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PATHOGENESIS OF TYPE - I (hepato renal) TYROSINEMIA, TYPE -II (occulo cutaneous) TYROSINEMIA, TYPE - III (neonatal) TYROSINEMIA AND CAUSES, SYMPTOMS, DIAGNOSIS AS WELL AS TREATMENT OF TYPE -I, TYPE - II, TYPE - III TYROSINEMIA

Vinayasree. C[1] , Mohan Naidu.K[2], Muralinath. E[2], Amrutham Sandeep[3] ,Venkat Naveen. A[2] Guruprasad. M[4], Sravani Pragna.K[2]

[1]College of Veterinary Science, Korutla, PVNRTVU, Telengana, India
[2]College of veterinary science, Proddatur, Andhra Pradesh, India
[3]Indian Veterinary Research Institute (IVRI), Izathnagar 243122 Barielly district, Utter Pradesh, India
[4]Vaishnavi microbial Pvt. Ltd. Hyderabad. India.
Corresponding author mail id: muralinathennamuri@gmail.com

Abstract
Tyrosinemia is a rare metabolic disorder manifested by the deficiency of enzymes participated in the breakdown of the amino acid tyrosine. This leads to the collection of toxic metabolites, primarily tyrosine and its byproducts, affecting multi-systemic damage. There are three types of tyrosinemia, namely Type I (hepatorenal), Type II (oculocutaneous), and Type III (neonatal). Each type presents with distinct clinical features and requires specific diagnostic approaches and treatment strategies. This article gives an information about a comprehensive review of the pathogenesis, clinical manifestations, diagnosis, and management of tyrosinemia.

Keywords: Hepatorenal tyrosinemia, oculocutaneous tyrosinemia, neonatal tyrosinemia, autosomal rexessive disorder, succinyl acetate, fumaryl acetoacetate, fumaryl acetoacetate hydrolase, hepatomegaly, jaundice, liver failure, excessive urination, dejydration and rickets, seizures, developmental delays, intellectual disability, gene mutations, nitisone, photophobia, excessive tearing, eye pain, eye inflammation, blistering skin lesions on palms, soles and buttocks, TAT gene, 3- methyl crotonyl-CoA carboxylase and 3-hydroxy valeric acid.

INTRODUCTION

Tyrosinemia is a rare autosomal recessive disorder caused by the lack of enzymes participated in the tyrosine degradation pathway. The most common and severe form is Type I tyrosinemia, also termed as hepatorenal tyrosinemia, which affects the liver, kidneys, and other organs. Type II tyrosinemia primarily affects the eyes and skin, while Type III tyrosinemia is a transient and benign form that resolves spontaneously. This article focuses on Type I tyrosinemia because of its clinical significance and impact on patient outcomes.

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PATHOGENESIS:-

The underlying pathogenesis of tyrosinemia is linked to the collection of toxic metabolites, such as succinyl acetone and fumaryl acetoacetate, resulting from the impaired catabolism of tyrosine. These metabolites cause oxidative stress, mitochondrial dysfunction, and DNA damage, leading to cellular injury as well as organ dysfunction. The exact mechanisms by which these toxic metabolites contribute to specific manifestations in different organs are still being investigated.

Types of Tyrosinemia:

There are 3 types
Type I (hepatorenal)
Type II (oculocutaneous)
Type III (neonatal)

1. UNDERSTANDING TYPE I TYROSINEMIA:-

Type 1 Tyrosinemia is a rare genetic disorder manifested by the deficiency of the enzyme fumaryl acetoacetate hydrolase (FAH). This enzyme plays a critical role in the catabolism of the amino acid tyrosine. Without FAH, toxic byproducts build up in the body, leading to severe health complications. In this article, we will provide an information about the causes, symptoms, diagnosis, and treatment options for Type 1 Tyrosinemia.

Causes:

Type 1 Tyrosinemia is an autosomal recessive disorder caused by mutations in the FAH gene. Both parents act as carriers of the faulty gene for their child to inherit the condition. If both parents carry the gene mutation, there is a 25% chance with each pregnancy that their child will be affected by Type 1 Tyrosinemia.

Symptoms:

Symptoms of Type 1 Tyrosinemia often appear within the first few months of life and can vary in severity. Common signs and symptoms include:

Failure to thrive: Infants with Type 1 Tyrosinemia may exhibit difficulty gaining weight and show poor growth.

Liver dysfunction: Hepatomegaly (enlarged liver), jaundice (yellowing of the skin and eyes), and liver failure can happen.

Renal tubular dysfunction: Kidney problems may manifest as excessive urination, dehydration, and rickets (weakening of bones).

Neurological complications: Some individuals may experience neurologic crises, which can cause seizures, developmental delays, and intellectual disability.

Cabbage-like odor: Due to the collection of tyrosine and its byproducts, affected individuals may exhibit a distinct odor resembling boiled cabbage.

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Diagnosis:
Early diagnosis is critical to obstruct severe complications related to Type 1 Tyrosinemia. The following diagnostic methods are commonly used:
Newborn screening: Many countries include Type 1 Tyrosinemia in their newborn screening programs, allowing early detection and intervention.

Blood and urine tests: Elevated levels of tyrosine, succinylacetone, and other metabolites can be observed through blood and urine tests.

Genetic testing: Identification of FAH gene mutations proves the diagnosis and helps in determining carrier status in family members.

Treatment:
Type 1 Tyrosinemia needs lifelong management to minimize the accumulation of toxic metabolites and prevent organ damage. Treatment options include:

Dietary management: A low-protein diet, particularly restricted in tyrosine and phenylalanine, is essential to reduce the production of toxic byproducts.

Medications: Nitisinone (NTBC) is a medication that inhibits the production of toxic metabolites and shows significantly improved outcomes for individuals with Type 1 Tyrosinemia.

Liver transplantation: In severe cases where liver damage has occurred or when NTBC is not effective, a liver transplant may be necessary.

Ongoing monitoring: Regular follow-up visits, blood tests, and urine tests are critical to assess treatment efficacy, adjust dietary restrictions, and detect potential complications.

2. UNDERSTANDING TYPE II TYROSINEMIA:-
Type 2 Tyrosinemia, also known as Richner-Hanhart syndrome, is a rare genetic disorder that influences the body's ability to break down the amino acid tyrosine. This article provides an overview of Type 2 Tyrosinemia along with its causes, symptoms, and available treatment options.

Causes:
Type 2 Tyrosinemia is caused by a mutation in the TAT (tyrosine aminotransferase) gene, which is responsible for the production of an enzyme called tyrosine aminotransferase. This enzyme is participated in the catabolism of tyrosine, an amino acid found in many protein-rich foods. The mutation in the TAT gene results in a deficiency or complete absence of tyrosine aminotransferase, resulting in the accumulation of toxic byproducts of tyrosine metabolism in the body.

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Inheritance Pattern:
Type 2 Tyrosinemia follows an autosomal recessive pattern of inheritance, meaning that an affected individual must inherit two copies of the mutated gene (one from each parent) to develop the disorder. If both parents carry one copy of the mutated gene, they have a 25% chance of having an affected child with each pregnancy.

Symptoms:
The symptoms of Type 2 Tyrosinemia typically appear during early childhood, usually within the first few months of life. The severity and presentation of symptoms can vary from person to person, but common signs and symptoms may include:

Eye-related problems: Light sensitivity (photophobia), excessive tearing, eye pain, and eye inflammation.

Skin abnormalities: Painful, blistering skin lesions that may appear on the palms, soles, and buttocks.

Intellectual and developmental delays: Some individuals result in developmental delays, learning difficulties, or intellectual disabilities.

Intellectual disabilities: Progressive intellectual disabilities may occur in some individuals.
Behavioral and psychiatric issues: Behavioral problems, including aggression, self-injury, and attention deficit hyperactivity disorder (ADHD)-like symptoms, have been reported in some cases.

Diagnosis:
Diagnosing Type 2 Tyrosinemia involves a combination of clinical evaluation, laboratory tests, and genetic testing. Blood and urine tests lead to the occurrence of elevated levels of certain amino acids, such as tyrosine and phenylalanine. Genetic testing can support the presence of mutations in the TAT gene.

Treatment:
The main goal of treatment for Type 2 Tyrosinemia is to reduce the collection of toxic metabolites and manage the symptoms. The treatment approach typically involves:

Dietary restrictions: A low-protein diet, especially limiting tyrosine and phenylalanine intake, is often recommended to reduce the levels of toxic metabolites in the body.

Medications: Nitisinone, a medication that inhibits an enzyme participated in the catabolism of tyrosine, is commonly prescribed to reduce the production of toxic metabolites.

Supportive care: Depending on the individual's symptoms and associated complications, additional medical interventions, such as eye drops for eye-related symptoms or behavioral therapies for behavioral issues, may be recommended.

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Prognosis:
The long-term outlook for individuals with Type 2 Tyrosinemia varies. Early diagnosis and appropriate management can help in elucidating outcomes and prevent or minimize complications. Whatever it may be, some individuals may still experience long-term complications, namely intellectual disabilities or behavioral challenges, despite treatment.

3. UNDERSTANDING TYPE III TYROSENEMIA:-

Type 3 Tyrosinemia, also known as 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD), is an autosomal recessive disorder. It is caused by a deficiency of the enzyme 3-methylcrotonyl-CoA carboxylase, which plays a critical role in catabolism of proteins that contain the amino acid leucine. The deficiency leads to the occurrence of the collection of toxic byproducts, namely 3-hydroxyisovaleric acid, causing various health complications.

Causes and Inheritance:
Type 3 Tyrosinemia is manifested by mutations in the MCCC1 gene or the MCCC2 gene, which provide instructions for the production of the 3-methylcrotonyl-CoA carboxylase enzyme. These mutations impair the enzyme's function, leading to the characteristic metabolic abnormalities observed in affected individuals. Type 3 Tyrosinemia follows an autosomal recessive pattern of inheritance, meaning that both parents must carry a mutated gene for their child to develop the condition.

Symptoms and Clinical Presentation:-
The symptoms of Type 3 Tyrosinemia can vary widely among affected individuals, ranging from mild to severe. Common clinical features are

Metabolic crises: Some individuals may experience episodes of metabolic crises triggered by infections, prolonged fasting, or excessive protein intake. These crises can lead to the occurrence of vomiting, dehydration, lethargy, and neurological abnormalities.

Developmental delays: Children with Type 3 Tyrosinemia may exhibit delays in reaching developmental milestones, namely crawling, walking, and talking.

Intellectual disability: In severe cases, intellectual disability may be present, influencing cognitive abilities and learning.

Hypotonia: Weak muscle tone, or hypotonia, is often seen in infants with Type 3 Tyrosinemia, resulting in reduced strength and mobility.

Other symptoms: Additional features can include failure to thrive, diarrhea, seizures, and a distinctive odor in the urine.

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Diagnosis and Treatment:-

The diagnosis of Type 3 Tyrosinemia is related to the collection of clinical evaluation, biochemical testing, and genetic analysis. Elevated levels of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine in the blood or urine can provide valuable clues for diagnosis.

Currently, there is no cure for Type 3 Tyrosinemia. Management primarily focuses on dietary interventions and close monitoring. A low-protein diet, particularly limiting leucine intake, is often recommended to obstruct the collection of toxic metabolites. In some cases, supplementation with special formulas and essential nutrients may be necessary. Regular follow-ups and monitoring of metabolic markers are essential to ensure optimal management.

Conclusion

Tyrosinemia is a rare metabolic disorder with significant implications for affected individuals. Early recognition, prompt diagnosis, and multidisciplinary management are critical for minizing outcomes. Advances in understanding the pathogenesis and the availability of targeted therapies, namely nitisinone, have significantly improved the prognosis for patients with Type I tyrosinemia. Continued research and collaboration among doctors and researchers are essential to further increase the understanding and management of this complex disorder.

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