RECORDATI RARE DISEASES CANADA GROUP

Rare, really?

Genetic conditions: individually rare, collectively common

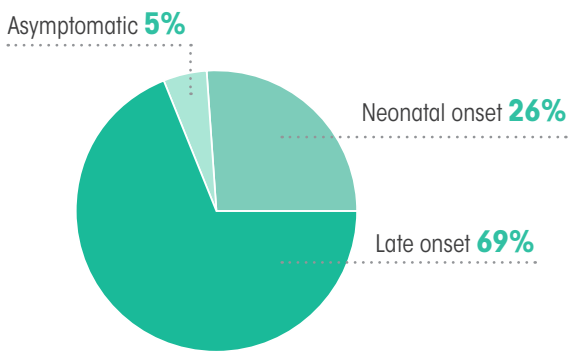
- >10,000 single gene disorders are estimated to affect 1 in 100 individuals at birth on a global basis[1]
- Inborn errors of metabolism (IEMs) result from the absence or deficiency of an intrinsic component of a metabolic pathway, often an enzyme, which disrupts cellular function due to impairment in synthesis of cellular components essential to neuronal function, or the accumulation of neurotoxic substances[2]
- IEMs are estimated to occur in ~1 of every 2500 live births[3]
- A number of IEMs are treatable, and new diagnostic methods and therapies are available[3]
- There is evidence of successful treatment and improved outcomes with early treatment in several of these diseases[3-6]

Urea cycle disorders (UCDs)

- UCDs are inborn errors of nitrogen detoxification/arginine synthesis due to defects in the urea cycle enzymes[7]
- The incidence of UCDs in the US is currently estimated at 1 in 35,000 births[8]
- Hyperammonemia due to a UCD can affect patients at any age[7]

Early clinical suspicion and rapid ammonia measurement in an emergency setting is crucial, since patient outcome correlates with the duration and peak level of hyperammonemia. The start of ammonia detoxification and of measures to reverse catabolism must not be delayed.[7]

Most patients with UCDs present with symptoms outside the newborn period



Data from a longitudinal study of 614 UCD patients conducted by the UCDs consortium, a member of the NIH Rare Disease Clinical Research Network.[9]

In the neonate (days 1–28), hyperammonemia is a rare, life-threatening problem that requires prompt intervention.[10] The clinical presentation of neonatal hyperammonemia, which can mimic sepsis, includes non-specific symptoms that are mainly neurological in origin.[11,12]

Hyperammonemia in infants, children, adolescents, and adults

Hyperammonemia in infants, children, adolescents and adults may be more episodic, difficult to recognize, and precipitated by catabolic events, protein overload, or certain drugs.[7,13,14] Although their hyperammonemia may be less severe, patients may nonetheless face serious health risks.[9,13] Non-specific symptoms may be attributed to a wide variety of neurological and psychiatric disorders.[15,16]

Signs and symptoms may include:

Neurological

- Confusion, lethargy, and dizziness[7]
- Migraine-like headaches[7]
- Tremor, ataxia, dysarthria[7]
- Intellectual/ learning disabilities, neurodevelopmental delay[7]
- Seizures[11]
- Hemiplegia[12]
- Coma[20]

Gastrointestinal

- Abdominal pain,[7] nausea,[17,18] vomiting[11]
- Protein aversion, self-selected low-protein diet[7]
- Failure to thrive[7]
- Hepatomegaly, elevated liver enzymes[7]

Psychiatric

- Behavioural changes, mood alteration, hyperactivity, aggressiveness,[7] combativeness[17]
- Delusions, psychosis[13]
- Sleep disorders[19]

Check ammonia immediately in infants, children, adolescents with unexplained:[7,9,11,21,22]

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

Hyperammonemia triggers

A precipitating catabolic event can trigger hyperammonemic crisis in patients with a UCD.[13,14] Known triggers may include:

- Traumatic injury or surgery[13,23]
- Illness, including viral or bacterial infections, fever, or vomiting[7,11]
- Internal bleeding[7]
- Protein overload, such as eating barbecue[7]
- Decreased protein intake, such as fasting pre-surgery[7]
- Prolonged or intense physical exercise, such as bodybuilding[7,26]
- Peripartum period[19]
- Rapid growth[25]
- Medications
  - Valproate[7]
  - Certain chemotherapy drugs[7]
  - High-dose glucocorticoids[7]
  - Salicylic acid or aspirin (aspirin use in children with viral illness may cause Reye syndrome)[11,24]

Failure to recognize hyperammonemia can lead to brain damage or death[13]

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