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A Mini Review on Origins, Mechanisms, and Treatment Approaches for Reye's Syndrome

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Abstract

Reye's syndrome is a fatal biphasic disorder characterized by a preceding viral illness, prolonged vomiting preceding encephalopathy, and liver dysfunction onset. Clinical manifestations include delirium, fever, convulsions, vomiting, respiratory collapse, stupor, seizures, or coma, typically following an earlier viral infection. Encephalopathy rapidly progresses from lethargy to coma within 24 to 48 hours. The primary etiology of Reye's syndrome involves universal mitochondrial injury and triglyceride accumulations. High concentrations of ammonia contribute to encephalopathy and anicteric hepatitis, accompanied by a threefold increase in liver enzymes. Mitochondrial permeability transition induction is a frequent pathophysiological mechanism. Reye's syndrome carries a high mortality rate, and treatment involves symptomatic management, including intensive care to correct metabolic abnormalities (hypotension, hypoglycemia, acidosis), seizure control, and monitoring intracranial hypertension due to cerebral edema. Agents to decrease serum ammonia concentrations, such as neomycin sulfate or lactulose, are commonly used, along with anti-emetics like ondansetron to inhibit vomiting and prevent potential aspiration.

1. Introduction

Reye's syndrome is a rare and life-threatening condition characterized by acute, non-inflammatory encephalopathy and fatty degeneration of the liver. This syndrome typically manifests with minimal or no clinical signs of liver involvement, often following a mild viral illness. The clinical presentation includes a constellation of symptoms such as delirium, fever, convulsions, vomiting, respiratory collapses, stupor, seizures, or coma, commonly occurring after a preceding viral infection. Reye's syndrome is further defined by an acute, non-inflammatory encephalopathy with sterile cerebrospinal fluid, hepatic impairment leading to elevated serum transaminases and ammonia levels, and liver biopsy revealing fatty degeneration [1].

In pediatric cases, blood glucose levels drop while ammonia and acidity rise, leading to liver swelling with fatty deposits. Brain swelling may also occur, resulting in seizures, convulsions, or loss of consciousness. As the condition progresses, additional clinical manifestations may include unusual behavior, psychiatric disorders, paralysis of limbs, epilepsy, and lowered levels of consciousness. Clinical features differ between younger children (below age two) and older children and teenagers.

The reduction in the use of aspirin in pediatric populations has significantly decreased the incidence of Reye's syndrome. The World Health Organization experts recommend avoiding acetylsalicylic acid for fever in children under twelve years old. Reye's syndrome has been associated with adenovirus infection and the use of medications such as nimesulide and acetylsalicylic acid.

Reye's syndrome is classified into five categories based on clinical features. The effect of aspirin, marketed under the trademark Aspirin, is linked to the development of Reye's syndrome, causing mitochondrial damage intensified by viral illness, endotoxin, and cytokines. Aspirin's anti-inflammatory, analgesic, antipyretic, and antithrombotic effects are attributed to its irreversible inactivation of cyclo-oxygenase-1 and cyclo-oxygenase-2, preventing prostaglandin and thromboxane synthesis.

2. Etiology

2.1 Reye's syndrome is clinically categorized into two groups:

Reye's-Like Syndrome: Caused by enzymatic abnormalities, such as medium-chain acyl-CoA dehydrogenase deficiency (affecting beta-oxidation of lipid acids) or ornithine-transcarboxylase inadequacy (resulting in elevated ammonia levels in the blood).

Idiopathic Reye's Syndrome: Found in genetically predisposed individuals and associated with exogenous factors triggering metabolic defects. These factors include the ingestion of salicylates, paracetamol, certain toxins (e.g., aflatoxin), and viral infections (commonly chickenpox, influenza A or B, adenoviruses, and hepatitis A viruses) [2].

Microvesicular fatty degeneration of the liver and non-inflammatory encephalopathy are key characteristics of Reye's syndrome. Common findings include low blood sugar, elevated ammonia levels, and bleeding disorders. Organic, amino, and free fatty acids are often elevated in serum and urine due to impaired metabolic steps and enzyme activities in the mitochondria, affecting processes like the citric acid cycle, glucose formation from non-carbohydrates, urea formation, and β-oxidation.

The primary etiological factors involve universal mitochondrial injury and triglyceride accumulations. Reye's syndrome typically affects children and teenagers recovering from viral illnesses, with varicella zoster and influenza virus being the most common culprits. While classically associated with a preceding infection and salicylate consumption, cases have been observed with other non-steroidal anti-inflammatory drugs, including diclofenac sodium and mefenamic acid. Additionally, correlations with the intake of paracetamol, obsolete TTC, valproic acid, warfarin, AZT, and certain anticancer medicines have been reported.

Inborn errors of metabolism (IEM) contributing to Reye's syndrome involve abnormalities in fatty acid oxidation (especially MCAD and LCAD inherited and acquired forms), urea cycle anomalies, amino and organic acidopathies, carnitine inadequacy, and deformities of carbohydrate metabolism. Recognizing IEM is crucial and is supported by factors such as recurrent symptoms, predisposing conditions like prolonged fasting or changes in diet, intercurrent diseases, neurological abnormalities, family history of similar symptoms, and unexplained infant deaths [3-9].

The administration of acetylsalicylic acid is linked to an increased generation of tumor necrosis factor by macrophages. This mediator, when secreted into the circulation, interacts with target cells, leading to numerous intracellular alterations.

3. Pathophysiology

In Reye's syndrome and cases related to medication toxicity, the initiation of the mitochondrial permeability transition (MPT) is a suggested pathophysiological mechanism causing liver damage due to impaired mitochondrial beta-oxidation. The MPT is triggered by the opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane, resulting in swelling, depolarization, and uncoupling of oxidative phosphorylation. The advancement of Reye's syndrome is linked to the dose of aspirin consumed during preceding respiratory diseases. Metabolites of acetylsalicylic acid, such as salicylate, hydroxy Hippurate, and gentisate, directly inhibit palmitate oxidation in skin fibroblasts from Reye's syndrome individuals. Salicylate and hydroxy Hippurate reversibly inhibit the long-chain 3-hydroxyacyl-CoA dehydrogenase activity of the mitochondrial trifunctional enzyme, affecting beta-oxidation, with Reye's syndrome cells showing heightened sensitivity to salicylate inhibition [10,11].

In the liver, metabolic failure leads to reduced gluconeogenesis, and elevated fatty acid and ammonia production. In the central nervous system, low blood sugar and increased ammonia levels contribute to cerebral fluid retention and elevated intracranial pressure. Tumor necrosis factor alpha (TNF) is a crucial mediator, secreted by various cells, including macrophages, monocytes, lymphocytes, and Kupffer cells. It plays a role in infection, tissue damage, inflammation, and lethal shock. Children developing Reye's syndrome may have an altered sensitivity or reduced capacity to clear endotoxin, leading to heightened endotoxin-stimulated macrophage generation and TNF synthesis.

4. Diagnosis

Liver biopsy during the acute phase reveals mitochondrial alterations, distinguishing Reye's syndrome from other acute metabolic encephalopathies. Electron microscopy shows fat globules, swollen mitochondria, and nucleolar prominence. Histologically, the liver biopsy appearance aligns with Reye's syndrome. Consider Reye's syndrome in individuals presenting with profuse vomiting and altered mental status after a viral illness or non-steroidal anti-inflammatory drug ingestion, exhibiting elevated blood ammonia and transaminases with normal cerebrospinal fluid [12-17].

5. Treatment

Reye's syndrome has a significant mortality rate, and treatment is symptomatic, involving intensive care with correction of metabolic disorders (hypotension, hypoglycemia, and acidosis), convulsion control, and monitoring intracranial hypertension due to cerebral fluid retention. Mechanical ventilation, nasotracheal tubes, arterial and central venous pressure lines, nasogastric tubes, Foley catheters, and controlled hyperventilation are employed [18,19]. Hypertonic glucose solutions, insulin, and prothrombin time adjustment may be necessary. Intracranial pressure is managed using osmotic diuretics, and anti-emetics like ondansetron are administered to inhibit vomiting and potential aspiration. Specific interventions targeting hyperammonia involve hemofiltration and gut decontamination with a high-carbohydrate diet. Agents like neomycin sulfate or lactulose are used to lower serum ammonia concentrations.

6. Conclusion

Reye's syndrome signifies a sudden, profound failure of mitochondria, with micro vesicular fatty degeneration of the liver and non-inflammatory encephalopathy as cardinal features. The syndrome's clinical manifestations vary in different age groups, emphasizing the need for vigilance in diagnosis. Avoidance of acetylsalicylic acid for fever in children under twelve years is recommended by health experts. Exchange transfusion and intracranial pressure management, including the use of osmotic diuretics, are crucial in severe cases. Tumor necrosis factor plays a pivotal role in the pathogenesis, influencing multiple organ damage, and its inhibition is considered in the treatment strategy. Ongoing research is essential to unravel the complexities of Reye's syndrome and improve therapeutic approaches.

7. References

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