

Hyperammonemia

Pathophysiology and Clinical Manifestations From Nitrogen Accumulation to Brain Injury

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Learning Objectives

At the end of this lecture, participants will be able to:

1. Understand physiological ammonia handling
2. Explain mechanisms of ammonia-induced brain injury
3. Recognize the clinical spectrum
4. Identify red flags for metabolic disease
5. Recognize hyperammonemia as a medical emergency

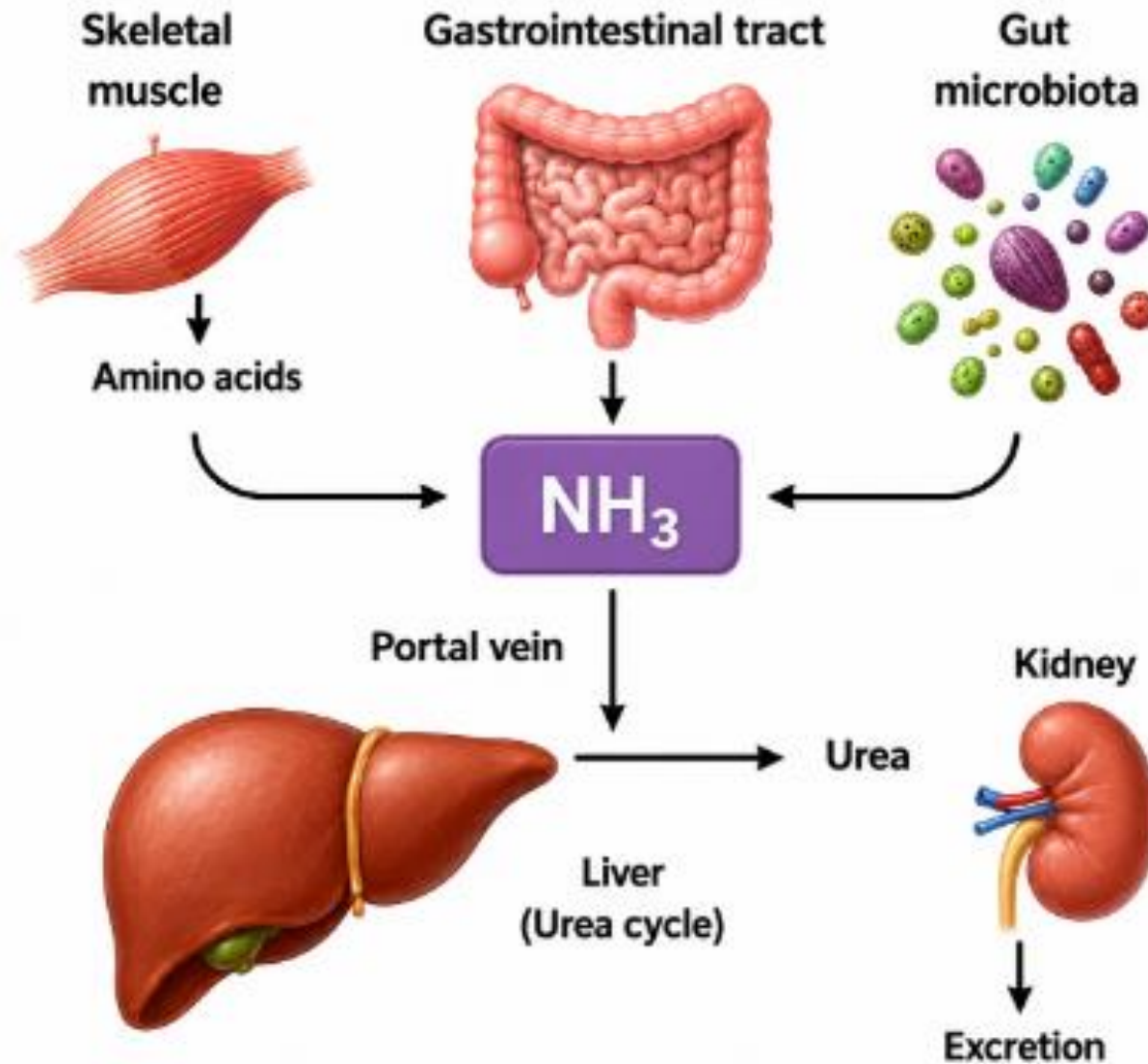
Ammonia: A Product of Nitrogen Catabolism

Major sources:

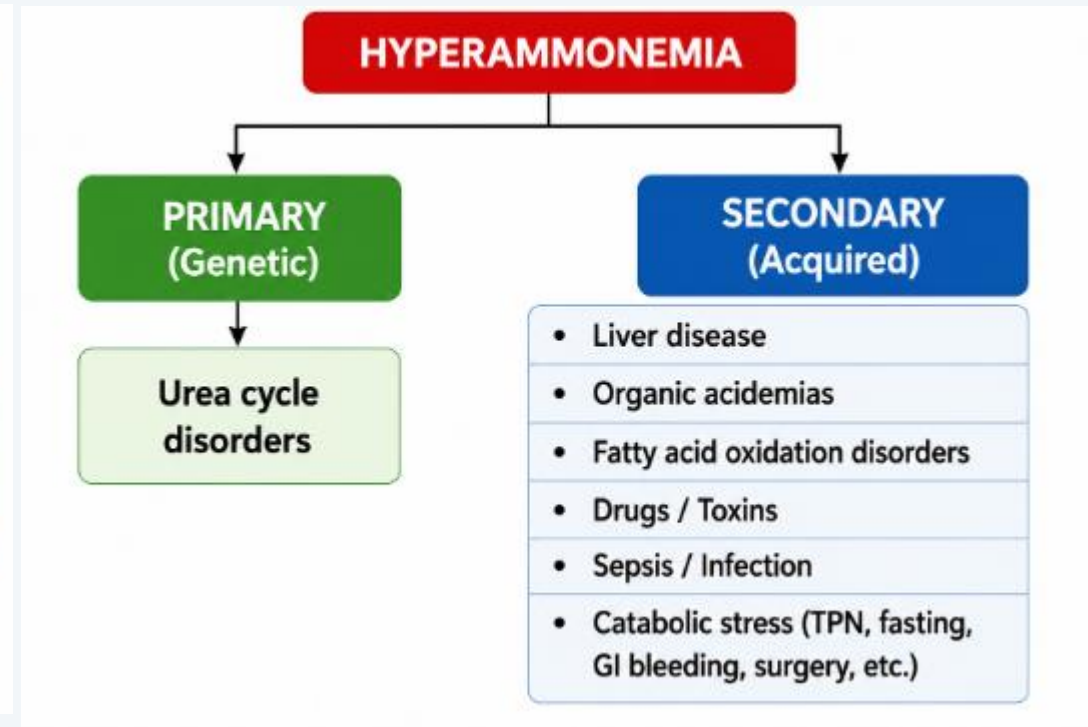
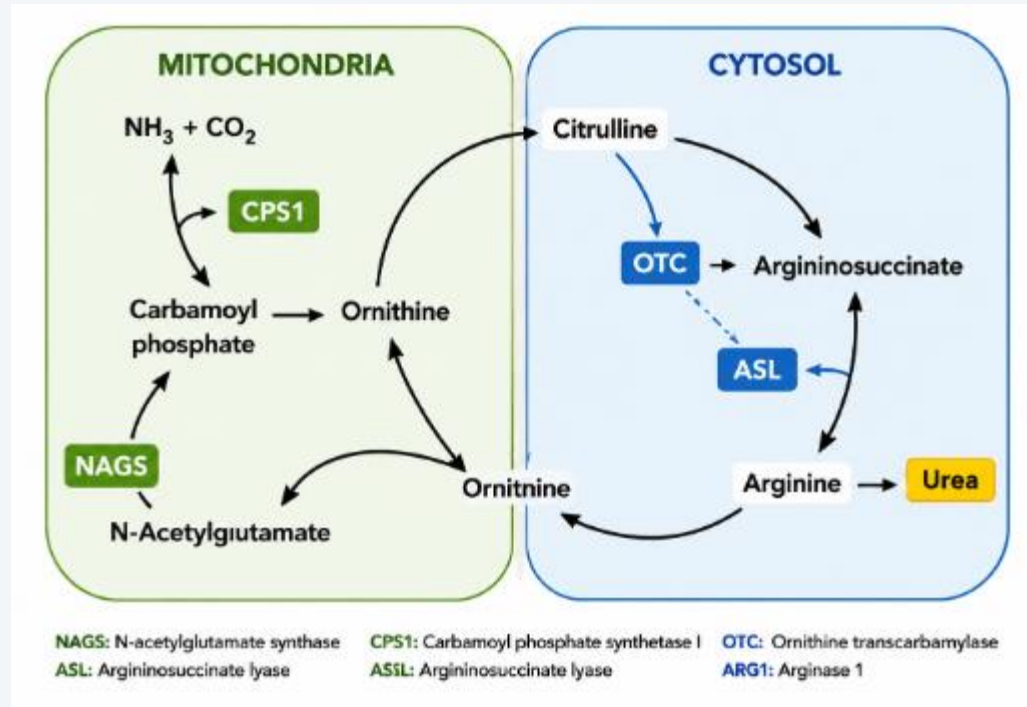
- Amino acid catabolism
- Intestinal bacterial metabolism
- Glutamine metabolism
- Skeletal muscle metabolism

Major disposal: Liver → Urea cycle → Urea → Kidney

Normal Ammonia Metabolism



The Urea Cycle: The Nitrogen Disposal Pathway



The Urea Cycle: Primary Hyperammonia

$\text{NH}_3 + \text{HCO}_3^- \rightarrow \text{Carbamoyl phosphate} \rightarrow \text{Citrulline} \rightarrow \text{Argininosuccinate} \rightarrow \text{Arginine} \rightarrow \text{Urea}$

Key enzymes: NAGS, CPS1, OTC, ASS1, ASL, ARG1

Transporters: ORNT1 / SLC25A15

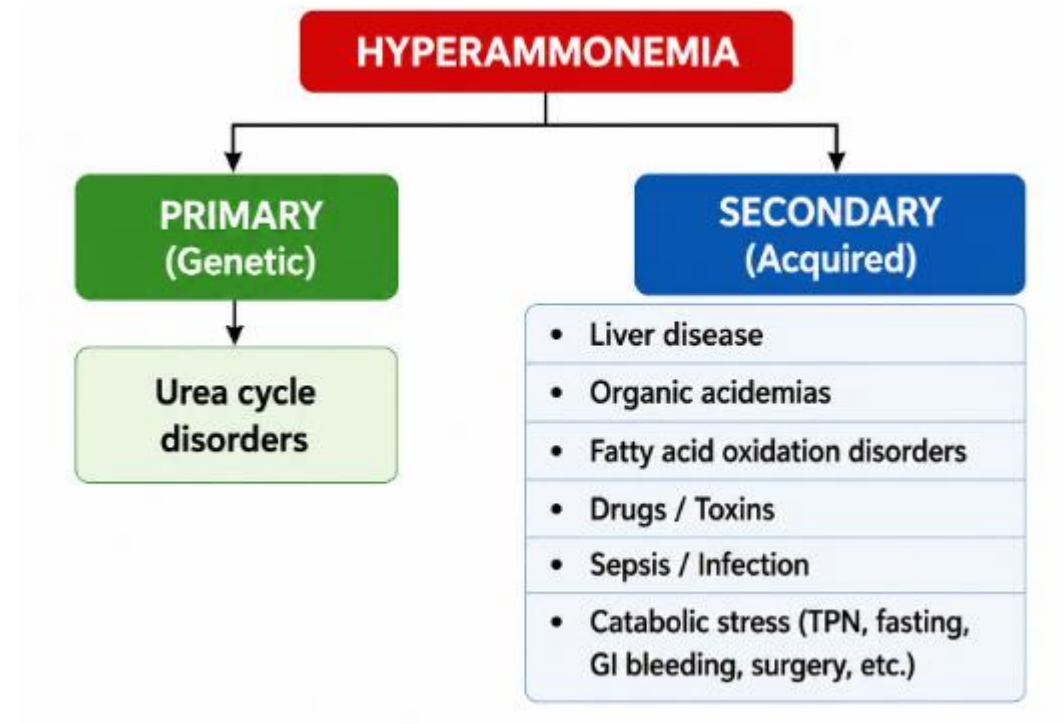
 NAGS deficiency	NAGS (17q21.31)	 
 CPS1 deficiency	CPS1 (2q33.2)	 
 OTC deficiency	OTC (Xq26.2)	 
 ASS1 deficiency	ASS1 (9q34.11)	 
 ASL deficiency	ASL (7q11.23)	 
 ARG1 deficiency	ARG1 (6q23)	 
Enzyme defect	Gene (Location)	Inheritance

Hyperammonemia: Imbalance Between Production and Disposal

↑ Nitrogen production + ↓ Ammonia detoxification → ↑ Plasma ammonia

Causes:

- Urea cycle disorders
- Liver failure / portosystemic shunting
- Organic acidemias
- Fatty-acid oxidation disorders
- Drugs (especially valproate)
- Severe catabolic states / infections



Secondary Hyperammonemia

Metabolic Disorders

- Propionic acidemia
- Methylmalonic acidemia
- Isovaleric acidemia
- Glutaric acidemia type 1
- Fatty acid oxidation disorders (MCAD, VLCAD)
- HHH syndrome
- Lysinuric protein intolerance
- Mitochondrial disorders
- Congenital disorders of glycosylation

Acquired Causes

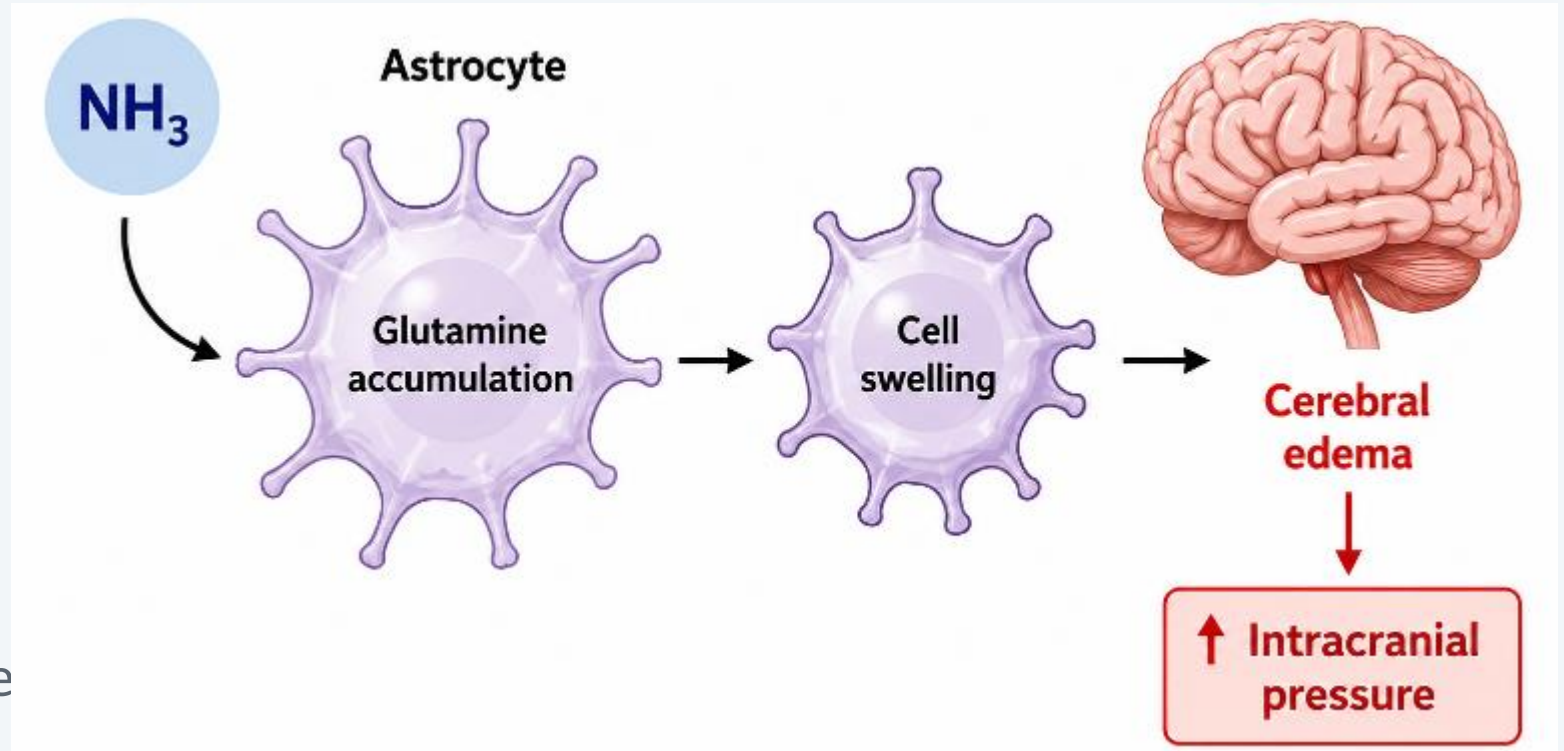
- Acute liver failure
- Valproate
- Topiramate
- Carbamazepine
- Chemotherapy
- Total parenteral nutrition
- Gastrointestinal bleeding
- Sepsis / Shock
- Burns / Trauma

Why Is Ammonia Neurotoxic?

Ammonia crosses the blood–brain barrier

$\text{NH}_3 + \text{Glutamate} \rightarrow \text{Glutamine}$
(glutamine synthetase)

↑ Intracellular glutamine
→ Astrocyte swelling
→ Cerebral edema
→ Increased intracranial pressure

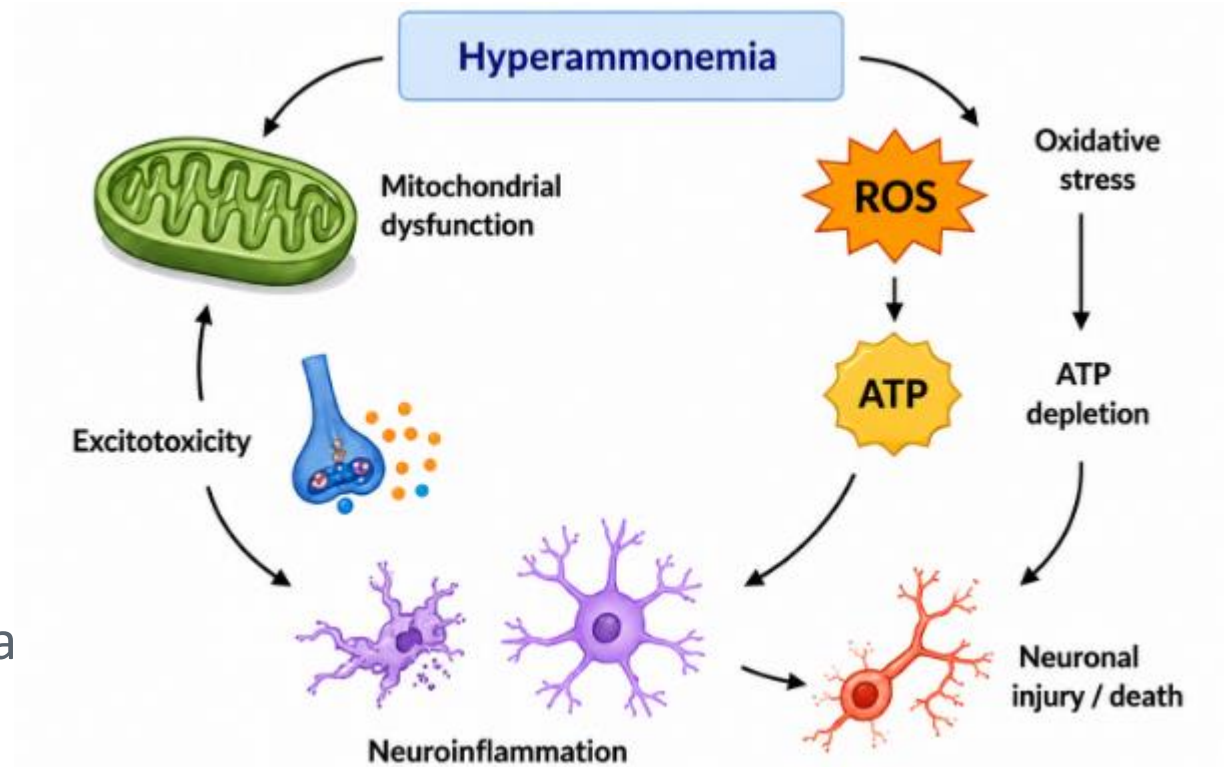


Beyond Glutamine: Multiple Mechanisms of Brain Injury

- Astrocyte swelling
- Mitochondrial dysfunction → ↓ ATP
- Neurotransmitter imbalance
- Oxidative / nitrosative stress
- Altered cerebral blood flow

FINAL PATHWAY:

Neuronal dysfunction + cerebral edema



The Hyperammonemia–Cerebral Edema Cascade

↑ Plasma ammonia



↑ Brain ammonia



↑ Astrocytic glutamine



Astrocyte swelling



CEREBRAL EDEMA



↑ Intracranial pressure → ↓ Cerebral perfusion



Seizures → Coma → Herniation → Death

Clinical Spectrum of Hyperammonemia

EARLY

Poor feeding • vomiting • headache • behavioral change • somnolence

PROGRESSIVE

Lethargy • irritability • confusion • ataxia • encephalopathy

SEVERE

Seizures • altered consciousness • coma • cerebral edema • herniation

Clinical Presentation by Age

NEONATES

Poor feeding • vomiting • lethargy • hypothermia • abnormal respiration • seizures • coma

CHILDREN

Recurrent vomiting • episodic encephalopathy • ataxia • developmental regression • behavior change

ADOLESCENTS / ADULTS

Headache • confusion • psychiatric symptoms • vomiting • altered consciousness



Poor feeding



Vomiting



Hypotonia



Tachypnea



Respiratory alkalosis



Seizures



Coma

Clinical Manifestation in Neonates

Clinical Manifestation in Infant & Children



Recurrent vomiting



Irritability



Lethargy



Ataxia



Confusion



Behavioral changes



Seizures

Clinical Manifestation

in Older Children & Adolescents

Neurological & Psychiatric Manifestation



Altered mental status



Acute psychosis



Cognitive decline



Migraine-like episodes



Encephalopathy



Coma

When Should I Think “Ammonia”?

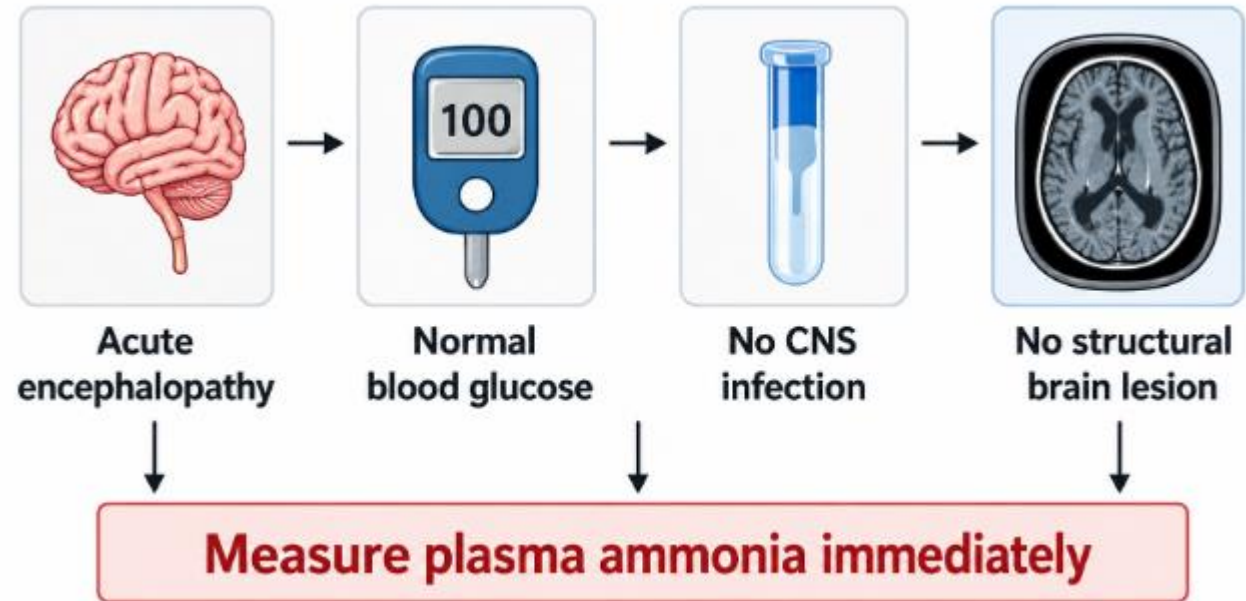
RED FLAGS

- Unexplained encephalopathy
- Recurrent vomiting
- Acute neurological deterioration
- Seizures without obvious cause
- Protein aversion
- Episodic symptoms
- Developmental regression
- Psychiatric / behavioral changes

Triggers:

infection • fasting • surgery • high protein • medications

UNEXPLAINED ENCEPHALOPATHY → CHECK AMMONIA



CASE 1 | The Sick Neonate

CLINICAL PRESENTATION

- Term male newborn; initially well.
- Day 3–4: poor feeding and recurrent vomiting.
- Progressive lethargy → reduced responsiveness.
- No fever; no clear infectious focus.
- Initially treated as neonatal sepsis.
- Neurologic status worsens despite antibiotics.

DIAGNOSTIC CLUES

- Hyperventilation / respiratory alkalosis
- Glucose and lactate not markedly abnormal
- No major hepatic failure pattern
- Low/normal BUN may be a clue
- Think: impaired nitrogen disposal

AUDIENCE VOTE

Sepsis, encephalitis—or a metabolic emergency?

Pause here: ask for 2–3 answers before revealing the ammonia.

REVEAL — AFTER VOTE

STAT ammonia: 780 $\mu\text{mol/L}$

→ Hyperammonemic crisis
→ Male neonate: severe UCD;
OTC deficiency is a leading consideration.

CASE 2 | When the Diagnosis Hides

CLINICAL PRESENTATION

- 9-year-old girl; previously normal development.
- Acute viral illness + reduced intake.
- Repeated vomiting followed by confusion and unusual behavior.
- Initially considered: gastroenteritis / encephalitis.
- Then progressive somnolence and ataxia.
- No hepatomegaly; no striking liver-failure phenotype.

DIAGNOSTIC CLUES

- AST/ALT only mildly elevated; bilirubin normal
- Respiratory alkalosis
- BUN low-normal
- Plasma amino acids + urine orotic acid guide the next step

AUDIENCE VOTE

**Inherited UCD—or
acquired
hyperammonemia?**

Pause here: ask for 2–3 answers before revealing the ammonia.

REVEAL — AFTER VOTE

STAT ammonia: 286 $\mu\text{mol/L}$

→ Partial UCD pattern
→ ↑ urinary orotic acid + low citrulline: consider OTC deficiency

A Critical Clinical Clue

HYPERAMMONEMIA / UCD



Central respiratory stimulation



Hyperventilation

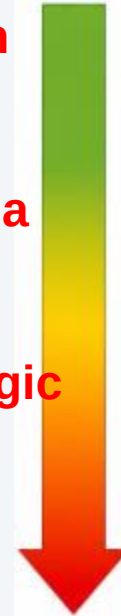


RESPIRATORY ALKALOSIS

Clinical pearl:

Unexplained encephalopathy + respiratory alkalosis → THINK UCD

**Relation
Between
Plasma
Ammonia
&
Neurologic
Injury**



Plasma Ammonia (μmol/L)	Typical Clinical Findings
100	Irritability
150	Vomiting
200	Lethargy
300	Encephalopathy
500	Coma
>800	Cerebral herniation / Death

Hyperammonemia Is a Medical Emergency

SUSPECTED HYPERAMMONEMIA



STAT plasma ammonia



STOP PROTEIN TEMPORARILY

+

PREVENT CATABOLISM WITH ADEQUATE CALORIES

+

START AMMONIA-LOWERING THERAPY

+

INVESTIGATE CAUSE SIMULTANEOUSLY

Do not wait for the final diagnosis.

The Diagnostic Mindset

Hyperammonemia → Find the Cause

First-line studies:

- Plasma ammonia
- Blood gas / electrolytes / glucose
- Lactate
- Plasma amino acids
- Urine orotic acid
- Urine organic acids
- Acylcarnitine profile

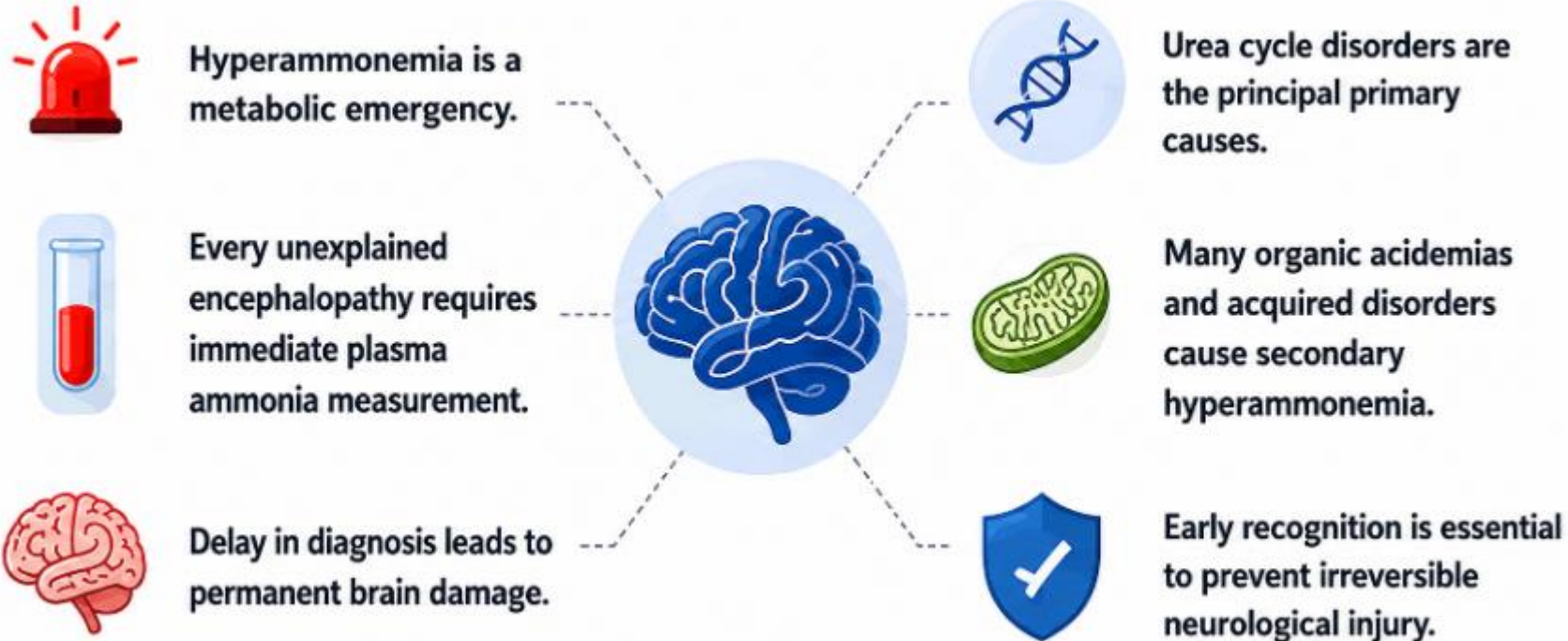
UCD | Organic acidemia | FAO disorder | Liver disease | Drug-induced | Other acquired causes

Take-Home Messages

1. Hyperammonemia is a neurological emergency.
2. Brain injury is multifactorial—especially astrocytic glutamine accumulation, cerebral edema, mitochondrial dysfunction and neurotransmitter disturbance.
3. Presentation is age-dependent and often nonspecific.
4. UCD should be considered in unexplained encephalopathy at ANY age.
5. Early recognition and rapid ammonia reduction are critical.

THINK AMMONIA. CHECK AMMONIA. TREAT EARLY.

Take Home Messages



Selected References (2024–2026)

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