onset of symptoms in this case has been gradual, a stroke is unlikely to be the cause.

PROPOSED MANAGEMENT

Patients with unexplained monoparesis and loss of co-ordination should undergo nerve conduction tests. The symptoms should be observed to identify any deterioration or improvement. M should be advised to reduce time spent leaning on her left elbow and possibly try to control her wheelchair with her right hand for a time to see if this brings about an improvement in her symptoms.

As M has been admitted for review of HOCM, an echocardiogram should be performed and compared with previous reports to identify any progression of cardiomyopathy. An electrocardiogram should be obtained to look for T-wave changes characteristic of HOCM.

Kyphoscoliosis can be assessed by a scan to assess the degree of antero-posterior and lateral curvature of the spine. Pulmonary function tests can be used to determine whether air entry is restricted. An evaluation of overall severity of the deformity and its impact on respiratory function will allow the team to see if it is severe enough to benefit from surgical intervention.

A physiotherapy review should include limb use, activities of daily living, joints, exercises and assessment of the pes cavus deformity.

M's diabetes should also be reviewed. Her blood glucose recordings should be reviewed, as should her HbA_{1C} level. As M is using the subcutaneous method of insulin delivery, the adequacy of doses should be considered and a dietician review obtained. Blood pressure and serum cholesterol levels are simple but important investigations in any diabetic patient. M reports a good foot-care regime but this should be reassessed and appropriate advice offered.

Urinalysis is necessary to rule out asymptomatic urinary tract infection. Psychological support for the patient and family is important and may especially be required given M's poor diabetic control in the past. Thyroid function tests should be performed to assess M's hypothyroidism. A coeliac screen may be appropriate given the existing diagnoses of diabetes mellitus and hypothyroidism.

FRIEDREICH'S ATAXIA

Friedreich's Ataxia (FA) was first described by the German physician Nikolaus Friedreich (1825-1882). He published a series of papers on the condition between 1861 and 1876.[5]

Epidemiology

The prevalence of Friedreich's Ataxia is thought to be one to two per hundred thousand of the population.[2]

Genetics

Friedreich's Ataxia is an autosomal recessive spinocerebellar degenerative disease. This means that once a couple have one affected child, the subsequent risk of another affected child is 25%. The risk of a subsequent child being a carrier (as in this case) is 50%.

The ataxia results from a mutation of the gene on chromosome 9q that encodes for a protein called Frataxin.[6] This results in spinocerebellar degeneration.

Neuropathology

The ataxia is due to a combination of sensory neuropathy and degeneration of both cerebellar afferent neurons and efferent neurons from the dentate nuclei. Peripheral sensory nerves are also severely affected. M's peripheral neuropathy may be complicated by poor diabetic control. Diabetic neuropathy has a multifocal causation; some focal lesions may be of ischaemic origin, while others are due to the susceptibility of the diabetic nerve to compression.[2]

Diagnostic Criteria (Harding's criteria)[7]

A noticeable omission from Harding's criteria (table 1) is HOCM. However, in some more recent studies over sixty percent of patients have been diagnosed with HOCM.[6]

Clinical Features

Onset typically occurs before 20 years of age and usually between 8 and 15 years. Late-onset cases have been described.[8]

Gait Ataxia

Presentation is usually with ataxia of gait. This manifests as increasingly slow and clumsy walking.[8] This is typically followed by limb ataxia, dysarthria, distal loss of joint position and vibration sense, upper limb wasting, generalised areflexia, pyramidal lower limb weakness and extensor plantar responses.[1]

Kyphoscoliosis

Kyphoscoliosis and foot deformities such as pes cavus are common. Kyphosis refers to exaggerated forward curvature of the spine, while scoliosis is lateral bowing. Severe kyphoscoliosis may reduce lung capacity and increase the work involved in breathing.[9]

Hypertrophic Obstructive Cardiomyopathy (HOCM)

Cardiomyopathy occurs in most cases of FA and is accompanied by ECG changes, for example widespread T-wave inversion. This is an important aid to the diagnosis of cardiomyopathy.[4]

HOCM is abnormal hypertrophy of the muscle in the left ventricular or right ventricular outflow tract. In FA an echocardiogram (ECHO) will often show normal systolic and diastolic function, typically with concentric hypertrophy of the myocardium. In Friedreich's Ataxia, HOCM usually runs a more benign course than that of the genetic type and arrhythmias are rare.[4]

Symptoms of HOCM include dyspnoea (as in M's case), angina (this may explain M's episodes of chest pain) and syncope. The arterial pulse may be sharp-rising and jerky and the jugular venous pulse may have a prominent a-wave due to forceful atrial contraction against a non-compliant right ventricle. On palpation there may be a double or triple apical impulse. A late systolic murmur at the left lower sternal border may be present on auscultation and a fourth heart sound (S4) may be present. None of these signs were present in this case.[4]

Abnormalities of coronary arteries can also occur in HOCM.[4] M has not had a coronary angiogram but is at high risk given her poorly controlled Type 1 DM.

Table 1. Harding's Criteria

Essential criteria	**Additional criteria** (present in 2/3 or more)	**Other features** (present in less than 50% of cases)
Onset before 25 years of age	Scoliosis	Nystagmus
Autosomal recessive inheritance	Pyramidal weakness of lower limbs	Optic atrophy
Ataxia of limbs and gait	Absent upper limb reflexes	Deafness
Absent knee and ankle jerks	Loss of vibration and joint position sense in the legs	Distal muscle wasting
Extensor plantar responses	Abnormal ECG	Diabetes
Motor conduction velocity greater than 40m/s	Pes cavus	
Small or absent sensory nerve action potentials	Cardiomyopathy	
Dysarthria within 5 years of onset		

Type 1 Diabetes Mellitus (Type 1 DM)

Ten percent of patients with FA will develop Type 1 DM. In M's case, however, diabetes appears to be a coincidental finding; she presented with diabetes three years before the onset of her first symptoms of Friedreich's Ataxia and a maternal and a paternal aunt, who are not carriers of the abnormal FA gene, also suffer from Type 1 DM.

Life Expectancy

Most patients with FA will die before the end of their 4th decade. Harding et al found the average age of death to be 37.7+/- 14.4 years, with a range of 21 to 69 years.[10] Death occurs from cardiac origin in 5% of cases.[4] In others, respiratory restriction due to kyphoscoliosis ultimately leads to death.

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