Case Report:

Friedreich's Ataxia with Diabetic Ketoacidosis

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Abstract:

Friedreich's ataxia (FRDA) is autosomal disease in which 98% patients have causative mutation as an expansion of a guanine–adenine–adenine (GAA) tri nucleotide repeat located in the first intron of the frataxin gene on chromosome 9q13. The disease affects central and peripheral nervous systems, heart, skeleton and endocrine pancreas. Ocular, auditory & vestibular dysfunction is uncommon. Here we present a case of FRDA with involvement of nervous system & pancreas leading to diabetes mellitus in 10 yrs old girl child. The child presented with diabetic ketoacidosis.

Introduction:

Friedreich's ataxia (FRDA) is the commonest inherited ataxia (1). It was first described in 1863 by Nikolaus Friedreich, a professor of medicine in Germany. It accounts for at least 50% of cases of hereditary ataxias in most large series. The estimate of incidences ranges from 1 in 22,000 to 2 in 100,000. The incidence of FRDA in Asians and in those of African descent is very low (2).

In about 98% of patients with FRDA, the causative mutation is an expansion of a guanine–adenine–adenine (GAA) tri nucleotide repeat located in the first intron of the frataxin gene on chromosome 9q13. The mutation causes a defect of transcription, and lack of frataxin, a small mitochondrial protein, is the accepted cause of the entire complex clinical and pathological phenotype of FRDA. The disease affects central and peripheral nervous systems, heart, skeleton, and endocrine pancreas. This is the first disease-causing, autosomal recessive GAA expansion found in an intron. Most autosomal dominant cerebellar ataxias are due to short cytosine- adenine-guanine repeat expansions (CAG expansions) in coding regions. The size of pathological expansion in FRDA is variable, ranging from 90 to 1700 units. Most normal alleles carry 6 to 9 repeats and never exceed 34 repeats.(3,4,5)

Friedreich's ataxia is typically a disease of young people and affects male and females alike. After genetic testing became available in 1996, the clinical spectrum of FRDA expanded greatly, and the inclusion of older patients shifted the age of onset to 15.5±8 years (range 2–51) (6). Age of onset (13±10 years), age of death (40±20 years), and disease duration (26±14 years) reflect the inclusion of older patients as well. Onset at the age of 50 years is now occasionally recognized, and some patients are not diagnosed during life. Children with beginning FRDA may raise concern in parents and teachers because they appear "clumsy" and their motor skills do not match those of unaffected sibs. Scoliosis and foot deformity (pes cavus) may also be early signs and precede ataxia. In some patients, cardiomyopathy is the first clinical manifestation whereas diabetes mellitus is invariably delayed in the course of the illness. The following neurological signs are most frequent: Gait ataxia, dysmetria of arms and legs, dysarthria, head titubation, atrophy and weakness of the distal extremities, absence of muscle stretch reflexes, Babinski's sign, loss of joint and vibratory senses, and superimposed stocking-and-glove type sensory neuropathy. Muscle tone is generally normal in the arms but variable in the legs. Spasticity and hyperreflexia in the legs are no longer rare. Nearly all patients become paraplegic and require wheelchairs Diabetes mellitus occurs in 8–32% of FRDA patients and most of them ultimately require insulin. Scoliosis is extremely common in FRDA (60–79%) and is clearly progressive. Advanced technology shows complex oculomotor disturbances, among which abnormal saccades and square wave jerks are characteristic. Optic atrophy is uncommon but some patients become blind. Clinically apparent hearing loss is relatively uncommon though it may be severe enough to cause deafness in approximately 1% of patients. Despite normal pure-tone audiometry, patients with FRDA may have problems with speech perception. A suitable term is "auditory neuropathy / dysynchrony". There is also evidence of vestibular dysfunction.

Diagnosis of Friedreich's ataxia: Diagnosis is made through a complete physical examination and history that may include tests for reflex and sensory responses. Laboratory tests such as an electromyogram (EMG), that measures the electrical activity of muscle and nerve cells may be used to confirm the diagnosis. In addition, the physician may do an electrocardiogram (EKG) to determine if there are abnormalities in the heart beat. Blood and urine tests may be done to check for

problems related to diabetes. X-rays are used as a diagnostic tool if scoliosis is suspected.

As a result of finding the gene Frataxin, accurate diagnostic testing is available for people with FA and their families. Magnetic resonance imaging (MRI) in the diagnosis of FRDA was used before gene testing was available (7, 8), and thinning of the cervical spinal cord was a consistent observation. Atrophy of cerebellum and brain stem was more variable, but in more recent studies (9,10), the images clearly disclosed degeneration of the superior cerebellar peduncles. This finding is not surprising because the superior cerebellar peduncles contain most of the efferent fibers of the dentate nuclei (DN). At high magnetic field strengths, iron-related hypointensity of the DN on T_2-weighted images may be a potential bio-marker of FRDA (11,12).

History and Examination:

A 10 yr old female child, weighing 20 kg, was brought to our casualty with complaints of breathlessness and altered sensorium. Patient was not responding to verbal commands and had hyperpnoea followed by apnoea. Then again restart of respiration, hyperpnoea, apnoea (Kussmaul's breathing) and ketotic breath. On enquiring we came to know that patient is a known diabetic and on insulin 10 U subcutaneous in morning and 8 U in evening. Detailed history suggested onset and diagnosis of Diabetes Mellitus 2 yrs. back ie at the age of 8 yrs. Patient wasn't taking the treatment regularly and this was second time that she got admitted in hospital with similar presentation. Since 2 years she also developed progressive weakness and loss of power in both the lower limbs. Family history was suggestive of elder sibling (female) developing similar complaints at same age and death at the age of 12 years, death being attributed to Diabetic Ketoacidosis (DKA). Patient was a second child born of a 3° consanguineous marriage.

Examination at admission revealed tachycardia with Heart Rate 152/min and tachypnea with Respiratory Rate 30 /min with Kussmaul's breathing. She was moderately dehydrated, hypotensive and had characteristic ketotic breath. Blood Sugar Level (Random) was 435mg/dl (finger strip by glucometer). Urine for Ketones by Dip stick was positive. The patient was thus in diabetic ketoacidosis. Blood Samples were collected and sent for CBC, Electrolytes and Sugar estimation.

Treatment for diabetic ketoacidosis was begun following Milwaukee protocol as under-

- 1st hr 20ml/kg NS bolus with 0.1U/Kg/hr insulin drip
- 2nd hr till resolution of DKA 0.45% NS ml/hr = (85ml/kg + Maintenance – bolus)/23hr
- 20 mEq/L Potassium phosphate and 20 mEq/L Potassium acetate

BSL monitoring was done hourly.

At 250 mg/dl of BSL 5% glucose was started (at 12 hrs after admission)

Serum electrolytes were: Na$^+$ 130 mEq/L, K$^+$ 4 mEq/L, Cl$^-$ 102 mEq/L

Repeat electrolytes at 12 hrs: Na$^+$ 138 mEq/L, K$^+$ 4.5 mEq/L, Cl$^-$ 99 mEq/L

Patient regained consciousness after 28 hrs. Oral intake was stared, insulin drip rate reduced to 0.5U/kg/hr and subcutaneous insulin as 8U in morning and 6U in evening were started. Insulin drip was tapered off and patient gradually shifted to subcutaneous insulin 12U morning and 10U evening.

After regaining consciousness patient was re-examined and was found to have waddling gait (ataxia). Detailed neurological examination revealed gait and limb ataxia, areflexia, loss of vibration and position sense and a progressive motor weakness and pseudoathetosis. Further investigations were done to rule out causes of autosomal recessive ataxias. Ophthalmic examination was done to rule out ataxia telangiectasia. Magnetic Resonance Imaging (MRI) cervical spine was found to be normal. Echocardiography was suggestive of restrictive cardiomyopathy. Molecular Genetic Analysis for Friedreich's ataxia was done (for GAA trinucleotide repeats) and found to be positive for Friedreich's ataxia.

Patient was discharged from the hospital on 10th day after controlling BSL with

subcutaneous insulin 12U morning and 10U evening.

Key Message: Friedreich's ataxia is common disorder with endocrine involvement

also.

Conflict of interest: None

References:

1. Harding A. The hereditary ataxias and related disorders. Edinburgh: Churchill Livingstone, 1984.
2. Pandolfo M, Montermini L. Prenatal diagnosis of Friedreich's ataxia. Prenat. Diagn. 1998;18: 831-3.
3. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: Autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996; 271:1423-27.
4. Durr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia N Engl J Med 1996;335:1169-75.
5. Epplen C, Epplen IT, Frank G, Miterski B, Santos EJ, Schols L. Differential stability of the (GAA) tract in the Freidreich ataxia (STM7) gene. Hum Genet 1997; 99:834-36.
6. Dürr A, Cossée M, Agid Y, Campuzano V, Mignard C, Penet C, et al. Clinical an genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med 1996;335: 1169–75.
7. Wessel K, Schroth G, Diener HC, Müller-Forell W, Dichgans J. Significance of MRI-confirmed atrophy of the cranial spinal cord in Friedreich's ataxia. Eur Arch Psychiatry Neurol Sci 1989; 238: 225–30.
8. Mascalchi M, Salvi F, Piacentrini S, Bartolozzi C. Friedreich's ataxia: MR findings involving the cervical portion of the spinal cord. AmJ Roentgenol 1994;163:187–91.
9. Pagani E, Ginestroni A, Della Nave R, Agosta F, Salvi F, De Michele G, et al. Assessment of brain white matter fiber bundle atrophy in patients with Friedreich ataxia. Radiology 2010; 255: 882–9.
10. Akhlaghi H, Corben L, Georgiou-Karistianis N, Bradshaw J, Storey E, Delatycki MB et al. Superior cerebellar peduncle atrophy in Friedreich's ataxia correlates with disease symptoms. Cerebellum 2010, doi:10.1007/s12311-010-0232-3.

11. Waldvogel D, van Gelderen P, Hallett M. Increased iron in the dentate nucleus of patients with Friedreich's ataxia. Ann Neurol 1999; 46:123–5.
12. Boddaert N, Le Quan Sang KH, Rötig A, Leroy-Willig A, Gallet S, Brunelle F, et al. Selective iron chelation in Friedreich ataxia: biologic and clinical implications. Blood 2007;110:401–8.