Hyperammonemia

Hyperammonemia is a metabolic disturbance characterized by excess ammonia in the blood. Ammonia is a nitrogen-containing byproduct of protein metabolism and is highly toxic to the body. Normally, the urea cycle, which occurs primarily in the liver, converts ammonia into less toxic urea, which is then excreted by the kidneys. Hyperammonemia can be classified as primary or secondary. Primary hyperammonemia is caused by hereditary urea cycle enzyme defects that impair the conversion of ammonia to urea. Secondary hyperammonemia is commonly associated with liver disease, where hepatocyte dysfunction leads to impaired urea cycle activity. Other causes include bacterial overgrowth in the gut, which increases ammonia production, and gastrointestinal (GI) bleeding, where the breakdown of blood proteins in the GI tract generates excess ammonia. Pathophysiologically, hyperammonemia inhibits the tricarboxylic acid (TCA) cycle by depleting alpha-ketoglutarate, a critical substrate, disrupting cellular energy metabolism and contributing to the condition's neurotoxic effects. Symptoms include somnolence, slurred speech, tremor (asterixis), cerebral edema, blurred vision, nausea, vomiting, and, in severe cases, hepatic encephalopathy. Treatment involves multiple strategies to lower ammonia levels. These include limiting dietary protein, as protein metabolism generates ammonia. Lactulose is commonly used to treat hyperammonemia. It is metabolized by gut bacteria into short-chain fatty acids, which increases gut hydrogen ion concentration and favors the conversion of absorbable ammonia (NH3) into nonabsorbable ammonium (NH4+), which is excreted in stool. Rifaximin, an antibiotic, reduces ammonia-producing bacteria in the gut. Sodium benzoate binds ammonia to glycine, forming a compound that is excreted in the urine. Phenylbutyrate works by conjugating with glutamine to form a water-soluble compound that is also excreted in the urine. These treatments aim to reduce the ammonia load on the body, mitigate symptoms, and prevent life-threatening complications like cerebral edema and intracranial hypertension.



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CAUSES

Hereditary Urea Cycle Defects

Hair-red U-rainbow Cycle Broken

Hyperammonemia can be primary or secondary in origin. Primary hyperammonemia is caused by hereditary urea cycle enzyme defects. Normally, the urea cycle converts ammonia to less toxic urea, which can be excreted by the kidneys. However, a defect in the urea cycle will cause a buildup of ammonia, leading to hyperammonemia.

Acquired Through Liver Disease

Diseased Liver

Hyperammonemia can be of primary or secondary origin. Liver failure is a common cause of secondary hyperammonemia. In liver disease, hepatocyte dysfunction impairs the urea cycle, which primarily occurs in the liver, leading to ammonia accumulation. Patients with congenital liver diseases or acquired liver conditions, such as toxin exposure, hepatitis, or alcoholic cirrhosis, are at increased risk for developing hyperammonemia. In severe cases, hepatic encephalopathy may develop, which is a clinical syndrome characterized by altered mental status, ranging from confusion to coma, due to the accumulation of toxins, including ammonia, in the brain. It is a medical emergency.

Bacterial Overgrowth in Gut

Bacteria-guy Overgrowth in Guts

Excessive growth of gut bacteria leads to increased ammonia production as a byproduct of protein metabolism. This excess ammonia can enter the bloodstream, particularly in patients with liver dysfunction, as the liver's impaired ability to detoxify exacerbates hyperammonemia.

GI Bleeding

GI-guy Bleeding

Blood is rich in proteins, and when it is degraded inside the gastrointestinal tract during bleeding, ammonia production will be increased, too. Then, ammonia is absorbed inside the bloodstream and overwhelms the liver's capacity to detoxify it, especially in patients with liver dysfunction or compromised ammonia metabolism.

Pathophysiology

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Inhibits the Citric Acid Cycle

Inhibiting-chains on Citric-lemon Cycle

The tricarboxylic acid cycle (TCA cycle) is inhibited in patients with hyperammonemia because of alpha-ketoglutarate depletion, a substrate of the citric acid cycle. In hyperammonemia, alpha-ketoglutarate is depleted when it is deaminated by NH3, forming glutamate. Thus, excess ammonia depletes alpha-ketoglutarate, leading to inhibition of the TCA cycle.

Signs & Symptoms

Somnolence

Sleepy-guy

Somnolence is a commonly seen symptom of increased ammonia levels in the blood. It is primarily a result of the neurotoxic effects of elevated ammonia levels on the brain and leads to decreased brain function. Increased blood ammonia levels also lead to disorientation, confusion, combativeness, agitation, stroke-like symptoms, lethargy, and delirium.

Slurring of Speech

Slurpee Speech-bubble

In hyperammonemia, patients may display slurring of speech. It occurs due to ammonia's neurotoxic effects on the brain, leading to motor dysfunction and impaired coordination of speech muscles involved in speaking.

Tremor

Trimmer

In cases of abnormal ammonia metabolism, such as hyperammonemia, patients can display asterixis, which is also called a flapping tremor or liver flap. This tremor is described as a tremor of the hand when the wrist is extended and is sometimes said to resemble a bird flapping its wings.

Cerebral Edema

Cerebral Edamame

Ammonia in the blood can cross the blood-brain barrier and accumulate in the brain. Once in the brain, astrocytes convert ammonia to glutamine, a process that helps detoxify ammonia but also leads to the accumulation of glutamine and intracellular osmolarity, drawing water into the cells. This water influx causes the astrocytes to swell, leading to cerebral edema. Cerebral edema is a potentially life-threatening complication of hyperammonemia, as patients can rapidly develop intracranial hypertension and death.

Blurring of Vision

Blurry Eyes

Another consequence of hyperammonemia is blurred vision, which is primarily a result of increased intracranial pressure due to cerebral edema, combined with potential direct effects on the retina and visual processing centers in the brain.

Vomiting

Vomit

High levels of ammonia in the blood can lead to nausea and vomiting. Older patients may display cyclic vomiting and episodic headaches, which are related to the cerebral edema that develops in hyperammonemia.

Treatment

Limit Protein In Diet

Limit Mr. Protein in Food

Dietary protein is a metabolic source of ammonia; thus, patients should limit the protein ingested in their diet. In these patients, caloric intake should be mainly through glucose and fats. These dietary modifications are typically combined with other treatments, such as medications, to help reduce ammonia levels in the blood.

Lactulose

bLack-tulip

Lactulose is commonly used to treat hyperammonemia. Lactulose is metabolized in the colon by bacterial flora into short-chain fatty acids, working to increase the concentration of hydrogen in the gut. This process favors the formation of NH4, which is nonabsorbable, rather than NH3. Through this mechanism, lactulose helps prevent the absorption of nitrogenous substances in the body. Rifaximin is another medication that can be used to treat hepatic encephalopathy.

Rifaximin

Rifle-fax-machine

Rifaximin is an antibiotic used to treat hyperammonemia, primarily in the context of hepatic encephalopathy, a condition caused by liver failure that leads to elevated ammonia levels. It decreases ammonia levels primarily by reducing the gut's ammonia-producing bacteria. It decreases ammonia production and absorption into the bloodstream.

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Sodium Benzoate

Salt-shaker Benz

Sodium benzoate helps treat hyperammonemia by binding ammonia to glycine, forming a substance that can be excreted in the urine. It helps lower blood ammonia levels, particularly in patients with urea cycle disorders, where the natural detoxification mechanism, the urea cycle, is disrupted.

Phenylbutyrate

Phoenix-butt

Phenylbutyrate treats hyperammonemia by forming a conjugate with glutamine, which is excreted in the urine. This process reduces the nitrogen load and helps manage ammonia levels, especially in patients with urea cycle disorders.

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