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Etiology, pathophysiology and management of reye's syndrome

Abstract

Reye's syndrome is defined as a fatal biphasic disorder that clinically described by preceding viral illness, protracted vomiting from one to two days before the onset of encephalopathy and liver dysfunction. Reye's syndrome can be characterized as a constellation of delirium, fever, convulsions, vomiting, respiratory collapses, stupor, seizures, or coma typically following an earlier viral illness. Encephalopathy can be frequently progresses rapidly from lethargy to coma within twenty four to forty eight hrs. Both universal mitochondrial injury and triglyceride accumulations are the cornerstone etiology of Reye's syndrome. Accumulation of high concentration of ammonia leads to encephalopathy and anicteric hepatitis with three times rise in liver enzymes. A frequent pathophysiological mechanism of Reye's syndrome is induction of the mitochondrial permeability transition. The syndrome is correlated with a high mortality rate and the treatment is symptomatic including intensive care management with correction of metabolic abnormalities especially of hypotension, hypo glycaemia and acidosis, control of convulsions, and monitoring of intracranial hypertension due to cerebral edema. Agents to decrease serum ammonia concentrations are also usually used, the most frequent being are neomycin sulfate or lactulose. Anti-emetic such as ondansetron should be given to inhibit vomiting and potential aspiration.

Keywords: etiology, management, pathophysiology, reye's syndrome

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Abbreviations: AZT, zidovudine; CNS, central nervous system; ECG, electroencephalogram; FFP, fresh frozen plasma; IEM, inborn errors of metabolism; LCAD, long chain acyl dehydrogenase deficiency; MCAD, medium chain acyl dehydrogenase; MPT, mitochondrial permeability transition; NSAIDs, non-steroidal anti-inflammatory drugs; RS, reye's syndrome; TTC, tetracycline; TNF, tumour necrosis factor; WHO, world health organization

Introduction

Reye's syndrome is characterized as a rare syndrome described by an acute, life-threatening, non-inflammatory encephalopathy and fatty degeneration of the liver with minimal or no clinical signs of liver involvement usually following a mild illness notably viral in nature and also characterized as a constellation of delirium, fever, convulsions, vomiting, respiratory collapses, stupor, seizures, or coma typically following an earlier viral illness.[1] Reye's syndrome can be described by an acute, non- inflammatory encephalopathy with sterile cerebrospinal fluid containing less than nine white blood cell/millimeter or cerebral fluid retention, hepatic impairment leading to elevation of serum transaminases and serum ammonia, liver biopsy observing fatty.[2] In Reyes syndrome a pediatrics blood glucose level typically drops while the levels of ammonia and acidity rise in child's blood. At the same time the liver perhaps swell and develop fatty deposits. Swelling perhaps also occurs in the brain which can cause seizures, convulsions or loss of consciousness. Eventually while the conditions progresses and complicates Reyes syndrome clinical manifestations comprises unfamiliar behavior, psychiatric disorders (hallucinations, disorientation etc.), paralysis of arms and legs, epilepsy, and lowered level of consciousness.[1] The clinical manifestations of Reyes syndrome in pediatric younger than age two and older children and teenagers; the clinical manifestations of pediatric younger than two years comprises diarrhea and rapid breathing whereas in older pediatric and teenagers comprises unusual sleepiness and persistent vomiting.[3] The World Health Organization experts were recommended not using acetylsalicylic acid for fever in children under twelve yrs. The incidence of RS disorder has dramatically lowered after reduction in the use of aspirin in pediatric. Reye's syndrome developed in individuals with adenovirus infection while taking medicines such as nimesulide and acetylsalicylic acid.[3] There are five clinical classifications of Reye's syndrome; which described in turn below as class I is often calm, lethargic, and sleepy; vomiting; and laboratory confirmation of liver deformities; class II is deep lethargy, confusion, delirium, combative, hyperventilation, and hyper-reflexia; class III is obtunded, light coma with/out seizures, decorticate rigidity, and intact pupillary reaction; class VI is seizures, deepening coma, decerebrate rigidity, loss of oculocephalic reflexes, and fixed pupils; class V is coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, flaccidity or decerebrate, and isoelectric ECG.[4] Acetylsalicylic acid were marketed in 1899 under the registered trademark of Aspirin, has anti-inflammatory, analgesic, antipyretic, and antithrombotic effects. The effect of aspirin was acquired because acetylsalicylic acid prevents prostaglandin and thromboxane synthesis by irreversible inactivation of both cyclo-oxygenase-1 and cyclo-oxygenase-2.[5,6] Acetyl salicylic acid may be rendering to the advancement of Reyes syndrome by causing the tiny structures within the cells called mitochondrial damage that can be caused by salicylates, which perhaps intensified during viral illness by endotoxin and cytokines.[7]

Etiology

There are two categorization of Reye's syndrome in clinical practice; which are 1) the Reye's-like syndrome caused by enzymatic

abnormalities, example; medium-chain acyl-CoA dehydrogenase deficiency (injured beta-oxidation of lipid acids), or ornithine-transcarbamylase inadequacy (raised amount of ammonia in the blood), and 2) the so called «idiopathic» Reye's syndrome demonstrated in genetically predisposed individuals, correlated with exogenous factors rendering to induction of this metabolic defect, such as ingestion of salicylates, paracetamol, certain toxins (e.g. aflatoxin), as well as viral infections (commonly chickenpox, influenza A or B, adenoviruses, and lately hepatitis A viruses).[8] Etiologically, micro vesicular fatty degeneration of the liver and non-inflammatory encephalopathy is cardinal characteristics of Reye's syndrome. Lowered sugar in the blood, raised amount of ammonia in the blood and bleeding disorders are distributively available. Organic, amino and free fatty acids are frequently accelerated in both serum and urine because of injured metabolic steps and enzyme activities in the mitochondria, involving the citric acid cycle, formation of glucose from non-carbohydrates, formation of urea and β-oxidation.[9] Both universal mitochondrial injury and triglyceride accumulations are the cornerstone etiology of Reye's syndrome. It initially affects children and teenagers recovering from viral illness most frequently varicella zoster and influenza virus.[10] The syndrome was classically explained with a preceding infection and consumption of salicylates but; cases have been observed with intake of other non-steroidal anti-inflammatory drugs involving diclofenac sodium and mefenamic acid. Paracetamol, obsoleted TTC, valproic acid, warfarin, AZT and certain anticancer medicines have also been correlated with RS.[11] Inborn errors of metabolism that generate RS involve fatty-acid oxidation abnormalities, especially MCAD and LCAD inherited and acquired forms, urea cycle anomalies, amino and organic acidopathies, initially carnitnie inadequacy and deformities of carbohydrate metabolism. IEM is proposed by recurrence of symptoms, predisposing factors involving prolonged fasting, alters in diet, inter-current diseases, neurological deformities and malfunction, history of identical symptoms in family members and unexpressed infant deaths.[12] The administration of acetyl salicylic acid leads to accelerated macrophage generation of tumour necrosis factor. Following the secretion of tumour necrosis factor into the circulation, this mediator binds to and interacts with target cells and generates numerous intracellular alters.[13]

Pathophysiology

In Reye's syndrome and Reye's syndrome-related medicine toxicities, the initiation of the MPT was proposed to be a frequent pathophysiological mechanism causing liver damage because of impairment of mitochodrial beta-oxidation. The MPT was initiated by opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane, which resultant in swelling, depolarization and uncoupling of oxidative phosphorylation. A relationship between the advancement of Reye's syndrome and the dose of aspirin consumed during the antecedent of respiratory diseases was resulted. It also happened that acetylsalicylic acid metabolites, such that salicylate, hydroxyhippurate and gentisate, but not acetylsalicylic acid, directly prevented palmitate oxidation in skin fibroblasts acquired from Reye's syndrome individuals and controls. Salicylate and hydroxyhippurate reduced beta-oxidation in intact cells by reversible prevention of the long-chain 3-hydroxyacyl-CoA dehydrogenase activity of the mitochondrial trifunctional enzyme, and beta-oxidation in Reye's syndrome cells was inherently more sensitive to prevention by low concentrations of salicylate.[14,15] In the liver specifically, this metabolic failure leads to reduced gluconeogenesis with elevated fatty acid and ammonia production. In the central nervous system, the resulted lowered sugar level in the blood and raised ammonia level in the blood perhaps lead to cerebral fluid retention and accelerated intracranial pressure.[16] Tumour necrosis factor alpha is a small polypeptide (also known as cachectin) secreted initially by initiated macrophages with pleotropic effects on biological and immunological procedures. NF belongs to a group of hormone like molecules termed cytokines, a class of soluble factors that involves interferons, interleukins, and haematopoietic growth factors. These cytokines form a complex network of interactive signals that regulate their own generation and the growth, differentiation or work of cells included in inflammation, immunity, and haematopoiesis. It is currently well-known that TNF is an initial mediator in the pathogenesis of infection, tissue damage, inflammation, and lethal shock. It is secreted by several initiated phagocytic and non-phagocytic cells, involving macrophages, monocytes, lymphocytes, natural killer cells, astrocytes, microglial cells of the brain, and Kupffer cells of the liver. A broad range of infectious or inflammatory stimuli are able of triggering tumour necrosis factor biosynthesis, for instance, bacterial endotoxin, enterotoxin, toxic shock syndrome toxin-l, mycobacterial cord factor, viruses, C5a, fungal or parasitic agents, interleukins, and interferons, where endotoxin is the most potent stimulator of Tumour necrosis factor secretion from the monocyte/macrophage system.[17,18] Pediatric who advance RS perhaps have an altered sensitivity or lowered capacity to clear endotoxin by the reticuloendothelial system, or both. The accelerated genetic or acquired sensitivity to endotoxin leads to endotoxin stimulated macrophage generation and synthesis of Tumour necrosis factor.[19]

Diagnosis

Liver biopsy is used in the acute phase reveals swollen and pleomorphic mitochondria, which identifies RS from other acute metabolic encephalopathies. Electron microscopy revealed many small fat globules in cells, swollen mitochondria with degenerative alters, and predominant nucleoli. The histologic appearance of liver biopsy of the individual classically happened as that of RS. Reye's syndrome should be thought-out in the differential diagnosis of individuals presenting with profuse vomiting and changed mental status after a viral disease, non-steroidal anti-inflammatory drugs ingestion, exhibiting enhanced blood ammonia and transaminases with normal CSF.[1,20]

Treatment

Reye's syndrome is correlated with a huge mortality rate and the management is symptomatic such as intensive care treatment with correction of metabolic disorders especially of hypotension, hypoglycaemia and acidosis, control of convulsions, and monitoring of intracranial HTN owing to cerebral fluid retention.[21] Nasotracheal tubes are electively inserted and arterial and central venous pressure lines, as well as nasogastric tubes and Foley catheters. Mechanical ventilation is used and patients are paralyzed with a neuromuscular blocking agent such as pancuronium bromide. Controlled hyperventilation is often used in an effort to reduce intracranial pressure. Cooling mattresses are used to keep body temperatures at normal range. Hypertonic glucose solutions given intravenously, as well as insulin, are usually used. The prothrombin time and other coagulation deformities perhaps adjusted by administration of FFP. Exchange transfusion is used in some centers to correct various metabolic and hematologic abnormalities. Intracranial pressure elevations are treated by administering osmotic diuretics, involving mannitol, other agents such as glycerol or furosemide and controlling hyperventilation and muscular paralysis. Intracranial pressure is frequently monitored by using intraventricular, subarachnoid or epidural monitors.[22–24] Irrespective of the causative agent, treatment of these individuals is intended on hyperammonia. This involves elevating ammonia removal through haemofiltration

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or lowering ammonia secretion through gut decontamination and a high carbohydrate diet which intends to decrease endogenous protein cascade. Agents to lower serum ammonia concentrations are also frequently used, the most often being are neomycin sulfate or lactulose. Anti-emetic such as ondansetron should be given to inhibit vomiting and potential aspiration.[25,26] Administration of human recombinant tumour necrosis factor that is virtually endotoxin free generates a many of cardiovascular, haematological, inflammatory, and metabolic abnormalities, which are almost similar to those resulted in endotoxic or septic shock syndrome. The strongest evidence implicating tumour necrosis factor as a principal mediator of multiple organ damage in infection is that anti-tumour necrosis factor antibodies inhibit the sequelae of endotoxic and Gram negative septic shock and tissue damage.[27]

Conclusion

Reye's syndrome represents an abrupt, profound failure of mitochondria, the cause of which is uncertain. Etiologically, micro vesicular fatty degeneration of the liver and non-inflammatory encephalopathy is cardinal characteristics of Reye's syndrome. The World Health Organization experts were recommended not using acetylsalicylic acid for fever in children under twelve yrs. The clinical manifestations of Reyes syndrome in pediatric younger than age two and older children and teenagers; the clinical manifestations of pediatric younger than two years comprises diarrhea and rapid breathing whereas in older pediatric and teenagers comprises unusual sleepiness and persistent vomiting. In the central nervous system, the resulted lowered sugar level in the blood and raised ammonia level in the blood perhaps lead to cerebral fluid retention and accelerated intracranial pressure. Exchange transfusion is used in some centers to correct various metabolic and hematologic abnormalities. Intracranial pressure elevations are treated by administering osmotic diuretics, involving mannitol, other agents such as glycerol or furosemide and controlling hyperventilation and muscular paralysis. TNF is a small polypeptide (also known as cachectin) released initially by activated macrophages with pleotropic effects on biological and immunological processes. Anti-emetic such as ondansetron should be given to inhibit vomiting and potential aspiration.

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