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Case Report

A rare case report of tyrosinemia type I

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ABSTRACT

Tyrosinemia type I is a rare genetic disorder that occurs due to the deficiency of enzyme Fumarylacetoacetate hydrolase, resulting in elevated levels of tyrosine in the bloodstream. This case study focuses on a 4-year-old boy with a previous medical history of tyrosinemia type I, who has been admitted to the hospital multiple times due to this condition. The objective of presenting this case is to bring awareness regarding the challenges encountered while managing tyrosinemia, specifically medication adherence and dietary restrictions, which play a crucial role. This case report intends to provide education to medical professionals, healthcare advisors, family members, and caregivers about the rare and severe nature of tyrosinemia type I, while emphasising the importance of implementing an appropriate treatment strategy along with dietary modifications.

Keywords: Tyrosinemia Type I, Fumarylacetoacetate Hydroxylase, Tyrosine, Phenylalanine, Nitisinone, Low-protein Diet.

INTRODUCTION

Tyrosinemia is a rare genetic condition characterised by excessive levels of "Tyrosine" in the blood, which eventually accumulates in various organs and tissues, leading to serious health complications.[1] This case report provides insight on tyrosinemia type I, a metabolic disorder that occurs due to the deficiency of an enzyme called fumarylacetoacetate hydrolase (FAH), which is essential for the final stage of tyrosine breakdown. Due to the body's inability to metabolise tyrosine properly, tyrosine and its byproducts may build up abnormally in the liver, leading to potentially serious liver disease. Additionally, tyrosine may also accumulate in the kidneys and the central nervous system.[2] Globally, approximately 1 in every 1,00,000 people are affected by tyrosinemia type I.[3]

Nitisinone effectively hinders the production of harmful metabolites, such as fumarylacetoacetate and succinyl acetoacetate, by inhibiting the enzyme 4-hydroxyphenylpyruvate dioxygenase. The administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) significantly elevates plasma tyrosine levels. Therefore, this therapy should be used in conjunction with a diet that restricts the intake of tyrosine and its precursor, phenylalanine (Phe), rather than being administered as a stand-alone treatment. By combining NTBC treatment with dietary restrictions, liver dysfunction is effectively managed in over 90% of patients, and any additional manifestations outside of the liver have been either eliminated or substantially improved.[4]

The primary objective of this case report is to present a unique and rare case of tyrosinemia type 1, a condition known for its infrequent occurrence and complex diagnosis and treatment process. The limited awareness among healthcare professionals regarding this condition further accentuates the need to address this knowledge gap. This case report aims to contribute to the existing medical

literature and enhances its quality by shedding light on the significance of diet management, particularly the importance of a low-protein diet that restricts tyrosine and phenylalanine intake. Additionally, it serves as a valuable resource for educating the immediate family members of the affected child about the necessary dietary modifications required to prevent the accumulation of tyrosine in their blood.

CASE REPORT

A 4-year-old child, second in birth order and born out of a non-consanguineous marriage, was brought to the Paediatric Intensive Care Unit with chief complaints of seven episodes of vomiting, characterised by forceful projectile expulsion of the contents accompanied by the rolling up of eyes that lasted approximately 15 minutes, during which the child was unresponsive. A seizure-like activity was successfully terminated with the administration of Midazolam 0.1 mg/kg. The child was previously admitted to the Neonatal Intensive Care Unit for jaundice and congenital hyperbilirubinemia, during which tyrosinemia type 1 was diagnosed. The disease kept on progressing and led to repeated hospital admissions due to non-adherence to a treatment plan, but the family members and the caregivers were well counselled regarding the same, which would aid in better recovery.

Upon head-to-toe examination, the eyes and oral cavity appeared normal. The child exhibited moderate activity and was afebrile. The pulse rate was 110 beats per minute, and the peripheral pulses were normal. The respiratory rate was 26 breaths per minute. Cardiovascular examination revealed normal S1 and S2 heart sounds with no murmurs detected. Respiratory examination yielded clear breath sounds bilaterally. The abdominal examination indicated a soft and non-tender abdomen. The laboratory data revealed several findings including the 2D Echo, which indicated a patent foramen ovale (PFO) measuring 1.5 mm with a left-to-right shunt. The TORCH Profile [Toxoplasmosis, others (Syphilis, Hepatitis B), Rubella, Cytomegalovirus, and herpes simplex] results showed negative for anti-toxoplasma antibody immunoglobulin antibody-G (IgG) and immunoglobulin antibody-M (IgM), weakly positive for anti-rubella antibody IgG, and negative for anti-rubella antibody IgM. Additionally, the anti-cytomegalovirus antibody IgG was positive, while IgM was negative. Similarly, anti-herpes simplex virus IgG was positive, and IgM was negative. Serum biochemistry and complete blood picture revealed the following values mentioned in Table 1.

After considering the patient's current health condition, past medical history and laboratory test results, and by conducting a comprehensive physical examination, it was determined that the child was diagnosed with tyrosinemia type 1 presenting with status epilepticus.

Table 1: Laboratory test results.

S. No	Diagnostic test	Abnormal values
Serum biochemistry:		
1.	Urea	14 mg/dL
2.	creatinine	0.38 mg/dL
3.	ALT	15 IU/L
4.	AST	26 IU/L
5.	ALP	205 IU/L
6.	Albumin	4.01 g/dL
7.	Direct bilirubin	0.66 mg/dL
8.	Total bilirubin	0.38 mg/dL
9.	Total protein	7.07 g/dL
10.	Uric acid	2.4 mg/dL
11.	Calcium	9.6 mg/dL
12.	Phosphate	3.5 mmol/L
13.	Globulin	2.9 g/dL
14.	Sodium	135 mmol/L
15.	Potassium	3.5 mmol/L
16.	Chlorine	100 mmol/L
Complete blood picture:		
1.	WBC	9.61×10^9/L
2.	RBC	4.16×10^9/L
3.	Haemoglobin	11.7 g/dL
4.	Haematocrit	35.3%
5.	MCV	84.9 fL
6.	MCH	28.1 pg
7.	MCHC	33.1 g/dL
8.	Platelets	314×10^9/L
9.	Neutrophils	80.4%
10.	Lymphocytes	14.0%
11.	Monocytes	5.4%
12.	Eosinophils	0.1%
13.	Basophils	0.1%

TREATMENT

The treatment plan consisted of various interventions to address the condition comprehensively. To manage seizures, the child received an injection of levetiracetam at a dosage of 30 mg/kg/day and an injection of midazolam (1.5 mL normal saline) intravenously on an as-needed basis. Paracetamol syrup was prescribed to treat fever, while domperidone syrup (0.2 mg/kg) and ondansetron injection (2 mg) were administered orally twice daily to alleviate nausea and vomiting. Based on the TORCH profile results, cefotaxime injection (100 mg/kg/dose) was prescribed as an intravenous antibiotic. For digestive issues, lactic acid bacillus sachets were given twice daily by mixing 1 sachet in 25 mL of water. Intravenous fluids consisting of dextrose normal saline (DNS) at a rate of 30 mL/hr, supplemented with 5 mL of multivitamin in 500 mL DNS, were administered. Additionally, oral rehydration solutions (ORS) sachets were mixed in 1 L of water and given as much as the child could drink to manage diarrhoea. The patient was closely monitored for seizures, while it was emphasised to maintain a low-protein diet and

ensure ample fluid intake. These treatment interventions aimed to address the immediate symptoms, provide proper seizure control, manage fever and digestive issues, administer appropriate antibiotics and maintain hydration and nutrition. Nitisinone 0.5 mg/kg for every 12 hours was given as a starting dose, followed by increasing the dose to a maintenance dose of 2 mg/kg. The drug was prescribed by strictly advising the patient and caretakers regarding a protein-restricted diet, especially a diet devoid of amino acids tyrosine and phenylalanine, which included avoiding foods such as meat, poultry, dairy, legumes, nuts, and seeds.

DISCUSSION

The 4-year-old child was presented with severe vomiting, with a previous medical history of tyrosinemia type I and jaundice. The child also had seizures due to neurological abnormality. Tyrosinemia is a genetic disorder that affects the breakdown of the amino acid tyrosine that leads to its accumulation in various organs and tissues, potentially leading to significant health issues if left untreated.[3] Both males and females are equally susceptible to tyrosinemia type I, and is estimated to affect 1 in 1,00,000–1,20,000 newborns worldwide.[2] It is a severe genetic disorder that is characterised by various symptoms that become evident during infancy, which include failure to thrive, as affected infants have difficulty tolerating high-protein foods that result in diarrhoea and vomiting. They may also exhibit jaundice, a distinctive odour resembling that of boiled cabbage and a propensity for bleeding, particularly nosebleeds. Tyrosinemia type I can lead to liver and kidney failure, rickets and an increased risk of liver cancer. Some affected children also experience recurrent neurologic crises, which can last for several days and are associated with changes in mental state, peripheral neuropathy, abdominal pain and respiratory failure. If left untreated, the life expectancy of individuals with tyrosinemia type I is typically less than 10 years.[5] Tyrosinemia type II (TYRSN2) is characterised by elevated serum tyrosine levels. The deficiency of aminotransferase is responsible for causing this disorder.[5] It typically manifests in early childhood, and the symptoms include eye pain; redness; and sensitivity to light (photophobia), keratitis as well as thickened, painful skin on the palms and soles of the feet (palmoplantar hyperkeratosis); and mental retardation.[5] Tyrosinemia type III is a hereditary condition that arises due to the deficiency of 4-hydroxyphenylpyruvate dioxygenase, an enzyme primarily expressed in neurons, neutrophils, kidney and liver cells.[6] It is distinguished by symptoms such as seizures, intermittent ataxia (periodic loss of balance and coordination) and intellectual disability.[5]

Untreated tyrosinemia type I typically manifests in two ways: either in young infants, where the liver is severely affected or later in the first year with liver and renal tubular dysfunction accompanied by stunted growth and the development of rickets. Children who do not receive treatment may experience recurrent neurologic episodes lasting from 1–7 days, which are often unnoticed. It involves alterations in mental state, abdominal pain, peripheral nerve damage, and/or respiratory failure necessitating the use of a mechanical ventilator.[7] The combined approach of administering Nitisinone along with a low-tyrosine diet has shown remarkable outcomes, with a survival rate exceeding 90%. This treatment regimen not only promotes normal growth but also enhances liver function, prevents the development of cirrhosis, corrects renal tubular acidosis and brings about improvements in secondary rickets.[7] The diagnosis of this condition is confirmed through specific biochemical markers, such as elevated levels of succinyl acetone in the blood and urine, increased concentrations of tyrosine, methionine and phenylalanine in the plasma, as well as elevated urinary levels of tyrosine metabolites and the compound δ-ALA. Alternatively, the diagnosis can be established by identifying harmful variants in both copies of the FAH gene through molecular genetic testing.[7]

In India, the management of tyrosinemia faces several challenges. One major obstacle is the difficulty in accurately diagnosing the specific type of tyrosinemia, primarily due to the high cost associated with genetic analysis.[8] 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) is not easily accessible and comes with a significantly high cost, making it unaffordable for most patients. Similarly, the expenses associated with tyrosine-free formulas make them inaccessible to most patients.[8] Nonetheless, patients should follow a low-protein diet and abstain from consuming meat, eggs, cheese, milk, lentils, dried beans, nuts and soy-based products.[8] Due to a significant vegetarian population, it is comparatively easier for individuals to avoid meat and eggs. However, avoiding dals (lentils) and milk can be challenging because they are the staple food items in Indian diet.[8] NTBC therapy is a highly effective treatment that significantly enhances the prognosis of tyrosinemia. Therefore, it is strongly recommended to initiate early treatment with NTBC.[8]

CONCLUSION

A 4-year-old male child, second in birth order, presented with severe vomiting and seizures. The child had a past medical history of tyrosinemia type1 but had not followed the treatment plan in the past, resulting in multiple hospital admissions. However, this time, the parents and caretakers received counselling and education about the severity of the condition and the importance of implementing an effective treatment plan, including a low-protein diet. They agreed to adhere to the recommended treatment strategy. The treatment plan involved the use of Nitisinone in conjunction

with a restricted protein diet. The focus of this case report revolves around addressing the challenges and complications associated with adhering to the prescribed therapeutic plan and protein restriction in patients with tyrosinemia type 1.

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