orphanaesthesia

Anaesthesia recommendations for patients suffering from

Argininosuccinate Lyase Deficiency

Disease name: Argininosuccinate Lyase Deficiency

ICD 10: E72.2

Synonyms: ASA deficiency, ASL deficiency, Argininosuccinase deficiency, Argininosuccinatelyase deficiency, argininosuccinic acid lyase deficiency

Disease summary:

Defect:
Argininosuccinate Lyase (ASL) Deficiency, also known as Argininosuccinic Aciduria (AA), is the result of a mutated or deficient argininosuccinate lyase enzyme. This defective or deficient enzyme leads to inadequate ureagenesis, accumulation of argininosuccinic acid, and deficient endogenous arginine production. Aside from the hyperammonemia pervasive to urea cycle disorders as a group, ASL deficiency is specifically associated with higher rates of neurocognitive deficits, liver disease, trichorrhexis nodosa (coarse brittle hair), impairment of creatinine clearance, chronic diarrhea, and systemic hypertension. Electrolyte imbalances of unclear etiology have been identified, even in patients not treated with nitrogen scavenging drugs. This may be due to increased renal wasting. Nitrogen scavenging therapy (such as Sodium Benzoate or Sodium Phenylbutyrate) may lead to hypernatremia and hypokalemia. Like other urea cycle disorders, this disease is rare, with incidence of approximately 1/70,000. ASL deficiency is passed via autosomal recessive inheritance, and may manifest in one of two forms: neonatal onset disease or a less severe late-onset form.

Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Disease summary

Pathophysiology:
The urea cycle is a hepatic pathway, which converts excess nitrogen to urea. Urea is then excreted via renal pathways. As the breakdown of protein results in an increased nitrogen burden, urea cycle metabolism increases during physiologic states predominated by catabolism. Stressors such as sepsis, surgery, fasting, high-protein meal consumption and heavy exercise may all induce catabolic metabolism.

If the urea cycle is impaired, nitrogen accumulates in the form of ammonia. Hyper-ammonemia may be harmful to multiple organ systems. This may be particularly damaging to the neurocognitive system. Significant hyperammonemia may lead to encephalopathy associated with vomiting, lethargy, seizure, central respiratory depression and death.

Aside from the hyperammonemia that results from inadequate ureagenesis, patients with ASL deficiency experience symptoms related to decreased endogenous arginine and increased argininosuccinic acid. Human hair is more than 10% arginine by weight. Without supplementation, patients exhibit weak brittle hair often surrounded by some degree of alopecia. Arginine deficiency may also cause systemic hypertension due to secondarily reduced synthesis of nitric oxide. Conversely, excess argininosuccinic acid may be culpable for the liver disease observed in some ASL deficient patients. Additionally, specific neurocognitive deficits (including increased incidence of ADHD and seizure activity) are associated with the disorder, the pathophysiology of which remain unclear at this time.

Presentation:
Neonatal onset disease is clinically more severe, and presents similarly to other urea cycle disorders with hyperammonemia of acute concern. Neonates are often asymptomatic for the first 24-48 hours, before exhibiting lethargy, vomiting and feeding difficulties. Neonates initially present with tachycardia and tachypnea, which progress to respiratory depression, seizures and death as ammonia accumulates. In the early stages of disease, ASL deficiency may be difficult to distinguish from other commonly presenting urea cycle disorders. However, specific to ASL deficiency, cases of neonatal onset may exhibit the hallmark manifestations of liver disease or trichorrhexis nodosa. Alternatively, late-onset disease is characterized by transient hyperammonemia. Triggers may include stress, infection, dietary changes or any other event resulting in a predominately-catabolic state.

Management:
Long-term management focuses on prevention of metabolic crises via significant lifestyle modification, while supplementing patients with exogenous arginine. These lifestyle modifications include strict adherence to a stable diet that restricts protein and avoids fasting in an attempt to maintain anabolism. Metabolic decompensations resulting in hyperammonemia require immediate medical attention. If ammonia levels do not normalize with medical management, hemodialysis may be required. Orthotopic liver transplantation may be considered in patients with recurrent decompensation resistant to medical therapy.

Prognosis:
Due to the rarity of the disease and variable presentation, prognosis is difficult to assess. In general, life expectancy is decreased, with over 65% of long-term survival (Baruteau et al 2017) 80% of patients expiring before age 20, regardless of age at onset of disease. The implementation of new treatment strategies has resulted in greater survivability of infants with neonatal onset disease. However, this increase in survival is accompanied by a significant increase in intellectual disability.

Centres

Surgery should only be carried out in centers prepared for dealing with acute hyperammonemic decompensations and should not be performed in the outpatient setting.

Typical surgery

- ENT procedures (bilateral myringotomy tubes, tonsillectomy and adenoidectomy) may be performed to decrease the risk of recurrent infections leading to metabolic crisis.
- General surgery procedures such as gastrostomy tube placement, anti-reflux procedures such as Nissen Fundoplication and vascular access procedures are all common.
- Dental procedures under anaesthesia may be required due to developmental delay
- Anaesthesia for diagnostic procedures such as CT or MRI may be necessary
- Emergency procedures such as appendectomy or trauma surgery
- Some children may require liver transplant for recurrent hyperammonemia and/or liver failure.

Type of anaesthesia

- There are insufficient data to support the superiority of any particular anaesthetic agent or technique.
- Induction:
    - Sevoflurane, sodium thiopental, isoflurane, propofol and nitrous oxide have all been reported to be safe for induction of anesthesia in other urea cycle disorders.
- Maintenance:
    - Sevoflurane, isoflurane, nitrous oxide have been safely used for maintenance of anaesthesia in other urea cycle disorders.
    - Midazolam, s-Ketamine, fentanyl and morphine in combination with surgical infiltration of ropivicaine have been reported as safe anesthetic agents in other urea cycle disorders.
    - Pancuronium, atracurium, cisatracurium and vecuronium have been used without prolongation of neuromuscular blockade in other urea cycle disorders.
- Drugs that induce catabolism such as Dexamethasone or other steroids should be avoided
- Any anaesthetic agent should be used with caution and vigilant post-operative monitoring as the stress of surgery alone may trigger a metabolic crisis.
- ENT or dental procedures with potential bleeding into the GI tract should utilize OG tubes and/or throat packs to minimize the amount of blood ingested as this protein load may represent a metabolic stressor leading to decompensation.
- General anaesthesia should be used with caution and appropriate post-operative monitoring in conjunction with a clinical geneticist or metabolic physician.

Necessary additional diagnostic procedures (preoperative)

- The following laboratory values should be evaluated pre-operatively:
    - Blood glucose
    - Serum electrolytes
        - Patients may experience hypernatremia and hypokalemia
            - More common in patients receiving Sodium Phenylbutyrate or Sodium Benzoate therapy

- Plasma ammonia
  - Serves as a direct indicator of toxicity
- Liver function tests
- Coagulation studies
  - Patients with ASL deficiency are predisposed to hepatic dysfunction with resultant disruption of coagulation pathways.
- Arterial or venous blood gas may be considered.

Particular preparation for airway management

There are no specific recommendations or disease related concerns regarding airway management.

Particular preparation for transfusion or administration of blood products

There are no specific recommendations for the transfusion of blood products.

Particular preparation for anticoagulation

Patients with Argininosuccinate Lyase Deficiency do not routinely require anticoagulation.

Particular precautions for positioning, transport or mobilisation

There are no specific recommendations or disease related concerns regarding the positioning of these patients.

Probable interaction between anaesthetic agents and patients' long-term medication

No specific interactions between maintenance medications and routine anaesthetic medications exist. Iatrogenic hypernatremia should be avoided as Sodium containing IV fluids and Sodium Benzoate in addition to maintenance Sodium Phenylbuterate represent a significant sodium burden. 1g Sodium Benzoate contains 7mmol sodium and 1g Phenylbutyrate contains 5.4mmol sodium. Long term medications should be maintained before and after surgery with conversion to IV formulations if necessary.

Anaesthetic procedure

- Involve a clinical geneticist or metabolic physician in advance for preoperative planning
  - Patients routinely take Sodium Phenylbutyrate or Glycerol Phenylbutyrate or/and sodium benzoate (ammonia scavengers) and Arginine (substrate for urea cycle metabolism beyond the deficient enzyme)
    - Glycerol Phenylbutyrate is a clear liquid medication and may be taken pre-operatively prior to elective surgery.

        - Ammonia scavenging medication should not be held prior to elective surgery
- Elective surgery should not be performed in the outpatient setting
    - Patients should not fast for prolonged periods
        - Patients should be the first case on the surgical schedule
- Labs:
    - Blood glucose
    - Serum electrolytes
    - Plasma ammonia
        - Serves as a direct indicator of toxicity
    - Liver function tests
    - Coagulation studies
        - Patients with ASL deficiency are predisposed to hepatic dysfunction with resultant disruption of coagulation pathways.
- Identify catabolic stressors (e.g. infection, trauma, etc.)
    - Treat aggressively
- Avoid intraoperative hypothermia
- Minimize protein intake
- Optimize hydration
    - The night before surgery, 10% glucose solution with electrolytes should be infused at a rate to ensure anabolic metabolism.
    - This solution should be continued until the patient is known to be tolerating enteral nutrition
- Minimize catabolic metabolism
    - The patient should preferably be kept in a state of anabolic metabolism
- Promote nitrogen excretion
- It has been suggested to avoid prophylactic anti-emetic therapy as nausea and vomiting are an early sign of metabolic decompensation [9].
- Rapid extubation is recommended in order to facilitate evaluation of consciousness, nausea and vomiting as signs of metabolic decompensation.

Particular or additional monitoring

Electrolytes, ammonia levels and blood glucose should be evaluated pre-operatively. For prolonged procedures, intra-operative monitoring of arterial or venous blood gas, glucose and ammonia levels should be considered.

Possible complications

Patients are prone to life threatening hyperammonemia which may progress to coma, brain damage and death within hours.

Post-operative care

- Patients should be observed post-operatively for signs of hyperammonemia in coordination with a clinical geneticist or metabolic physician.
- Arterial or venous blood gas, electrolytes and serum ammonia should be evaluated post-operatively every 6 hours during the first 24 hours

    - These labs should also be checked if the patient experiences signs of metabolic decompensation such as vomiting, lethargy, tachypnea or seizures.
- Glucose containing IV fluids should be continued until the patient tolerates enteral nutrition.
- Oral feeds should be resumed as soon as possible to ensure optimal caloric intake and anabolic metabolism.
- In the first 24 hours post-op, it is recommended to follow the emergency regimen prescribed for times of metabolic stress (such as surgery, infection, vomiting or diarrhea).
- In the following days, proteins can be introduced progressively
    - IV glucose administration should stop only when the patient is well and metabolically stable.
- In case there is intolerance of feeding, lipids must to be added to the IV solution.
- Ambulatory surgery is not recommended.

Information about emergency-like situations / Differential diagnostics

- Patients are prone to life threatening hyperammonemia which may progress to coma, brain damage and death within hours
    - This may be triggered by:
        - Fasting
        - Poor feeding
        - Surgical stress
        - Hypothermia
        - Minor infections
        - Mild dehydration
        - Vomiting/diarrhea
        - Medication non-compliance
        - Corticosteroids
        - Diet non-compliance
            - High protein intake
            - Failure to take metabolic formula mix or low energy intake
    - Signs of metabolic crisis include:
        - Anorexia
        - Nausea/vomiting
        - Lethargy
        - Abnormal respiratory pattern
        - Spasticity
        - Hyper-reflexia/clonus
- A clinical geneticist or metabolic physician should be contacted immediately if signs of metabolic crisis are present
    - Recommended work-up:
        - Evaluate and treat any triggers
        - Check STAT ammonia level
        - Check CBC, CMP, ABG
    - Emergency treatment:
        - Cease all protein intake
            - Patient should be made NPO
        - Generous IV hydration to correct dehydration
            - IV Normal Saline Boluses
                - Avoid Lactated Ringers

        - Maintenance IVF with fluids containing D10% (or greater) at 1.5x maintenance rate
    - Start IV intralipid therapy
    - IV Ammonia Scavenger (Ammonul) therapy and IV Arginine
    - Acidosis may be corrected slowly with sodium bicarbonate
    - Critically high ammonia levels (>400 µmol/L in children and >200 µmol/L in adults) may require emergent dialysis

Ambulatory anaesthesia

Ambulatory surgery should not be performed in patients with Argininosuccinate Lyase Deficiency due to the possibility of surgical stress triggering a metabolic crisis which may not present until the post-operative period.

Obstetrical anaesthesia

Successful pregnancy has been described in patients suffering from Argininosuccinate Lyase Deficiency [13]. There is no evidence to support the superiority of regional or general anaesthesia in these patients. Choice of anaesthetic technique should be dictated by the clinical situation. Clinical geneticists or metabolic physicians should be involved early in the pre-natal care of these patients. Patients should be monitored for signs of metabolic crisis throughout labour, delivery and the post-partum period. Involution of the post-partum uterus may trigger protein catabolism and metabolic decompensation. Anabolic metabolism should be ensured during delivery and the post-partum period. Glucose containing IV solutions should be maintained until tolerance of feeding has been documented.

Literature and internet links

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Last date of modification: December 2017

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