wjpmr, 2023,9(11), 220-222

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Case Report

ISSN 2455-3301

WJPMR

A CASE OF FRIEDREICH'S ATAXIA ASSOCIATED WITH DIABETES MELLITUS

Shashikumar V. L.*, Ruchira M.[1], S. Sangeetha[2], Shobha Rani R. H.[3]

[*]Pharm D intern, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, India.
[1]Pharm D intern, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, India.
[2]Assistant Professor, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, India.
[3]Professor and Director, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, India.

***Corresponding Author: Shashikumar V. L.**

Pharm D intern, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, India.

Article Received on 10/09/2023 **Article Revised on 30/09/2023** **Article Accepted on 20/10/2023**

ABSTRACT

Nikolaus Friedreich originally discussed Friedreich's ataxia (FRDA) in 1863. FRDA is a rare, inherited (autosomal recessive), neurodegenerative movement disorder, resulting from a mutation (expanded guanine-adenine-adenine (GAA) triplet repeats) in the frataxin (FXN) gene on chromosome 9q centromere region which presents with ataxic gait, absent tendon reflexes, extensor plantar response (Babinski sign) and positive Romberg test. A 34 years old male patient came with complaints of involuntary movements of head (titubation), tinnitus from 12 years, progressive ataxia of gait, and dysarthria since 8 years since. He is a k/c/o Friedrichs ataxia since 8 years. He have associated newly diagnosed endocrine abnormality diabetes mellitus. No effective treatment for FRDA exists, multiple therapies are being developed to increase frataxin levels, such as protein and gene replacement therapies, antioxidants, iron chelators, and inflammation modulators. Symptomatic treatment can be provided to improve quality of life.

INDEXTERMS: Friedreich ataxia (FRDA), Frataxin (FXN) gene, Extensor plantar response (Babinski sign), Romberg's sign, Trinucleotide repeat (GAA), gait ataxia.

INTRODUCTION

Friedreich's ataxia (FRDA) is a rare, inherited (autosomal recessive), neurodegenerative movement complaint, performing from a mutation (expanded guanine- adenine- adenine (GAA) trinity reprises) in the frataxin (FXN) gene on chromosome 9q centromeric region. It was first reported in 1863 by the German croaker Nikolaus Friedreich.[1]

FRDA affects 1 in 50,000 people in the US, and people of Western European strain are more likely to get it and 1 in 40,000 people worldwide have FA.[2]

Multitudinous essential mitochondrial processes depend on frataxin. It supervises iron, detoxifies iron, and manages iron stocks to maintain iron homeostasis. Iron-sulfur clusters demanded for ATP conflation are produced through its action.[1] Individualities with FA generally have expanded tracts of GAA (guanine-adenine- adenine) ranging from 100 to 1300 reprises in both clones of the FXN gene, with the maturity containing> 400 reprises.[3] The mutation on the frataxin gene silences the gene, limiting the conflation of the frataxin protein. The most susceptible cells to FA are those that produce the most frataxin like neurons, cardiomyocytes, and pancreatic beta cells.[1]

Progressive Ataxia of the box and branches, dysarthria, and muscle weakness are nearly always present. Absent lower branch revulsions, swallowing disturbances, sphincter disturbances, visual disturbances (nystagmus, optical atrophy), Hearing impairment. Depression, cardiomyopathy, diabetes mellitus, scoliosis and pes cavus are complications of friedreich's ataxia.[4]

The gold standard for diagnosing FRDA is molecular testing. The complaint is truly vindicated by testing for expansions or mutations in the FXN (frataxin) gene.[5] There are clinical individual criteria used to help in the opinion of FA, which include Quebec Cooperative study of Friedrich's Ataxia (QCSFA), Harding Criteria. The most generally used is Harding scale criteria.[6]

Cases suspected of having FRDA should have an MRI of the brain and spinal cord, which will show atrophy of the cervical/ thoracic spinal cord and cerebellum. Electrocardiogram can show tachycardia or atrial fibrillation. An Echocardiogram generally shows symmetric concentric ventricular hypertrophy. Auditory

and vision testing also done.[7]

The pivotal advice to brake the complaint's progression and maintain function is physical therapy (PT). Strengthening posture and promoting muscular use are the two main objects of PT.[1] No effective treatment for FRDA exists, multiple antidotes are in clinical trials to increase frataxin, analogous as modulation of fratraxin controlled metabolic pathway, fratraxin relief stabilizers or enhancers and gene relief antidotes.[7] Antioxidants include Coenzyme Q10, Idebenone- A synthetic form of coenzyme Q10. It's a free revolutionary scavenger used in FA to combat free radical damage, Vitamin E (tocopherol), Vitamin B2 (riboflavin) and Vitamin B1, Iron chelators include Deferiprone inflammation modulators like steroids, INF gamma.[1] and Modulation of transcription factor Nrf2, found to be decreased in cells affected in FA, include Nuclear factor-erythroid 2 related factor 2 (Nrf2) activators like Skyclarys (Omaveloxolone) 50mg capsule is recently approved by FDA for treatment of friedreich's ataxia.[8]

CASE REPORT

A 34 years old male weighing 56kg presented to the general medicine department with complaints of involuntary movement of head (titubation), which is insidious onset, progressive in nature, aggravated with emotional distress since 12 years, difficulty in walking, getting up from squatting position and difficulty in talking (Dysarthria) since 8 years, Tinnitus in the bilateral ears since 12 years.

His past medical history revealed that he is known case of depression disorder 17 years back and was on antidepressants, which was advised for 6 months of therapy but patient continued to take it for 5 years. He has been diagnosed as friedreich's ataxia 8 years back, for which he is taking Tab. fluoxetine 20 mg (1-0-0). He has a family history of friedreich's ataxia to his sister and had been diagnosed at the age of 23 years.

On examination his blood pressure was found to be 106/70 mmHg on day 1 and 106/80 mmHg on day 2. The patient was conscious, oriented and lethargic. The respiratory, cardiovascular system were normal and abdominal exam revealed soft, non tendor and free of organomegaly.

His laboratory data suggests, haemoglobin levels were 10.8g/dL (13- 18), hematocrit- 34.6% (40 – 54), mean cell volume - 64.5 fL (83-101), mean cell haemoglobin-20.1pg (27-32), red cell distribution width - 15.6% (11.6-14). Electrocardiogram is normal, there is no conduction block. His urine routine shows glucose present (+++) and random blood glucose was 246mg/dL.

His neurological examinations revealed that, age of onset of FRDA before 25 years, progressive limb and gait ataxia, absent tendon reflexes in the legs, positive Babinski sign (Extensor plantar responses), positive Romberg sign and dysarthria (after 5 years of onset).

Based on his random blood glucose and urine routine examination, he was diagnosed as Diabetes Mellitus. He has anxiety attacks, which are triggered by situations and environmental factors. Mild depression is also present.

His medications in the hospital stay as follows; T. fluoxetine 20 mg (1-0-0) and T. [clonazepam (0.25mg) + propranolol (20mg)] (1/2-0-1/2) for anxiety attacks and Depression. T. metformin 500mg (1-0-0), T. glimepride 1mg (1-0-1) was used to begin the patient's treatment.

On discharge, he was prescribed with T. escitalopram 5mg (0-0-1) instead of T. fluoxetine 20mg, because patient as complaints of somnolence. T. metformin 500mg (1-0-0), T. glimepiride 1mg (1-0-1) to be continued.

He visited for review after 1 month, his functionality was improved, titubation is reduced, and speech is clear compared to the hospital stay. His GRBS was 256 mg/dL. Now T. primidone 25mg (1-0-0) and T. [Sitagliptine (150mg) + metformin (500mg)] (0-1-0) was added to previous medication.

DISCUSSION

FRDA results from a reprise expansion of the trinucleotide GAA (guanine- adenine- adenine) due to mutation in the frataxin gene located in the centromere region of chromosome 9q (9q13- 21.1) in 1988 by chamberlain and associates.[8] While a normal frataxin gene would have 7- 34 reprises, there can be as numerous as 66- 1700 trinucleotide reprises in FRDA.[1] The frataxin gene is responsible for producing frataxin, a protein that helps enzymes demanded for regulate iron stores and it works to produce iron- sulfur clusters needed for ATP product. It's set up in all apkins but produced in advanced attention in the nervous system, heart, and pancreatic beta cells.[5]

Scoliosis is present in roughly two thirds of individualities with FRDA when assessed clinically and 100 when assessed radiographically. A study set up that 49 of 77 individualities with FRDA had scoliosis by Milbrandt et al 2008.[9] Pes cavus is common but generally causes little problem for affected individualities by Frauscher et al 2011.[10] Heart failure from cardiomyopathy is the primary mode of death in 60 of cases with FRDA. In a recent retrospective review, Tsou and associates linked congestive heart failure in roughly 30 of cases dying from FRDA, and slightly lower than 20 of cases had severe arrhythmias contributing to, or causing, death. The cardiomyopathy associated with FRDA is hypertrophic (truly thick ventricular walls) and the heart generally maintains respectable systolic function52 until shortly before death.[11]

Dysphagia is common in FRDA with 92 of

individualities reporting issues with swallowing by Vogel et al 2014.[12] Dysarthria, present in the maturity of individualities with FRDA by Folker et al 2010.[13]

In the current case the patient is 34 years old with k/c/o friedreich's ataxia. The patient has a family history of FA to his sister. His Neurological examinations met the Harding's criteria, that is age of onset is before 25 years, progressive limb and gait ataxia, absent tendon reflexes in the legs, positive Babinski sign (Extensor plantar responses), positive Romberg sign and dysarthria (after 5 years of onset). He is newly diagnosed as diabetes mellitus. Recently Cnop et al, reported that 49% of 41 FRDA patients with no previously diagnosed diabetes had impaired fasting glucose and/ or impaired glucose tolerance. Moreover, 8 to 32% of patients with FRDA are considered to suffer from DM.[14] Confirmation of the genetic diagnosis was not possible in our case, because patient was emotionally not cooperative and financially unstable.

CONCLUSION

Genetic testing is the cornerstone of the evaluation of patients with FA. A trinucleotide repeat expansion assay is available, and FA is the only disease with pathological GAA repeats. A thorough history, comprehensive physical, general examination, neurological examination and laboratory investigations are necessary to know the disease progression. Physiotherapy, antioxidants, coenzyme Q10, Nrf2 activators include Omaveloxolone 50 mg capsule and symptomatic treatment helps to improve patient quality of life.

REFERENCE

1. Williams CT, De Jesus O. Friedreich Ataxia. [Updated 2023 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2023.
2. Zhu D, Burke C, Leslie A, Nicholson GA. Friedreich's ataxia with chorea and myoclonus caused by a compound heterozygosity for a novel deletion and the trinucleotide GAA expansion. Mov Disord, 2002 May; 17(3): 585-9.
3. https://rarediseases.org/rare-diseases/friedreichs-ataxia.
4. Delatycki MB, Corben LA. Clinical features of Friedreich ataxia. J Child Neurol, 2012 Sep; 27(9): 1133-7. doi: 10.1177/0883073812448230. Epub 2012 Jun 29. PMID: 22752493; PMCID: PMC3674491.
5. Koeppen AH. Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. J Neurol Sci., 2011 Apr 15; 303(1-2): 1-12.
6. https://www.physiopedia.com/Friedreich%27s_Ataxia.
7. Pharmacological therapeutics in Friedreich Ataxia: The present state - Scientific Figure on Research Gate. Available from: https://www.research gate.net/figure/Friedre ich- ataxia.
8. Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain, 1981; 104: 589-620.
9. Frauscher B, Hering S, Högl B, Gschliesser V, Ulmer H, Poewe W, Boesch SM. Restless legs syndrome in Friedreich ataxia: a polysomnographic study. Mov Disord, 2011; 26: 302–6.
10. Vogel AP, Brown SE, Folker JE, Corben LA, Delatycki MB. Dysphagia and swallowing-related quality of life in Friedreich ataxia. J Neurol, 2014; 261: 392–9.
11. Bidichandani SI, Delatycki MB. Friedreich Ataxia. 1998 Dec 18. [Updated 2017 Jun 1].
12. Folker J, Murdoch B, Cahill L, Delatycki M, Corben L, Vogel A. Dysarthria in Friedreich's ataxia: a perceptual analysis. Folia Phoniatr Logop, 2010; 62: 97–103.
13. Corben LA, Ho M, Copland J, Tai G, Delatycki MB. Increased prevalence of sleep- disordered breathing in Friedreich ataxia. Neurology, 2013; 81:46–51.
14. Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med, 2004; 82: 510–29.