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Hyperammonemia in review: pathophysiology, diagnosis, and treatment

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Abstract Ammonia is an important source of nitrogen and is required for amino acid synthesis. It is also necessary for normal acid-base balance. When present in high concentrations, ammonia is toxic. Endogenous ammonia intoxication can occur when there is impaired capacity of the body to excrete nitrogenous waste, as seen with congenital enzymatic deficiencies. A variety of environmental causes and medications may also lead to ammonia toxicity. Hyperammonemia refers to a clinical condition associated with elevated ammonia levels manifested by a variety of symptoms and signs, including significant central nervous system (CNS) abnormalities. Appropriate and timely management requires a solid understanding of the fundamental pathophysiology, differential diagnosis, and treatment approaches available. The following review discusses the etiology, pathogenesis, differential diagnosis, and treatment of hyperammonemia.

Keywords Hyperammonemia · Dialysis · Urea cycle defects · Treatment · Pathophysiology

Introduction

Ammonia is an important source of nitrogen and is required for amino acid synthesis. Nitrogenous waste results from the breakdown and catabolism of dietary and bodily proteins, respectively. In healthy individuals, amino acids that are not needed for protein synthesis are metabolized in various chemical pathways, with the rest of the nitrogen waste being converted to urea. Ammonia is important for normal animal acid-base balance. During exercise, ammonia is produced in skeletal muscle from deamination of adenosine monophosphate and amino acid catabolism. In the brain, the latter processes plus the activity of glutamate dehydrogenase mediate ammonia production. After formation of ammonium from glutamine, α-ketoglutarate, a byproduct, may be degraded to produce two molecules of bicarbonate, which are then available to buffer acids produced by dietary sources. Ammonium is excreted in the urine, resulting in net acid loss. The ammonia level generally remains low (<40 mmol/L) due to the fact that most ammonia produced in tissue is converted to glutamine. Glutamine is also excreted by the kidneys and utilized for energy production by gut cells, which convert the nitrogen byproduct into alanine, citrulline, and ammonia, which are transported to the liver via the bloodstream. Ammonia enters the urea cycle in hepatocytes or is ultimately converted to glutamine. [1–5]

Ammonia is toxic when present in high concentrations. Endogenous ammonia intoxication can occur when there is impaired capacity of the body to excrete nitrogenous waste, as seen with congenital enzymatic deficiencies. Patients with urea cycle defects (UCD), organic acidemias, fatty acid oxidation defects, bypass of the major site of detoxification (liver) (such as that seen in cirrhosis), Reye syndrome, postchemotherapy, or exposure to various toxins and drugs can all present with elevations in ammonia. Delayed diagnosis or treatment of hyperammonemia, irrespective of the etiology, leads to neurologic damage and potentially a fatal outcome, and thus it becomes a medical emergency when present. [6]
Ammonia toxicity (pathogenesis)

Hyperammonemia refers to a clinical condition characterized by elevated serum ammonia levels and manifests with hypotonia, seizures, emesis, and abnormal neurologic changes (including stupor). It may also exert a diabetogenic effect mediated by ammonia inhibition of the insulin secretion induced by a glucose load [7]. Hyperammonemia can cause irreparable damage to the developing brain, with presenting symptoms such as posturing, cognitive impairment (mental retardation), seizures, and cerebral palsy. The total duration of hyperammonemic coma and maximum ammonia level (but not the rapidity of ammonia removal), is negatively correlated with the patient’s neurological outcome. This is concerning when ammonia levels at presentation exceed 300 mmol/L. If left untreated, the outcome can be fatal. [7, 8]

Pathologic brain changes induced by hyperammonemia

Deaths secondary to hyperammonemia reveal upon autopsy cadaverum brain edema, brainstem herniation, astrocytic swelling, and white-matter damage [8]. Neuropathologic findings seen in children with hyperammonemia include ventriculomegaly, cerebral cortical atrophy, basal ganglia lesions, neuronal loss, gliosis, intracranial bleed, and areas of focal cortical necrosis and myelination deficiencies. Electroencephalogram (EEG) denotes slow delta-wave activity, consistent with a metabolic disturbance [9–19]. The brains of neonates and infants with hyperammonemia demonstrate areas of cortical atrophy or gray/white matter hypodensities, which are remnants of lost neuronal fibers. There is also an increased number of oligodendroglia and microglia in striatum. [17]

Amino acid disturbances in the brain

Glutamine

Glutamine synthesis mediated by the astrocytic enzyme glutamine synthetase is the major pathway for ammonia detoxification in the brain and cerebrospinal fluid. In conditions in which excess ammonia exists, brain osmotically active glutamine concentrations increase, leading to astrocytic damage and swelling. Consequently, the astrocyte promotes intercellular glutamate release, which decreases the glutamate intracellular pool and ultimately leads to cell death of the glutamatergic neurons [17, 20–22]

Arginine

Although arginine is an essential amino acid for the fetus and the neonate, they still synthesize part of it through intestinal expression of carbamyl phosphate synthetase 1 (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), and argininosuccinase (AL). In the adult, arginine is synthesized through two pathways: in the intestine, CPS-1 and OTC synthesize citrulline; and AS and AL in the renal proximal tubules synthesize arginine from citrulline. Thus, patients with UCD (except Arginase deficiency I) have low serum arginine levels and need this amino acid to be replaced, although citrulline is a better replacement choice for patients with CPS-1 and OTC [17, 23]

Alterations in neurotransmission systems

Glutamatergic system

An excess of extracellular glutamate accumulates in brain when the latter is exposed to ammonia. The mechanism involves astrocytic swelling, pH and calcium (Ca²⁺)-dependent release of glutamate by astrocytes, inhibition of glutamate uptake by astrocytes through inhibition of the glutamine aspartate transporter (GLAST), and excess depolarization of glutamatergic neurons. Excess extracellular glutamate secondary to ammonia exposure promotes toxic cellular hyperexcitability through activation of N-methyl-D-aspartate (NMDA) receptors and leads to alteration in nitric oxide (NO) metabolism, disturbances in sodium/potassium adenosine triphosphatase (Na⁺/K⁺−ATPase), (causing neuronal sodium/potassium influx), ATP shortage, mitochondrial dysfunctions, free-radical accumulation, and oxidative stress, leading ultimately to cell death. Toxic stimulation of NMDA receptors can also be caused by quinolinic acid, which is an oxidation product of tryptophan acting on NMDA receptors and plays a role in the neurotoxicity seen in UCD patients (associated with death of spiny neurons in the striatum). Tryptophan and quinolinic acid concentration increases in brain and cerebrospinal fluid, respectively, in the presence of hyperammonemia. [17, 24–28]. In experimental animal models, as a protective cellular mechanism against excitotoxicity, a reduction in NMDA receptors is noted secondary to the increased release of glutamate. Nevertheless, in patients with UCD, despite the downregulation of NMDA receptors, there is still a certain degree of cellular toxicity that leads to cell death. Interestingly, prolonged cortical neuron survival has been reported to occur in hyperammonemic animals given the NMDA receptor antagonists MK-801 and 2-amino-5-phosphonovaleric acid (APV) [29]. The glutamatergic stimuli secondary to prolonged brain exposure to ammonia can also affect activation of other neurotransmission systems, such as gamma-aminobutyric acid (GABA) or benzodiazepine receptors [30]
**Cholinergic system**

This system plays a key role in cognitive development. Cholinergic neurons loss, with decreased choline acetyltransferase (ChAT) activity level, has been observed in animal models with hyperammonemia. [17, 31]

**Serotonergic system**

Tryptophan (precursor for serotonin) and 5-hydroxyindoleacetic acid (5-HT) (metabolite of serotonin) are elevated in cerebrospinal fluid of children with UCD. Experimental hyperammonemic animal models demonstrate alterations in serotonergic activity through loss of 5-HT2 receptors and an increase in 5-HT1A receptors. These physiologic responses may play a role in anorexia and sleep disturbances noted in children with UCD [32–34]

**Cerebral energy deficit**

Hyperammonemic experimental animal models develop increased superoxide production and decreased activities of antioxidant enzymes in brain cells. Blockage of nitric oxide synthase by nitroarginine or NMDA receptor antagonists prevent the latter changes, suggesting therefore that ammonia-induced oxidative stress is due to the increased nitric oxide formation as a consequence of NMDA receptor activation [34]. Indeed, excessive formation of nitric oxide seen with ammonia exposure impairs mitochondrial respiration, depletes ATP reserves, and increases free radicals and oxidative stress, which ultimately leads to neuron death [17, 26]. Creatine, too, plays a key role in cellular energy formation and is decreased in the brain cells of hyperammonemic animals due to altered creatine transport and synthesis. Acetyl-L-carnitine enhances restoration of ATP and phosphocreatine levels in ischemia and has been reported to enhance the recovery of cerebral energy deficits caused by hyperammonemia, thus having a neuroprotective effect (through restoration of cytochrome C oxidase activity and free-radical scavenging) [35–37]. Cotreatment with creatine (while there is exposure to ammonia) protects axonal growth, thereby suggesting a possible neuroprotective role for this substance. [17, 38]

**Cerebral exposure**

Once the brain has been exposed to ammonia, intracerebral endogenous protective mechanisms that prevent or limit brain damage are triggered. Astrocytes express an injury-associated survival protein—ciliary neurotrophic factor (CNTF)—which is upregulated by ammonia through p38 mitogen-activated protein kinase (MAPK) activation. Ammonia activates a variety of kinase pathways including extracellular signal regulated kinase (ERK)1/2, stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), and p38 in astrocytes. Phosphorylation of ERK1/2 and p38 are responsible for ammonia-induced astrocyte swelling, and phosphorylation of SAPK/JNK and p38 are responsible for ammonia-induced inhibition of astrocytic uptake of glutamate. Adjunct treatment with CNTF has shown to induce protective effects on oligodendrocytes by reversing the demyelination induced by hyperammonemia [17, 39, 40]

**K+ and water channels**

Although the brain edema that develops in hyperammonemic patients with UCD has been thought to occur secondary to astrocytic swelling, recently, this has been challenged. In astrocytes of hyperammonemic animals, it has been noted that a reduction of proteins that regulate the K+ and water transport at the blood–brain barrier, including connexin 43, aquaporin 4 (aquaporins are membrane proteins that mediate water movement across the membrane), and the astrocytic inward-rectifying K+ channels Kir4.1 and Kir5.1, allows ammonia to easily permeate through the aquaporin channels. In the setting of hyperammonemia, downregulation of aquaporins occurs (reflecting a protective mechanism of astrocytes to prevent ammonia entering the cell), but simultaneously, the excretion of K+ and water is altered, and an increase in brain extracellular K+ and water develops, contributing to brain edema formation [41, 42].

**Differential diagnosis of hyperammonemia**

Diagnostically, the presence of acidosis, ketosis, hypoglycemia, and low bicarbonate levels indicate that the root cause of hyperammonemia is probably due to an organic acidemia, systemic carnitine deficiency, Reye syndrome, toxins, drug effect, or liver disease. On the other hand, if there is normal lactate and no metabolic acidosis associated with the hyperammonemia, then UCD, dibasic aminoaciduria, or transient hyperammonemia of the newborn are more likely. The association of elevated liver enzymes with hyperammonemia is most consistent after insult from hepatotoxins, Reye syndrome, or carnitine deficiency [6] (Table 1).

**Urea cycle disorders**

The urea cycle produces arginine by de novo synthesis. Six enzymatic reactions comprise the cycle, which occurs in the liver. The first three reactions are located intramitochondrially and the rest are cytosolic. The enzymatic substrates are ammonia, bicarbonate, and aspartate. After each turn of the cycle, urea is formed from two atoms of nitrogen (see Fig. 1) [43]. Key enzymes in the urea cycle include CPS-1.
OTC, AS, AL, and arginase. There are cofactors necessary for optimal enzyme activity, the most clinically important of which is N-acetyl glutamate (NAG). In UCD, there is an increase in glutamine, which transports nitrogen groups to the liver for ammonia formation within hepatic mitochondria, and ammonium combines with bicarbonate in the presence of NAG to form carbamyl phosphate. If NAG is absent, hyperammonemia develops [1, 6].

The presence of an enzymatic defect in the urea cycle results in arginine becoming an essential amino acid (except in arginase deficiency), and waste nitrogen accumulates mainly as ammonia and glutamine [6]. Measurement of plasma amino acids aids in differentiating between the different urea cycle enzyme deficiencies. Citrulline is the product of CPS and OTC and the substrate for AS and AL, thus its value is of critical importance. In CPS and OTC deficiencies, plasma citrulline levels are low. These two defects are differentiated by the fact that orotic acid is elevated in OTC deficiency and absent in CPS deficiency. In AS (citrullinemia) and AL (argininosuccinic aciduria) deficiencies, plasma citrulline levels are increased (see Fig. 2). If the serum citrulline level is normal, then disorders such as argininemia, lysinuric protein intolerance, and the hyperammonemia-hyperornithinemia-homocitrullinuria syndrome should be considered [6].

The prevalence of UCD is estimated at 1:8,200 in the USA. The overall incidence of defects presenting clinically is estimated at approximately 1 in 45,000 live births [1, 44]. Each specific disorder is considered below.

### Argininosuccinic aciduria: argininosuccinase deficiency-1

The genetic deficiency responsible for this disorder is located on chromosome 7-q11.2. The diagnosis is suspected by observing hyperammonemia without acidosis in the presence of increased AL levels in plasma and urine. Plasma citrulline is also elevated. Measuring AL activity in erythrocytes or fibroblasts confirms the diagnosis. Distinguishing clinical features include mental retardation, trichorrhexis nodosa (fragile hair with a nodular appearance), and an erythematous maculopapular skin rash. The latter two are associated with arginine deficiency and disappear with arginine supplementation. Liver involvement is characterized by hepatomegaly and elevated transaminases, and the associated histopathology displays enlarged hepatocytes and fibrosis [6, 45].

### Citrullinemia: argininosuccinate synthetase deficiency

The genetic deficiency responsible for this disorder is located on chromosome 9q34. Common findings include hyperammonemia and low serum urea nitrogen and arginine levels, but the pathognomonic finding is a markedly elevated plasma citrulline level in the absence of AS. Affected individuals are able to partially incorporate the waste nitrogen into urea-cycle intermediates, which makes treatment easier [6, 45].

### Carbamyl phosphate synthetase (CPS) deficiency-1

This represents the most severe form of UCD, with early development of hyperammonemia in the neonatal period, although it can also become apparent in adolescence. The genetic deficiency responsible for this disorder is located on chromosome 2q35. Biochemical findings in this entity include recurrent hyperammonemia, absent citrulline, and low levels of arginine, urea nitrogen, and urinary orotic acid. Diagnosis is confirmed by demonstrating <10% normal CPS activity in hepatic, rectal, or duodenal tissue [6, 45, 46].

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**Table 1** Differential diagnosis of hyperammonemia

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Pediatr Nephrol
Ornithine transcarbamylase deficiency

This represents the most common urea cycle enzyme defect, with an incidence of 1 in 14,000, and is the only one inherited as a sex-linked trait. OTC catalyzes the reaction of ornithine and carbamoyl phosphate to produce the amino acid citrulline. The OTC gene is located on the short arm of the X chromosome at Xp21, which is expressed specifically in the liver and gut. Around 350 pathological mutations have been reported, and in approximately 80% of patients, a mutation is found. In girls in whom there is partial expression of the X-linked OTC deficiency disorder, mild symptoms can be seen. Only 15% of female carriers are symptomatic, and most asymptomatic carriers have a normal IQ score. Biochemical diagnostic findings include hyperammonemia, absent serum citrulline, and elevated urinary orotic acid. Liver biopsy helps confirm the diagnosis [1, 45, 47, 48].

Argininemia: arginase deficiency-1

Afflicted patients do not develop symptoms in infancy. Children develop toe walking as a characteristic feature, which progresses to spastic diplegia. Finding elevated serum arginine, urine orotic acid, and ammonia levels makes the diagnosis.

Organic acidemias

This group of autosomal recessive inherited disorders results from enzyme deficiencies in amino acid degradation pathways. Most of the disorders are due to...
defective metabolism of branched-chain amino acids (leucine, isoleucine, and valine), tyrosine, homocysteine, methionine, threonine, lysine, hydroxylysine, and tryptophan. This results in the accumulation and excretion of non-amino (organic) acids in plasma and urine. Hallmark findings in organic acid disorders include high anion gap metabolic acidosis, ketoacidosis (due to the accumulation of lactate and organic acids), and pancytopenia. Hyperammonemia is seen and is caused by accumulation of coenzyme A (CoA) derivatives, which inhibit carbamyl phosphate synthetase activity [6].

Propionic acidemia

The defect responsible for this disorder is in the enzyme propionyl-CoA carboxylase, which converts propionyl CoA to D-methylmalonyl CoA. Consequently, plasma ammonium, propionate, and glycine levels are elevated. The diagnosis is confirmed by measuring propionyl-CoA carboxylase activity in leukocytes or skin fibroblasts [6].

Methylmalonic acidemia

This disorder results from the inability to convert methylmalonyl CoA to succinyl CoA. Patients develop metabolic ketoacidosis, hypoglycemia, hyperglycinemia, pancytopenia, and hyperammonemia. There is also increased urinary excretion of methylmalonic acid [6].

Isovaleric acidemia

This entity results from a defect in leucine metabolism whereby isovaleryl CoA cannot be dehydrogenated to 3-methylcrotonyl CoA. This is characterized by a strong body odor resembling “sweaty feet.” Diagnostic features include elevated serum ammonia, isovaleric acid, and hypocarnitineemia [6].

Maple syrup urine disease

Maple syrup urine disease is characterized by maple syrup odor noted in the urine and elevated serum branched-chain amino acid concentrations (leucine, isoleucine, and valine) during the first 24 h of life. Hyperammonemia contributes to neurologic deterioration. Glutamate levels are decreased, with consequent decrease in urea synthesis [15].

Dibasic aminoacidurias

Lysinuric protein intolerance This autosomal recessive condition is characterized by lysinuria and inadequate urea formation with development of hyperammonemia. The primary defect resides in renal tubular, intestinal, epithelial, and hepatic dibasic amino acid transport mechanisms. This results in a drop of available serum levels of ornithine, lysine, and arginine, leading eventually to hyperammonemia. There are concomitant increases in urinary excretion of lysine, ornithine, arginine, and citrulline [49].

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**Fig. 2** Etiology of hyperammonemia. Urea cycle defects: ornithine transcarbamylase (OTC); carbamyl phosphate synthetase (CPS); argininosuccinate synthetase (ASS); transient hyperammonemia of the newborn (THN). Reproduced with permission from Walters and Brophy [43].
**Hyperammonemia-hyperornithinemia-homocitrullinuria**

This autosomal recessive condition results from low ornithine transport into abnormal mitochondria, resulting in decreased flow through OTC. Consequently, plasma ornithine levels rise with an associated increase in excretion of homocitrulline in the urine and hyperammonemia [6].

**Transient hyperammonemia of the newborn**

This disorder may be found in infants with a history of perinatal asphyxia, and symptoms can develop before the infant is 24 h of age. It presents in two forms: asymptomatic and symptomatic. The former is self-limited and is thought to occur secondary to a transient deficiency of one of the urea cycle enzymes, a renal transport defect of arginine or ornithine, or a deficient synthesis of ornithine. All of these presumably are related to developmental immaturity. In the second form (unknown etiology), patients present with respiratory distress, lethargy, and coma. In both forms, plasma amino acids show elevated glutamine and alanine levels. The neurologic outcome in these patients can range from normal intellectual capacity to profound mental retardation and seizures [6].

**Drug related causes**

**Salicylate** Salicylate overdose can lead to a Reye-like clinical presentation, including emesis, anorexia, fever, hyperventilation, irritability, and hallucinations. In the early phase, there is respiratory alkalosis, with later development of metabolic acidosis associated with hypoglycemia, hyperammonemia, elevated serum salicylate levels, and hepatotoxicity. The pathogenesis involves mitochondrial dysfunction and uncoupling of oxidative phosphorylation [6].

**Carbamazepine** Asterixis and hyperammonemia are uncommon complications associated with carbamazepine use. The mechanism by which hyperammonemia develops is unknown, and treatment for the latter is simply to discontinue the anticonvulsant [50–52].

**Valproic acid** Valproic acid use has been associated with the induction of hyperammonemic encephalopathy through astrocytic edema, renal tubular interference with glutamine synthesis, and/or increased renal glutaminase activity (resulting in enhanced ammoniogenesis). Valproic acid depends on carnitine for its metabolism and can deplete the latter. Hyperammonemia has been prevented by providing supplemental carnitine [53–55]. Once the valproic-acid-induced hyperammonemic encephalopathy has been identified, discontinuation of the drug results in recovery after a few days, with normalization of serum ammonia levels. In patients with inborn errors of metabolism who are having seizures, valproate should be avoided, as it can worsen the hyperammonemia [56].

**Topiramate** Topiramate in combination with valproic acid has been associated with the development of hyperammonemia [57]. The toxic effects of topiramate may relate to its ability to inhibit carbonic anhydrase, which in turn affects gamma-aminobutyric-acid-gated chloride ion conductance at the GABA A receptor and through its effect on the hepatic availability of bicarbonate (HCO3), which is also a substrate for carbamoylphosphate synthesis [53, 58]. In addition, topiramate inhibits glutamine synthetase activity in the brain, leading to toxic levels of ammonia [55].

**Tranexamic acid** This is an antifibrinolytic agent that has been associated with the development of hyperammonemia seen as cause or result of convulsions caused by the medication [59].

**Chemotherapy** Hyperammonemic coma has been described postinduction chemotherapy for acute myeloid leukemia. It has also been described in patients with multiple myeloma (as abnormal plasma-cell clones may produce ammonia) in those receiving chemotherapy with asparaginase, 5-fluorouracil (transient hyperammonemia), and in those receiving rituximab. The pathogenic mechanism is thought to be related to an acquired deficiency of glutamine synthetase of unknown cause. [60–65]

**Miscellaneous causes of hyperammonemia**

**Hypoglycin (Jamaican vomiting sickness)** This is caused by a toxin present in the unripe ackee fruit. The Jamaican vomiting sickness, which has a high mortality rate (up to 50%), is characterized by vomiting, lethargy, hallucinations, coma, hypoglycemia, hyperammonemia, and abnormal liver enzymes, which occur when this unripe fruit is ingested [6].

**Pregnancy** Hyperammonemic presentation occurs mostly during puerperium, but it has also been reported during pregnancy in patients with OTC and CPS deficiencies. During pregnancy, the healthy fetus can metabolize ammonia, whereas after delivery, this metabolic process is absent and ammonia accumulates in the mother. In addition, tissue breakdown occurs with postdelivery uterine involution, adding more waste nitrogen products to the urea cycle [66–68].

**Distal renal tubular acidosis (RTA)** Most renal production of ammonia occurs in the S1 and S2 segments of the
proximal renal tubule. The renal ammonia production and tubular reabsorption are stimulated by chronic metabolic acidosis and potassium depletion. Distal renal tubular acidosis (RTA) has been reported in association with hyperammonemia and should be considered in the differential diagnosis in infants with distal RTA who are hypokalemic [69–71].

Carnitine transport defects Carnitine transport enzyme defects manifest with hypoglycemia, lethargy, and potentially a Reye-like syndrome (hepatomegaly, elevated transaminases, and ammonia). Carnitine plays a key role as cofactor in fatty-acid metabolism and its deficiency can lead to abnormal fatty-acid oxidation, leading to development of hyperammonemia and encephalopathy. In primary systemic carnitine deficiency, an autosomal recessive condition, the organic cation transporter gene OCTN2 is mutated, resulting in hypocarnitinemia secondary to reduced renal tubular reabsorption of carnitine. Patients with this often present with hyperammonemia, encephalopathy, hypoglycemia, and myopathies [72].

Urinary tract dilatation Proteus is a bacteria that characteristically produces an alkaline urine pH due to the hydrolysis of urea to ammonia by the bacterial urease. Children with massively dilated urinary tracts whose urinary tract is infected/colonized by this bacterium may develop hyperammonemia [73].

Reye syndrome Reye syndrome is a disease of unknown etiology associated with hyperammonemia. Viruses (especially influenza B and varicella), toxins/drugs (valproic acid, salicylate, aflatoxin, pesticides, and bacillus cereus), and a genetic component (increased risk of occurrence in siblings) have been implicated as causal factors. The key physiologic findings noted are a consequence of hepatic mitochondrial injury (swelling and death) caused by inhibition of the mitochondrial respiratory chain. Abnormal findings include acute encephalopathy, hyperammonemia, lactic acidosis, hypoglycemia, elevated liver enzymes, fatty-liver infiltration, and increased intracranial pressure [6, 74].

Clinical symptoms of hyperammonemia

Symptomatology varies with patient age and ammonium level and may include, among the most common findings: hypotonia, vomiting, lethargy, seizures, coma, ataxia, anorexia, abnormal behavior patterns, dysarthria, weakness, liver enlargement, and dementia. Most patients with UCD present during the neonatal period with nonspecific symptoms (poor feeding, vomiting, somnolence, irritability, tachypnea, and lethargy).

Hepatic encephalopathy

Acute and chronic hepatic encephalopathy (HE), in which hyperammonemia plays a pivotal role, can be seen as a complication of acute (i.e., drug toxicity, infections) and chronic liver disease. Swelling of astrocytes can lead to increased intracranial hypertension, cerebral edema, brain-stem herniation, and death. Chemical abnormalities include a generalized aminoacidemia (except for branched-chain amino acid levels, which are normal), hypoglycemia, hypovolemia, electrolyte disturbances, and hyperammonemia. Once the latter is reduced to normal levels, then clinical manifestations of hepatic encephalopathy reverse [22].

Hyperammonemia treatment

Toxin removal, enzyme induction, and anabolism are the main goals of emergency treatment. Normal patient growth and development should be the main goal of long-term treatment. Given the correlation between the duration of hyperammonemic coma and prospective neurocognitive function, it is imperative to institute treatment for hyperammonemia as soon as possible to prevent further neurological damage (even prior to a definitive diagnosis being made). The infant/child neurologic status should be examined carefully to assess response to treatment and, simultaneously, to ascertain the degree of neurological impairment that has occurred as sequelae from the primary disease. Overall, the treatment approach is similar, irrespective of diagnosis. Dialysis should be immediately available and started if there is no response to conventional treatment (perhaps even at the same time).

Treatment for acute hyperammonemia should be started with the goal of decreasing serum ammonia rapidly by reducing the production of nitrogenous waste (achieved by discontinuing protein intake, for no more than 48 h) and providing a hypercaloric glucose-based solution to enhance anabolism [75]. Supportive treatment and correction of hydration, nutritional status, mineral (calcium, potassium), and electrolyte imbalances should be addressed. In patients with UCD, bacterial sepsis can lead to a fatal outcome due to catabolism, thus, antibiotic coverage should be considered even as prophylaxis, as patients often undergo multiple invasive procedures (such as line placements) that increase the infection risk [76].

If a urea cycle defect is suspected, once confirmed, treatment should be customized to the specific UCD. Attention must be paid to replacing the deficient product(s) of the UCD. Immediate arrangements for dialysis should made, and nitrogen scavengers [sodium benzoate (SB) and sodium phenylacetate (SP)] and arginine hydrochloride should be given (detailed below).
The placement of a central venous access should be considered in early acute stages in order to be able to provide parenteral nutrition, and if needed, dialysis. It is important to keep in mind, however, that placement of the central line itself causes additional stress and hence catecholamine release and protein catabolism, potentially worsening the hyperammonemia [77]. When the patient’s clinical condition is deteriorating, it is reasonable to ensure adequate airway support in the form of endotracheal intubation if necessary, as young infants can deteriorate rapidly to coma from an awake and responsive status.

Not infrequently, patients with UCD are dehydrated secondary to poor oral intake, and provision of isotonic parenteral fluid repletion helps maintain organ perfusion, hence decreasing tissue catabolism for nitrogen production as well as decreasing the risk of ischemic injury, particularly to the kidneys. Patients with UCD may have a certain degree of cerebral edema at presentation; therefore, overly aggressive hydration should be avoided and a meticulous balance of fluids should be maintained. Steroids should be avoided because they can increase the protein load via increasing the protein turnover [76].

N-carbamylglutamate (NCG) is a N-acetylglutamate analogue that helps increase ammonia clearance in N-acetylglutamate synthase (NAGS) deficiency, maple syrup urine disease, and methylmalonic and propionic acidemias. It is therefore suggested that NCG should be provided early in the course in acute neonatal hyperammonemia because it may remove the need for dialysis in some cases and can potentially improve long-term outcome [78–82]. However, it should be noted that it took between 4 and 8 h after NCG administration to affect a decrease in ammonia levels and that very high levels of ammonia were tolerated while waiting for the drug’s onset of action [78].

Ammonia scavengers

The presence of normal baseline renal function is an absolute requisite prior to ammonia scavengers being given. SP combines with glutamine to produce phenylacetylglutamine, which is excreted in the urine. In UCD, glutamine has been implicated as having neurotoxic effects; thus, its elimination may indeed prove beneficial. SP, a phenylalanine metabolite, may be teratogenic, and it also causes K+ depletion. Hence, serum K should be closely monitored. SB combines with glycine to produce hippuric acid, which is excreted in the urine, and glycine is further replaced by synthesis, thus removing more waste nitrogen. SB infusion could, in principle, lead to metabolic acidosis, hypernatremia, and hyperbilirubinemia by displacing bound bilirubin from albumin. In addition, SB is a caustic substance and can potentially cause dermatitis if it comes in contact with the skin, and may cause a burn if extravasated while being infused intravenously. SB can be used in pregnancy and has been safely infused to mothers shortly before birth of a fetus carrying a prenatal diagnosis of UCD. This strategy is successful in achieving therapeutic levels of benzoic acid in umbilical cord blood as well as in the neonate’s serum prior to delivery. SP and SB contain a considerable concentration of Na and chlorine (Cl); thus, it is recommended to avoid the concomitant use of isotonic saline solutions unless in the setting of dehydration [1, 76, 83–85].

In CPS, NAGS, and OTC defects, as well as AS and AL deficiencies, arginine becomes an essential amino acid due to defects impeding its synthesis. Arginine therapy helps prevent protein catabolism in the latter disorders. However, it is recommended to use it with caution, as in large amounts, arginine can accumulate and result in the production of large quantities of nitric oxide, which is a potent vasodilator and thus can lead to symptomatic hypotension [86, 87].

An example of a current protocol for the acute management of hyperammonemia (loading dose)

1. Arginine hydrochloride (600 mg/kg in a 10% solution)
2. A combination of SB and SP (250 mg/kg of each drug), infused in 25–35 ml/kg of 10% dextrose in water over 90 min

Reloading the patient with ammonia scavengers has to be done carefully, in particular during the first 24 h, as cumulative doses of >750 mg/kg/24 h of SB and SP have been shown to be associated with development of toxicity (vomiting, lethargy), which can be life-threatening. It can, however, be considered if dialysis is provided concomitantly [76].

An example of a current protocol for the acute management of hyperammonemia (maintenance dose)

Continuous IV infusion over 24 h is provided until the patient serum ammonia is within acceptable range and is tolerating the oral route.

1. SB/SP 250 mg/kg/24 h of each
2. In CPS, OTC, or NAGS deficiency, the arginine hydrochloride dose is 200 mg/kg/24 h
3. In AS and AL deficiency the arginine dose is 600 mg/kg/24 h
4. When awaiting final diagnosis, 200 mg/kg/24 h dose of arginine should be used in conjunction with SB and SP

In neonates with CPS or OTC deficiencies, citrulline can be provided (150–200 mg/kg/24 h) to enhance nitrogen clearance by bringing aspartate into the cycle. It is
imperative to have the underlying diagnosis in this case, as it would be detrimental to give citrulline to patients with AS and AL who already have large concentrations of this amino acid [76]. Acute intercurrent hyperammonemic crisis may be triggered by high dietary protein intake, infections, incorrect diet, or medications. Often, no obvious trigger is identified. An inadequately treated episode can lead to neurologic damage or even death. These episodes are treated again with IV infusion of SP and SB. Nitrogen excretion is promoted by large doses of arginine given to AS and AL patients, whereas citrulline is preferred for the treatment of CPS-1 and OTC deficiencies. Adequate caloric provision should be maintained with glucose-containing solution. Failure of the ammonium levels to fall toward normal within 4 h mandates initiation of dialytic therapy, which is provided until the ammonium level normalizes.

Nutrition

In the hyperammonemic acute phase, protein intake should be discontinued (because it is a source of waste nitrogen that will further increase ammonium levels), and adequate caloric supplementation from carbohydrate (10% glucose) and parenteral fat should be provided. This will avoid a catabolic state, which could raise the ammonia serum level in the UCD or organic acidemia patients. Use of total parenteral nutrition (TPN) is often the method of choice to provide adequate caloric supplementation to patients. Dietary protein restriction for >48 h should be limited, as it puts the patient at risk for protein catabolism with secondary increase of nitrogen products. Early into the treatment, 1.0–1.5 g protein/kg (of which 50% should be in the form of essential amino acids) is recommended. Insulin may be utilized, along with glucose-containing solutions to enhance the anabolic state and promote utilization of energy. Once ammonia levels have been decreased to an acceptable range in UCD, enteral feedings can be initiated at 25–50% of the patient’s total daily protein requirements (it is important not to wait >24–48 h before reintroducing the feeds) and supplementation with L-arginine and/or L-citrulline should be also included. It is possible to provide the required daily allowance (RDA) for protein when titrated appropriately with the coadministered ammonia-scavenging agents [4, 45, 76, 77, 80]. A target weight gain of 15–30 g/day reflects achievement of an anabolic state in an infant. Too much weight gain in children can lead to obesity, and this can occur if the caloric intake in the form of carbohydrates is excessive [4].

Treatment for transient hyperammonemia of the newborn is similar to that for UCD. Once ammonium levels are normalized if/when dialysis is provided, there is usually no rebound hyperammonemia. Past the neonatal period, no further episodes of hyperammonemia occur despite age-appropriate regular diet.

Dialysis

In view of the growing concern regarding the time that a developing brain is exposed to elevated ammonia levels, factors such as rapidity of ammonia clearance and hemodynamic condition of the patient should be taken into consideration when choosing a dialysis modality. Choice of modality must also take into account equipment availability and institutional experience/expertise. Early in the treatment, dialysis should be prioritized, as it is the ideal method for rapid ammonia removal. Furthermore, dialytic interventions through acute dialysis in hyperammonemic patients leads to improved outcome [88]. Upon confirmation of acceptable urine output, loading doses of ammonia scavengers to prevent ammonia from reaccumulating should be given initially, even when preparing to initiate dialysis. It is important to keep in mind that these agents often cannot remove the ammonia fast enough to keep up with the production rate, so dialysis plays a significant role in treatment.

The dialytic methods chosen should be accompanied by adequate nutritional support aiming for establishment of an anabolic state. Dialysis removes nutrients from plasma, creating a catabolic state, and plasma ammonia may rebound unless appropriate nutrition is concomitantly provided [4]. Ammonia is a small molecule that can be cleared rapidly by diffusion. Therefore, the preferred dialytic methods are hemodialysis (HD) and/or continuous renal replacement therapy (CRRT). It is of utmost importance to have a well-functioning catheter and adequate blood and dialysate flow in order to promote efficient ammonia clearance. Blood-flow rate should be set as fast as tolerated to enhance ammonia clearance [89]. Additionally, specific attention must be paid to the dialysate bath or continuous venovenous hemodialysis (CVVHD) solutions in order to maintain electrolyte homeostasis.

HD and CRRT can only be performed in specialized centers and require special vascular access, which can be difficult to obtain in the neonatal population, and complications secondary to access placement can develop (thrombosis, bleeding) [89]. In comparison, peritoneal dialysis (PD) can be provided in almost any intensive care nursery, and if no alternatives are available, it should be initiated until adequate transfer to a tertiary center is available. Whereas PD is able to provide ammonia removal, it is generally unable to keep up with the ammonia generation noted in severe cases (UCD) and so it usefulness is limited, but it may be indicated and adequate in patients with less
Severe forms of hyperammonemia and in some patients with UCDs [76, 90]. HD provides up to ten times better ammonia clearance compared with PD and can reduce plasma ammonia within hours. HD also enhances the efficiency of nitrogen removal through the clearance of amino acids such as citrulline, glycine, or glutamine. Current recommendations clearly point to HD as a primary therapy for patients with severe hyperammonemia (>1,500 mmol/L), and once serum ammonia levels are <200 µmol/L, treatment should be transitioned over to CRRT for rebound control [89, 91–93]. Whereas ammonia extraction via HD has been promoted as more efficient than other modalities, multiple dialysis sessions are often needed due to potential “rebound” in the circulation of toxic metabolites. Additionally, hypotension has been observed with HD (especially in hyperammonemic neonates), thus limiting its efficacy. In such cases, adequate clearance can be obtained using higher dose (i.e. 4,000–6,000 ml/m²/h dialysate flows) CRRT as a primary therapy rather than HD. Often, this is adequate to provide effective, safe, and hemodynamically stable clearance overall [77, 91, 94, 95]. PD is a safe, low-cost modality and can be started immediately upon catheter placement. If it is the only available modality, it can be prescribed using 1.5% standard dextrose fluid, exchange volumes of 40–50 ml/kg, with hourly cycles for up to 36 h (to allow removal of most of the ammonia burden), or longer in UCD. Potential complications of PD include obstruction, leakage, infection, and mechanical failure [13, 77, 96].

In recent years, technological progress in size and accuracy of dialyzers and lines has been made in regards to intermittent (HD) and continuous (CVVHD) therapies, continuous venovenous hemodiafiltration (CVVHDF), and continuous venovenous hemofiltration (CVVH), making these modalities more suitable for the neonatal population [88, 97]. A retrospective comparison of CVVHD versus continuous PD in hyperammonemic neonates demonstrated that CVVHD was well tolerated by neonates with hemodynamic instability, multiorgan failure, and sepsis. While CVVHD was being utilized, adequate parenteral nutrition was provided, thus avoiding potential acute catabolic protein malnutrition. Additionally, CVVHD was shown to reduce serum ammonia faster, to be associated with a reduced mortality rate (13% in CVVHD versus 50% with PD), higher survival without mental retardation (43% in CVVHD versus none with PD), and an overall reduction in prolonged hospital stay [88, 98, 99].

During acute CRRT, it is recommended to measure ammonia levels on an hourly basis, and the frequency of assessments can be spaced to every few hours once the ammonia level has decreased to <200 µmol/L [76], at which time discontinuation of therapy can be considered.

As SP and SB are small-molecular-weight molecules that are poorly protein bound and thus easily dialyzable, dose adjustments may be necessary. Both HD and CRRT have proven to clear these substances efficiently. However, therapeutic serum levels of these two ammonia scavengers can be obtained [16].

Neuroprotective interventions

Interventions have been attempted in order to provide neuroprotective effects in the setting of acute hyperammonemia, with inconclusive evidence-based results. Some of the interventions described in the literature include the use of N-methyl-D-aspartate (NMDA) receptor antagonists (i.e., memantine), because death in encephalopathic hyperammonemic patients is thought to be mediated by activation of the NMDA type of glutamate receptors in the brain. Other interventions that have been described include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and L-ornithine-L-aspartate (LOLA) (stimulates hepatic urea synthesis and increases skeletal muscle glutamine production, thereby increasing ammonia elimination) [1, 100–102]. Overall, the outcomes have been tepid at best.

Hepatic encephalopathy treatment

Identifying and correcting potential triggers (e.g., infection, high dietary protein intake, too aggressive diuresis, or gastrointestinal bleed) is imperative for treatment of hyperammonemia-associated hepatic encephalopathy. Protein intake should be limited, the gastrointestinal (GI) tract should be cleaned, sedatives discontinued, and antibiotics provided. Electrolyte disturbances should be addressed as well. The primary aim is to correct the hyperammonemia and amino acid imbalances. Lactulose or neomycin may help to reduce waste nitrogen products. Lactulose is a disaccharide that is not metabolized in the small intestine and is transported intact to the colon, where colonic bacteria transform it to lactic and acetic acids, slowing the growth of enteric bacteria that would normally metabolize urea to ammonia. Lactulose also increases colonic peristalsis, thereby decreasing nitrogen absorption and increasing fecal ammonia. Neomycin is a poorly absorbed aminoglycoside that eliminates proteolytic bacteria and reduces nitrogen load. Unfortunately, 1–3% of the neomycin is absorbed, and ototoxicity, renal tubular toxicity, and steatorrhea have been reported with long-term therapy.

Liver transplant

Orthotopic liver transplantation should be considered as a treatment option in severe UCDs, particularly CPS-1 and
OTC deficiencies) or refractory and recurrent symptomatic hyperammonemia despite conservative treatment. Transplant offers excellent survival (93% at mean follow-up 3 years), metabolic correction, and overall improved quality of life with a normal-protein diet. It has also been shown to improve, although not completely reverse, neurological deficits [103–106]. Liver-cell transplantation may offer a potential therapeutic alternative, as it has been shown to

Table 2 Protocol example: a general guide dependent on technical and personnel availability. Specific continuous venovenous hemodialysis (CVVHD) and/or hemodialysis approaches will depend on center-specific availability and standard of practice. Pediatric hyperammonemic teams will be composed of health care practitioners available at each center, as determined by standard of practice

1. Admission placement criteria:
   a. Patients suspected of hyperammonemia will be admitted to the Pediatric Intensive Care Unit (PICU) or Neonatal Intensive Care Unit (NICU).
   b. Patients with NH₃>200 will be considered for dialysis therapies.

2. Orders:
   a. Placement of hemocatheter: one double-lumen 8-F (neonates), larger for larger patients [may require another central line for TPN administration].
   b. Labs: NH₃, CBC, comprehensive electrolyte panel, ABG, and type and screen.
   c. Resuscitation with normal saline, if necessary; IV hydration to a goal UOP>2 ml/kg/h.
   d. Maintain glucose >90: usually achieved with a glucose infusion rate of 8–10 mg/kg/min. Total caloric intake requirements (glucose+intralipid) 100 kcal/kg/day for infants.
   e. Correct all electrolyte imbalances; specifically K⁺, Ca, HCO₃⁻.
   f. Diagnostic lab studies as per pediatric hyperammonemic team: initiation of scavenger therapies.

3. Treatment guidelines: The decision about when to use hemodialysis versus CVVHD will be made jointly by pediatric hyperammonemic team. This will take into account the availability of machinery, diagnosis, overall patient condition, trend in NH₃ levels, response to medical and/or dialytic therapies, age and size of the patient (infant versus older child), length of time already on dialysis, line capabilities and quality.

4. NH₃>200 and <500: Treatment with CVVHD. If NH₃>500, then high-dose CVVHD (4,000–6,000 ml/h/1.73m²)
   a. CVVHD orders:
      (i) BFR10 ml/kg/min
      (ii) DFR 2,000 ml/h/1.73 m²
      (iii) Goal UF: zero, continue hydration to maintain UOP>2 ml/kg/h.
      (iv) Hourly NH₃.
      (v) Comprehensive electrolyte panel, hematocrit, and ABG every 6 h
      (vi) NH₃ that rebounds to >200 for 2 consecutive hours should be treated with hemodialysis or significant increase in dialysate flow rate if using lower-dose dialysate flow rates for CVVHD.
      (vii) NH₃>500: treatment with hemodialysis followed by CVVHD (if required); alternately, repeated hemodialysis may be performed.
   b. Hemodialysis orders.
      (i) Age-appropriate lines and filters.
      (ii) DFR 500 ml/min.
      (iii) BFR 10 ml/kg/min.
      (iv) Dialysate bath–phosphorus bath 4.6; calcium bath 3.5; potassium 2.0 (at least, with adequate parenteral replacement as needed).
      (v) Goal UF: zero; continue hydration to maintain UOP>2 ml/kg/h; dialysis inline hematocrit monitoring (if available) should be performed during the entire hemodialysis treatment. The hematocrit must be maintained at the starting level or lower depending on the fluid status of the patient.
      (vi) Treatment time: minimum 3 h to maximum 5 h.
      (vii) Hourly NH₃.
      (viii) Comprehensive electrolyte panel, hematocrit, and ABG every 6 h.
      (ix) Goal NH₃<200 for conversion to CVVHD.

NH₃ levels ≥80 mmol/L are abnormal and require immediate attention; inborn errors of metabolism should be included in the differential diagnosis, and the pediatric hyperammonemnic team should be consulted and manage these cases

Sustained elevated NH₃ levels are associated with irreversible neurologic damage. The diagnosis, clinical condition, trend of blood ammonia elevations, or recommendations by pediatric hyperammonemnic team will be used to determine appropriate course of action

NH₃ levels >~300 require emergent hemodialysis/continuous renal replacement therapy (CRRT) intervention; patients with values <300 but increasing rapidly may also be candidates for hemodialysis/CRRT

NH₃ ammonia, TPN total parenteral nutrition, CBC complete blood count, ABG arterial blood gas, UOP urine output, K⁺ potassium, Ca calcium, HCO₃⁻ bicarbonate, CVVHD continuous venovenous hemodialysis, BFR blood flow rate, DFR dialysate flow rate

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reduce periods of hyperammonemic crises in neonatal UCD patients [107].

Genetic counseling for UCDs

All UCDs except OTC deficiency are inherited as autosomal recessive traits. Prenatal diagnosis is presently possible in citrullinemia and argininosuccinic aciduria by measuring enzyme levels in amniotic fluid. Prenatal diagnosis has been accomplished in OTC deficiency by fetal liver biopsy and measurement of OTC activity in fetal hepatocytes [6]. When available, molecular studies are preferable for diagnosing UCDs in both neonatal and prenatal settings given that they are less invasive than liver biopsies. Families with members that have genetically based hyperammonemia benefit from prenatal counseling.

Prognosis for patients with UCDs

In a large cohort of 299 patients with UCD who developed multiple episodes of hyperammonemia, a survival rate of 96% was noted and positively influenced by the prompt initiation of ammonia scavengers, provision of appropriate nutrition, and selective use of dialysis [11]. In the majority of children with UCD who survive, there are various degrees of mental retardation observed. The severity, duration, and age at onset of hyperammonemia correlates with the degree of IQ decrease, the level of developmental disabilities, and the gravity of brain abnormalities. Notably, the most severe impairments are associated with neonatal onset of hyperammonemia [17, 108]. The mortality rate of neonates presenting with their initial hyperammonemic episode differs from those who survive and have repeated hyperammonemic episodes, as well as children who present later in life (please see Enns [109] for an excellent review).

Summary

The acute approach and treatment of patients with hyperammonemia requires attention to detail and is best served by a multidisciplinary approach. Often, such patients present to the neonatal (NICU) or pediatric (PICU) intensive care unit and require initial resuscitation. A protocolized approach with members from nephrology, genetics/metabolics, nutritional, and critical care services often provides the best possible outcomes for these complex patients. A general protocol is outlined in Table 2 and represents one possible protocol. Each center must establish what resources and team members are available for their center and build their own to suit their specific patient requirements.

Questions (answers appear following the reference list)

1. In healthy individuals, the ammonia level stays within normal limits due to its conversion to:

   a) Glutamine
   b) Urea and Bicarbonate
   c) Alanine
   d) Arginine
   e) Alpha-ketoglutarate and urea

2. A 6-week-old male infant is brought to the primary care physician due to decreased responsiveness that progressed toward lethargy in the course of 3 days. The mother conveys that the infant was recently diagnosed with an upper respiratory tract infection. The infant appears lethargic on physical examination. Laboratory findings include a normal white blood cell count, hemoglobin, platelets, C-reactive protein, serum pH, electrolytes, glucose and lactate. Serum ammonia is highly elevated. Urinary ketones are absent. Of the following, the most likely cause for this infant’s status is:

   a) Urea cycle disorder
   b) Glycogen storage disorder
   c) Hyperinsulinemia
   d) Galactosemia
   e) Organic acidemia

3. The initial treatment approach in the above case should include the following except:

   a) Arginine hydrochloride
   b) Parenteral steroids
   c) Sodium benzoate
   d) Parenteral glucose solution
   e) Hemodialysis

4. The above infant is found to have OTC deficiency. The mother is G1 P1. The father is worried about him being responsible for the infant having the disease. You provide counseling to the father that:

   a) The father is an obligate carrier and responsible for the genetic transmission
   b) Nothing can be concluded unless the father undergoes genetic testing
   c) The father has most likely a de novo mutation
   d) The father inherited the OTC mutation from the patient’s paternal grandmother
   e) Reassurance should be provided that the father is not affected nor is a carrier of the OTC mutation

5. One of the key pathogenetic mechanisms for topiramate-induced hyperammonemic encephalopathy is:

   a) Renal tubular interference with glutamine synthesis
   b) Inhibition of brain glutamine synthetase activity
   c) Mitochondrial dysfunction
d) Elevation of creatine phosphokinase
e) Systemic carnitine deficiency

References
