RECOGNIZING HYPERAMMONEMIA

CHECK AMMONIA

HYPERAMMONEMIA CAN BE EXTREMELY TOXIC
TO THE CENTRAL NERVOUS SYSTEM IN INFANTS, CHILDREN, AND ADULTS.

HELP PROTECT THE BRAIN

HYPERAMMONEMIA OVERVIEW

Hyperammonemia—a metabolic condition characterized by excess ammonia in the blood—can affect patients at any age.[1]

In the neonate (days 1-28), hyperammonemia is a rare, life-threatening problem that requires prompt intervention.[2] The clinical presentation of neonatal hyperammonemia, which can mimic sepsis, includes non-specific symptoms that are mainly neurological in origin.[1,3]

Hyperammonemia in infants, children, and adults may be more episodic, difficult to recognize, and precipitated by catabolic events, protein overload, or certain drugs.[4,5,6] Although their hyperammonemia may be less severe, patients may nonetheless face serious health risks.[4,7] Nonspecific symptoms may be attributed to a wide variety of neurological and psychiatric disorders.[8,9]

The causes of hyperammonemia are diverse. Some of the more common causes include liver disease, reactions to drugs, hemolytic disease, gastrointestinal bleeds, and urea cycle disorders (UCDs) or other inborn errors of metabolism (IEMs).[3,10,11]

Untreated hyperammonemia can result in irreversible brain damage and death.[1] To improve the prognosis of patients, an increased awareness of hyperammonemia is needed.[1] Knowledge of common symptoms and triggers, along with prompt ammonia testing and treatment, is critical for improved outcomes.[1,5]

GO BEYOND SEPSIS: THINK INBORN ERRORS OF METABOLISM

Symptoms of sepsis mimic those of hyperammonemia.[3] However, when severe symptoms develop after 24 hours of age, the cause is usually a UCD or other IEM.[11]

Do not wait for sepsis results.[1]

In neonates with any unexplained alteration in consciousness or encephalopathy[1]:

- Check ammonia levels
- Call a metabolic geneticist

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HYPERAMMONEMIA IN NEONATES

The clinical presentation of neonatal hyperammonemia may include many symptoms that are neurological in origin.[1]

Signs and symptoms may include:

Neurological	Gastrointestinal*
Altered level of consciousness (from somnolence to lethargy to coma) —mimicking encephalitis or drug intoxication[6]	Progressive poor appetite[6] or poor feeding[1,13]
Irritability[12]	Vomiting[6]
Acute encephalopathy,[6] cerebral edema[12]	
Seizures (generally not isolated but with altered level of consciousness)[6,13]	
Hypotonia[14]	
Neurologic posturing[15]	
Hepatomegaly[12]	
Multiorgan failure[6]	
Peripheral circulatory failure[6]	
Respiratory distress,[6] tachypnea,[12] hyperventilation,[6] respiratory alkalosis[1]	
Sepsis-like picture[6,14] (including temperature instability,[6] hypo- or hyperthermia[1])	

*Gastrointestinal symptoms are neurological in origin.[1]

CHECK AMMONIA IMMEDIATELY IN NEONATES WITH UNEXPLAINED[1,6]:

- Poor feeding or vomiting
- Alteration in consciousness
- Encephalopathy
- Respiratory distress
- Sepsis-like symptoms

HYPERAMMONEMIA IN INFANTS, CHILDREN, AND ADULTS

The clinical presentation of hyperammonemia beyond the neonatal period may be less severe but more variable and episodic.[4,6] Because symptoms are non-specific, they may be attributed to a range of psychiatric or neurological disorders.[8,9] These symptoms may instead indicate a late-onset urea cycle disorder (UCD).

Signs and symptoms may include:

Neurological	Gastrointestinal	Psychiatric
Confusion, lethargy, dizziness[6]	Abdominal pain,[6] nausea,[13,14] vomiting[1]	Behavioral changes, mood alteration, hyperactivity, aggressiveness,[6] combativeness[13]
Migraine-like headaches[6]	Protein aversion, self-selected low-protein diet[6]	Delusions, psychosis[4]
Tremor, ataxia, dysarthria[6]	Failure to thrive[6]	Sleep disorders[15]
Intellectual/ learning disabilities, neurodevelopmental delay[6]	Hepatomegaly, elevated liver enzymes[6]	
Seizures[1]		
Hemiplegia[3]		
Coma[16]		

CHECK AMMONIA IMMEDIATELY IN INFANTS, CHILDREN, AND ADULTS WITH UNEXPLAINED[1,6,7,12,17]:

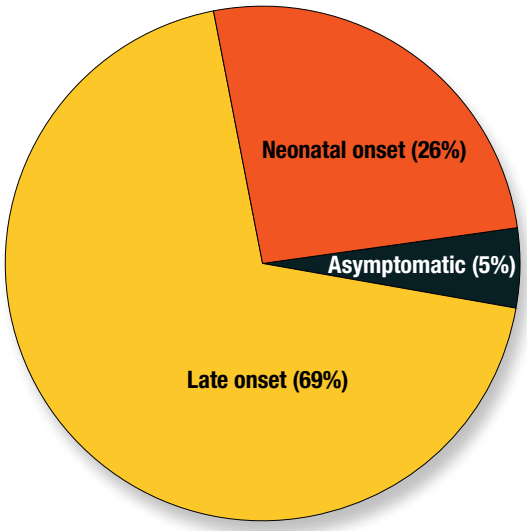
- GI presentations (e.g., vomiting, protein aversion)
- Alteration in consciousness
- Encephalopathy
- Movement disorders or seizures
- Learning problems or developmental delay
- Psychiatric presentations

LATE-ONSET UCDs AND HYPERAMMONEMIA

Hyperammonemia due to a late-onset urea cycle disorder (UCD) can occur at any age.[1,5] Adult patients, in particular, are being diagnosed with UCDs with greater frequency.[5]

Clinical Presentation of UCDs*

Most patients with UCDs present with symptoms outside the newborn period.[7]



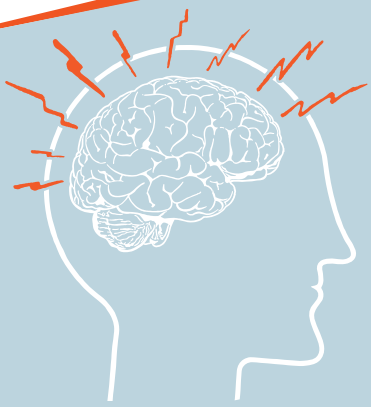
*Data from a longitudinal study of 614 UCD patients conducted by the urea cycle disorders consortium (UCDC), a member of the NIH Rare Diseases Clinical Research Network.[7]

GO BEYOND LIVER DISEASE: THINK INBORN ERRORS OF METABOLISM

In patients with any unexplained alteration in consciousness or encephalopathy, including patients with hepatic disease[1,20]:

- Consider late-onset UCDs or other IEMs
- Check ammonia levels
- Call a metabolic geneticist

Patients with milder UCDs may function relatively normally—for months or years—before their UCD is clinically recognized, although they may have experienced multiple episodes of mild to moderately severe hyperammonemia.[5,18,19] These patients typically face serious health risks, including a significant risk for developmental disabilities and a 10% risk of mortality.[7]



FAILURE TO RECOGNIZE HYPERAMMONEMIA CAN LEAD TO BRAIN DAMAGE OR DEATH.[4]

HYPERAMMONEMIA TRIGGERS

A precipitating catabolic event can trigger a hyperammonemic crisis in patients with a urea cycle disorder (UCD) or other underlying metabolic disorder.[4,5]

Known triggers may include:

- Traumatic injury or surgery[4,20]
- Illness, including viral or bacterial infections, fever, or vomiting[1,6]
- Internal bleeding[6]
- Protein overload, such as eating barbecue[6]
- Decreased protein intake, such as fasting pre-surgery[6]
- Medications
  - Valproate[6]
  - Certain chemotherapy drugs[6]
  - High-dose glucocorticoids[6]
  - Salicylic acid or aspirin (aspirin use in children with viral illness may cause Reye syndrome)[1,21]
- Rapid growth[22]
- Prolonged or intense physical exercise, such as bodybuilding[6,23]
- Peripartum stressors[15]

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HYPERAMMONEMIA: A MEDICAL EMERGENCY

The challenge is early detection.

Delayed diagnosis or treatment of hyperammonemia, regardless of cause, can lead to neurological damage and potentially a fatal outcome.[24]

Hyperammonemia in neonates:

- Initial non-specific symptoms often mimic sepsis.[3]
- Newborns who develop severe hyperammonemia >24 hours of age usually have a urea cycle disorder (UCD) or other inborn error of metabolism.[11]

Hyperammonemia in infants, children, and adults:

- More than two-thirds of UCD patients present later in life.[7]
- Catabolic events, protein overload, or certain drugs may cause a hyperammonemic crisis in patients with an underlying UCD.[6]

ACT QUICKLY TO IDENTIFY HYPERAMMONEMIA:

- Check ammonia levels
- Call a metabolic geneticist

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