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Case Report: Friedrich Ataxia Friedreich's Ataxia's Paradigm in Nuclear Family in Northern India

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ABSTRACT

Friedreich's ataxia (FA) is a debilitating neurodegenerative disorder characterized by progressive gait and limb ataxia, dysarthria, and cardiomyopathy. It is inherited as an autosomal recessive disease. Friedreich ataxia (FA) is the most common hereditary ataxia accounting for approximately 50% of all ataxia cases [1,2,3,4]. Unfortunately, symptoms worsen as time progresses, so most people affected by this disease end up requiring mobility aids such as wheelchairs, lose their vision and hearing, and develop other medical complications such as diabetes mellitus and scoliosis. This case report emphasis mainly on the unusual case of ataxia affecting the whole family (both children and mother being Carrier, Father expired due to some chronic medical illness) and detection of the Illness which was affecting them and genetic analysis suggesting of FA. This also reviews the evaluation and management of Friedreich ataxia and highlights the role of the interprofessional team in the care of patients with this condition.

Keywords: Friedreich's ataxia (FA); Vision; Hearing

INTRODUCTION

Friedreich's ataxia, first described by Nikolaus Friedreich in 1863, is an autosomal recessive disorder affecting approximately 1 in 50,000 individuals. It results from GAA trinucleotide repeat expansions in the FXN gene, leading to decreased synthesis of frataxin, a protein essential for mitochondrial function. This deficiency primarily impacts the nervous system and cardiac tissue, beta islet cells of pancreas as the FXN gene products are in excess amount compared to other body parts leading to the various clinical manifestations of the disease. Patients with FA have an abnormal amount of trinucleotide repeats on the frataxin (FXN) gene on chromosome 9[2,3]. The frataxin gene is responsible for producing frataxin, a protein that helps form enzymes needed for mitochondrial adenosine triphosphate (ATP) production and management of iron stores. In FA, the pathological trinucleotide repeats result in

gene silencing and a decrease in frataxin causing disturbance in iron homeostasis and ATP production. The most common cause of death in patients with FA is hypertrophic cardiomyopathy [5,6,7]

CASE

A 12-year-old male from Dehradun, Uttarakhand, Northern India presented with difficulty in walking since the age of 5, which progressively worsened. The patient exhibited persistent fatigue, weakness, and ataxia with a wide-based gait, increased bending posture, decreased hand swinging, and deterioration of speech. The patient had no history of decreased urine output, hematuria, headache, altered sensorium, shortness of breath, fever with rashes, seizures, abnormal body movements, vomiting, loose stools, constipation, falls, loss of consciousness, insect bites, or vision loss. The immunizations were up-to-date. Developmentally, the patient had delayed speech and walking, and was unable to run for the past two years, and was average in academics.

On Examination: Patient was conscious, alert, and active. Physical examination revealed chest atrophy, a lean and thin build, emaciation, bony prominence at the sternal point, scoliosis, and a low posterior hairline. The patient exhibited pallor without cyanosis, icterus, significant lymphadenopathy, or pedal edema.

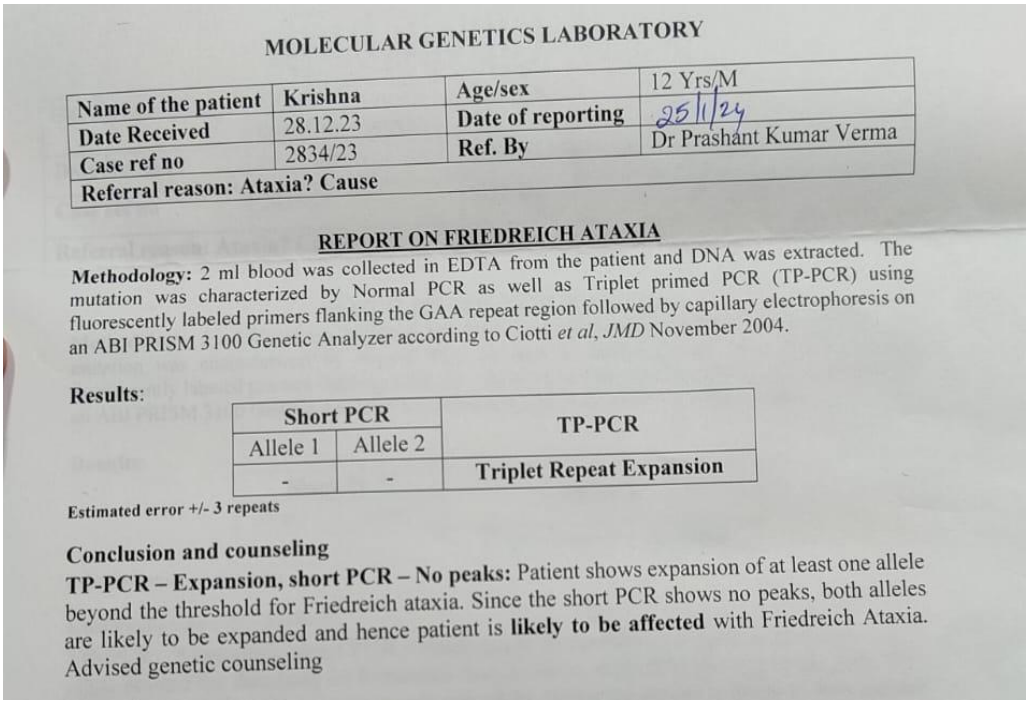
Vitals: Pulse rate-120/min, Respiratory rate-26/min, Blood pressure-112/60 mm Hg, SpO2 99%, Temperature-afebrile. Anthropometry: Weight 33 kg (-1 to -2 SD), Height 154 cm (median to -1 SD), Body Mass Index- 13.9 (-2 to -3 SD), arm span 168 cm (arm span to height ratio 1.09). The respiratory system showed equal bilateral air entry, Normal Vesicular Breath Sounds, no added sounds. Cardiovascular examination: S1 S2 present, no murmur. Abdominal examination: soft, non-tender, no organomegaly.

Neurological examination: conscious, oriented, bilateral pupil reaction normal, symmetrical limb wasting, decreased muscle tone, reflexes absent (knee, ankle), up going plantar reflex, positive Rhomberg, dysdiadochokinesia, absent finger-nose test, no coordination on knee-shin test, present ataxia, no nystagmus or intentional tremors.

Lab workup - Normal limits of various tests, including complete blood count, renal function tests, liver function tests, and serum electrolytes. Nerve conduction velocity (NCV) studies indicated polyneuropathy. Peripheral blood smear did not show acanthocytes. CPK-NAC was 203 (Elevated).Viral markers negative.

Given the clinical presentation, further imaging, including MRI of the brain and spine, and genetic testing were planned, but these could not be performed due to Technical issues. Possibilities that were suspected were Friedrich's ataxia, Neuro-metabolic disorder spectrum, Hereditary ataxias.

Further based on the similar complaints from the family in another sibling as potential need to rule out severe neurodegenerative disease prevailing in the family, Genetic analysis (father being expired at early age, Mother; son, daughter)were performed which showed as below



MOLECULAR GENETICS LABORATORY

Name of the patient	Krishna	Age/sex	12 Yrs/M
Date Received	28.12.23	Date of reporting	25/1/24
Case ref no	2834/23	Ref. By	Dr Prashant Kumar Verma
Referral reason: Ataxia? Cause			

REPORT ON FRIEDREICH ATAXIA

Methodology: 2 ml blood was collected in EDTA from the patient and DNA was extracted. The mutation was characterized by Normal PCR as well as Triplet primed PCR (TP-PCR) using fluorescently labeled primers flanking the GAA repeat region followed by capillary electrophoresis on an ABI PRISM 3100 Genetic Analyzer according to Ciotti *et al*, *JMD* November 2004.

Results:

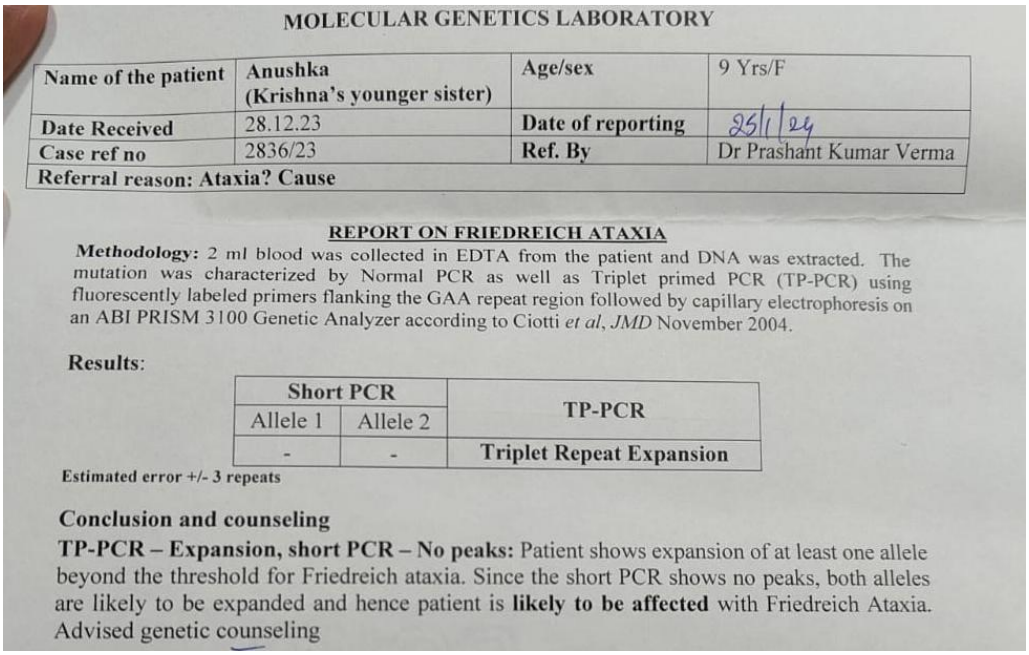
Short PCR		TP-PCR
Allele 1	Allele 2	
-	-	Triplet Repeat Expansion

Estimated error +/- 3 repeats

Conclusion and counseling

TP-PCR – Expansion, short PCR – No peaks: Patient shows expansion of at least one allele beyond the threshold for Friedreich ataxia. Since the short PCR shows no peaks, both alleles are likely to be expanded and hence patient is **likely to be affected** with Friedreich Ataxia. Advised genetic counseling

Figure 1. Molecular analysis of Index Case



MOLECULAR GENETICS LABORATORY

Name of the patient	Anushka (Krishna's younger sister)	Age/sex	9 Yrs/F
Date Received	28.12.23	Date of reporting	25/1/24
Case ref no	2836/23	Ref. By	Dr Prashant Kumar Verma
Referral reason: Ataxia? Cause			

REPORT ON FRIEDREICH ATAXIA

Methodology: 2 ml blood was collected in EDTA from the patient and DNA was extracted. The mutation was characterized by Normal PCR as well as Triplet primed PCR (TP-PCR) using fluorescently labeled primers flanking the GAA repeat region followed by capillary electrophoresis on an ABI PRISM 3100 Genetic Analyzer according to Ciotti *et al*, *JMD* November 2004.

Results:

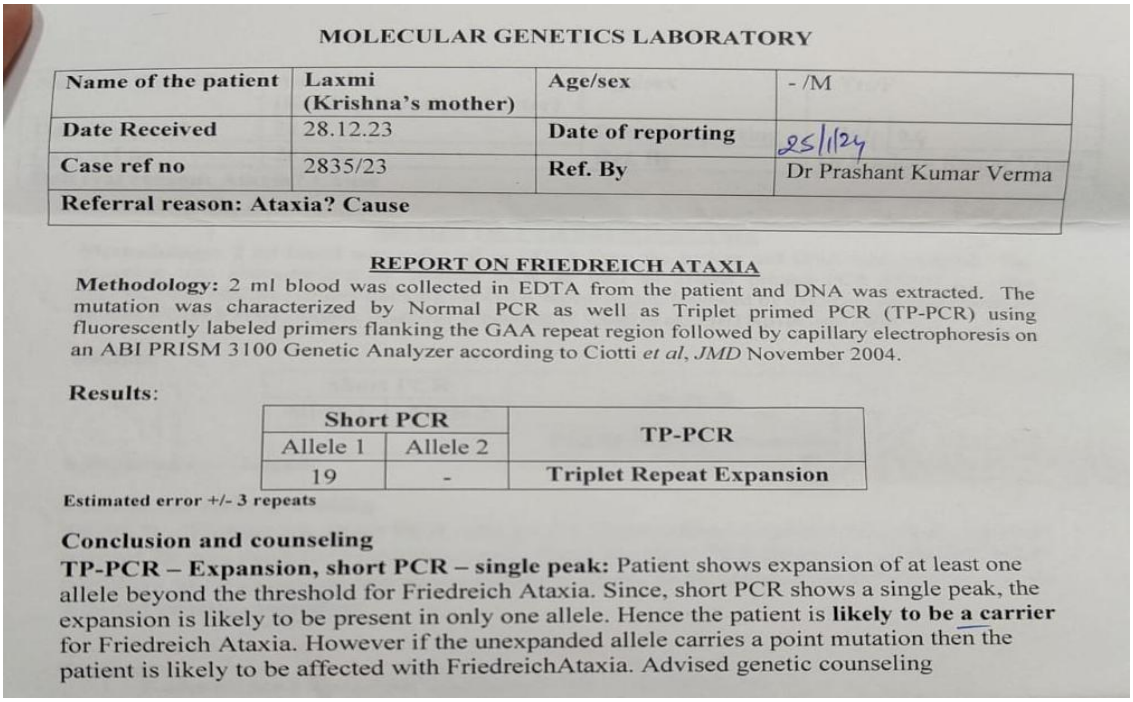
Short PCR		TP-PCR
Allele 1	Allele 2	
-	-	Triplet Repeat Expansion

Estimated error +/- 3 repeats

Conclusion and counseling

TP-PCR – Expansion, short PCR – No peaks: Patient shows expansion of at least one allele beyond the threshold for Friedreich ataxia. Since the short PCR shows no peaks, both alleles are likely to be expanded and hence patient is **likely to be affected** with Friedreich Ataxia. Advised genetic counseling

Figure 2. Molecular analysis of Sibling of Index case



MOLECULAR GENETICS LABORATORY

Name of the patient	**Laxmi (Krishna's mother)**	**Age/sex**	- /M
Date Received	28.12.23	**Date of reporting**	25/11/24
Case ref no	2835/23	**Ref. By**	Dr Prashant Kumar Verma
Referral reason: Ataxia? Cause			

REPORT ON FRIEDREICH ATAXIA

Methodology: 2 ml blood was collected in EDTA from the patient and DNA was extracted. The mutation was characterized by Normal PCR as well as Triplet primed PCR (TP-PCR) using fluorescently labeled primers flanking the GAA repeat region followed by capillary electrophoresis on an ABI PRISM 3100 Genetic Analyzer according to Ciotti *et al*, *JMD* November 2004.

Results:

Short PCR		TP-PCR
Allele 1	Allele 2	
19	-	**Triplet Repeat Expansion**

Estimated error +/- 3 repeats

Conclusion and counseling

TP-PCR – Expansion, short PCR – single peak: Patient shows expansion of at least one allele beyond the threshold for Friedreich Ataxia. Since, short PCR shows a single peak, the expansion is likely to be present in only one allele. Hence the patient is **likely to be a carrier** for Friedreich Ataxia. However if the unexpanded allele carries a point mutation then the patient is likely to be affected with FriedreichAtaxia. Advised genetic counseling

Figure 3. Molecular analysis of Mother of Index case

Treatment: Despite being first recognized more than 150 years ago, there is still no cure for FA. Treatment involves the management of symptoms and complications such as Diabetes mellitus and heart failure. Family was counselled appropriately after Genetic report and supportive management was given to the children.

DISCUSSION

This case underscores the complexity of diagnosing chronic progressive ataxia in children. Friedreich's ataxia, a common cause of inherited ataxia, remains a leading consideration. The presence of polyneuropathy, scoliosis, and absent reflexes aligns with this diagnosis. Early recognition and a systematic approach to investigation are crucial in managing such cases, as timely intervention can prevent complications and improve quality of life. The role of genetic counseling and multidisciplinary care is also highlighted. Friedreich's ataxia should be considered in pediatric patients presenting with ataxia and peripheral neuropathy.

CONCLUSION

Friedreich's ataxia remains a challenging neurodegenerative disorder with significant morbidity. Advances in genetic research and therapeutic development offer hope for more effective management and potential future cures. Continued collaborative research efforts are essential to translate these findings into clinical practice.

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