A Tale of Two Babies: Diagnostic Challenges in the NICU

Kaleidoscope 2017
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Disclosures: none
Objective

• Review the etiology of metabolic acidosis
• Discuss two cases that presented with metabolic acidosis
Outline

• Overview of Metabolic Acidosis

• Case 1
  • History and Presentation
  • Diagnostic work-up
  • Outcome

• Case 2
  • History and Presentation
  • Diagnostic work-up
  • Outcome

• Resources for Nurses and Parents
Metabolic acidosis is the balance between the production of hydrogen ions through metabolism & the excretion of hydrogen ions through the renal system.

- pH < 7.35
- Serum HCO₃⁻ less than 22 mEq/L
- Plasma lactate > 2.5 MMOL/L
Metabolic acidosis: Production

- Poor tissue oxygenation
  - Hypoperfusion
  - Hypoxia
  - Anemia
  - Asphyxia
  - Cold stress
- Inborn errors of metabolism
- Calorie deprivation
- Iatrogenic
- Intolerance of cow’s milk protein
Metabolic acidosis: Excretion

- Renal tubular acidosis = ↓↓ absorption of HCO3
- Premature kidneys
  - Fail to conserve HCO3
  - Fail to excrete H⁺ when faced with an acid load
- Diarrhea results in loss of buffer
The Cori Cycle

Liver

Glucose → 6 ATP → 2 Pyruvate → 2 Lactate

Muscle

Glucose → 2 ATP → 2 Pyruvate → 2 Lactate
Birth History

• Mother 40 Y/O G3P2
  – Uncomplicated pregnancy
  – Serology and GBS negative

• Infant
  – 39 week gestation, 3800 grams
  – SVD, Clear amniotic fluid
  – Delivery and nursery course uncomplicated
  – Discharged at 36 hours of life
Interim History

• Initially did well at home
• DOL 13
  – Feeding difficulty and increased WOB
  – Seen by the pediatrician
  – Formula changed from term to hypoallergenic formula
  – Improved over the next 3 days
Presentation

• DOL 16
  – Lethargic with poor feeding
• DOL 17
  – Cardiopulmonary arrest at home
  – Rescue breathing provided by mother
  – Taken to the Emergency Room
Resuscitation at Referring Hospital

• Treatment in the ER
  – Pulseless on arrival
    • Intubated
    • Epinephrine
  – Bilateral chest tube placement for pleural effusions
  – Multiple boluses of dextrose for hypoglycemia
  – NaHCO3 for severe metabolic acidosis
  – Echocardiogram → four chambers, small PFO
Stabilization at Referring Hospital

• Treatment in the PICU
  – Management of metabolic acidosis
  – Blood products for coagulopathy
  – Phenobarbital for seizures
  – Cultures and antibiotics

• Transfer to quaternary center due to abnormal NBS
Exam on Admission

- Generalized edema
- Lethargy
- Pinpoint but reactive pupils
- Bilateral chest tubes
- Grade II/VI systolic murmur
- Hepatomegaly
Case 1

History and Presentation

Diagnostic Work-Up

Outcome
Differential Diagnosis

- Infection
- Inborn Error of Metabolism
- Chylothorax
- Cardiac Disease
Significant Labs on Admission

• Anemia
  – Hgb 9, Hct 26%
• Coagulopathy
  – D Dimer >20
  – Platelets 42K
• Elevated liver enzymes
• Pleural fluid
  – Triglyceride 6.4 MMOL/L
  – WBC 13.8 (leukocytes)
Infection

- Late Onset Sepsis
  - Vancomycin resistant enterococcus (VRE) grew in pleural fluid at OSH; repeat negative
  - Blood and urine cultures negative
    - RX: Antibiotics X 5 days
- HSV
  - Onset Birth to 6 weeks
  - Seizures
  - Elevated LFTs
  - HSV PCR negative
    - RX: Acyclovir X 7 days
Inborn Error of Metabolism

• First NBS: normal
• Second NBS: **Medium / Very long chain acyl-CoA dehydrogenase deficiency (MCAD / VLCAD)**
  – Disorder of fat metabolism
  – Present with:
    • Severe metabolic acidosis
    • Seizures
    • Elevated LFTs
    • Lethargy and poor feeding
  – RX: Seen by genetics and ruled out
Chylothorax vs. Pleural Effusion

- Pleural Effusions
- Congenital or acquired
- Exudative (inflammatory)
  - Infection
  - Trauma
  - Malignancy
- Transudative
  (non-inflammatory)
  - CHF
  - Hypo-proteinemia
  - Fluid overload

Chylothorax vs. Pleural Effusion

- **Chylothorax**
  - **Effluent**
    - Milky (if feeds contain fat)
    - Increased lipid (>1-2 MMOL/L)
    - Increased lymphocytes

- Pleural effusions resolved and chest tubes removed after 7 days

Cardiac

- Murmur
- Repeat ECHO
- ECG showed pre-excitation
- Confirmed by 24 hour Holter
Diagnosis - Wolff-Parkinson-White

• Both antegrade and retrograde conduction through accessory pathways in the heart
• Develops during cardiogenesis
Wolff-Parkinson-White (WPW)

- ECG changes:
  - Short PR interval (<0.12 seconds)
  - Delta Wave
  - Widened QRS

The dotted lines represent how the PR interval and QRS complex would look without preexcitation of the ventricles through the accessory pathway.
Delta Wave
Wolff-Parkinson-White Syndrome

The dotted lines represent how the PR interval and QRS complex would look without preexcitation of the ventricles through the accessory pathway.
Wolff-Parkinson-White (WPW)

- Occurs in 0.4: 1000 live births
- 60-70% are male
- Most present before 2 months
- Most have a structurally normal heart
- More common in Ebstein’s anomaly due to displacement of the tricuspid valve
- 60-90% of WPW in infants resolve by 1 year of age

Wolff-Parkinson-White (WPW)

- During antegrade conduction to the ventricle
  - Some electricity goes through the normal pathways
    - AV node
    - Bundle of His
    - Bundle branches
  - Some electricity goes through accessory pathway(s)
  - Electricity that bypass the AV node “pre-excites” the ventricle creating a delta wave
Most common presentation: SVT (70%)

- 10-15% of infants with SVT have WPW
  - An ectopic beat travels to the ventricle through normal pathway
  - Then loops back to the atria via accessory pathway

Starts when the SA node is bypassed
Stops when blocked by the AV node
SVT Characteristics

- HR 220-280 BPM
- Diaphoresis & pallor
- Increased sleepiness
- Irritability
- Vomiting & poor feeding
Prolonged SVT

- Decreased ventricular diastolic filling time
- Decreased cardiac output
- Pulmonary vascular congestion
- CHF occurs within 24-48 hours
Sudden Cardiac Death

• Rare
• Risk when antegrade electrical flow bypasses the AV node altogether
  – Atrial fibrillation
  – Ventricular tachycardia
  – Ventricular fibrillation
Sudden Cardiac Death

• The risk of V-tach or V-fib depends on how “slick” or easily electrical impulses travel directly to the ventricle
  – 12% of patients with WPW presenting with cardiac arrest are asymptomatic
  – 20% have minor symptoms
Transesophageal Electrophysiology Study

• TEEPS
  – Risk stratification for SVT and life threatening arrhythmias
  – Identifies location of accessory pathway(s)
  – Measures conduction properties
  – Estimates risk for rapid conduction to the ventricles
  – Evaluates effectiveness of current treatment
Treatment of WPW

• Beta Blockers
• Antiarrhythmic
Case 1

History and Presentation

Diagnostic Work-Up

Outcome
In Retrospect

• Suspect prolonged arrhythmia resulted in
  – Poor feeding
  – Congestive heart failure
  – Liver failure
  – Acidosis
  – Coagulopathy
  – Pleural effusions
  – Dyspnea
Liver Dysfunction Resolved

• Coagulopathy resolved
• LFTs normalized
• Abnormal Urine Organic Acids (UOA) & Serum Amino Acids (SAA)
  – Improved over time
  – Consistent with liver failure
• Abnormal NBS cleared by Endocrine
Encephalopathy Resolved

• Developmental pediatric exam was normal
• EEG
  – No seizures
  – Phenobarbital discontinued
• MRI
  – Scattered micro-hemorrhages in periventricular white matter
  – May be at risk for attention deficit in the future
Discharge

• Propanolol
  – Holter repeated after steady state
  – Transesophageal Electrophysiology (TEEP) study
    • Unable to elicit atrial fibrillation
    • Considered moderate risk for life threatening arrhythmia and sudden death
• Full formula feedings
Follow-up

• Follow-up appointments
  – Primary pediatrician
  – Pediatric cardiology
  – Electrophysiology
  – Neurology
  – Developmental pediatrics
Case 2

History and Presentation

Diagnostic Work-Up

Outcome
Birth History

• 34 weeks PMA
• Primary C-section, AROM at delivery with clear fluid
• APGARS 5 and 7
• 1385 grams; FOC 29 cm; Length 37 cm (all <10%)
• PPV then intubation for poor respiratory effort and decreased HR
Hospital Course at Referring Hospital

• Intubated at birth, weaned to room air DOL 4
• Advanced to Similac 24 SC 125 mL/kg/day
• History of phototherapy for 24 hours
• Initial sepsis screen negative
Presentation on DOL #10 at Referring Hospital

• Seizures
  – Phenobarbital
  – Head US and CT WNL

• Apnea requiring intubation
  – Sepsis work-up
  – Vancomycin, Gentamicin, Acyclovir

• Poor perfusion

• Metabolic acidosis treated with sodium bicarbonate
Exam on Admission

- No spontaneous movement
- Unresponsive to stimulation
- No tone or reflexes
- Pupils fixed and dilated
- No spontaneous respirations
- Poor pulses, 4 sec CRT
- Hypotension
Case 2

History and Presentation

Diagnostic Work-UP

Outcome
Differential Diagnosis

- Infection
- Neurologic Event
- Inborn Errors of Metabolism
Significant Lab Work

• pH 7.48, PCO2 20, PO2 68, HCO3 15, BE -6
• Lactate 1.1
• Ammonia: 2574
• Abnormal NBS
  – Possible ASA or Citrullinemia
  – Confirmed by Citrullinemia ASS Sequence Analysis
• Blood culture - CONS
Diagnosis

- Citrullinemia Type I
- Age of onset varies
  - Acute - Neonatal (67%)
  - Mild - Late
  - Asymptomatic
  - Pregnancy/Postpartum
- ASS1 gene on chromosome 9
  - 22+ distinct mutations

Seminara et al, 2010; Roth, 2009; Bachmann 2003, Gene Reviews, 2016; Dimmock et al, 2008
Diagnosis

Citrullinemia Type I

http://www.newbornscreening.info/Parents/aminociddisorders/ASAS.html
Citrullinemia Type I Incidence

• 1:57,000 live births
• Included in the expanded newborn screen
  – Mass spectroscopy
  – Early detection may improve outcomes due to
    • Early use of nitrogen scavenging drugs
    • Rapid nutritional intervention

Preferred Nomenclature

- Common Nomenclature
  - Improves understanding
  - Supports research and collaboration in developing effective treatments
    - Argininosuccinate Synthetase Deficiency
    - Citrullinemia Type I
    - Classic Citrullinemia
    - ASS deficiency
    - AS deficiency

Genetics Home Reference, 2006; Seminara, et al 2010, NORD, GARD
Citrullinemia Type I

• Source of endogenous arginine production
• Conversion of citrulline to arginine is reduced by 50% resulting in high ammonia
• Metabolism occurs in liver, brain, kidney and skin fibroblasts to provide alternate pathways for elimination of waste nitrogen
• Osmotic effects of hyperammonemina result in brain edema

Berg et al, 2002; Roth 2009
Pathophysiology

Serial MRIs and EEGs in 1 patient with citrullinemia suggest that early and aggressive management of hyperammonemia can result in improved MRI findings.

Bindu, et al, 2009; Ruder, 3 et al, 2014
Clinical Presentation

- **Acute**
  - Poor feeding
  - Poor growth
  - Irritability
  - Vomiting
  - Somnolence

- **Crisis**
  - Hepatomegaly
  - Neurologic
    - Hypotonia
    - Tremors / Seizures
    - Pappiledema
    - Increased ICP
    - Decorticate posturing
    - Coma
  - Hypothermia
  - Tachypnea / respiratory failure

Roth, 2009; Genetics Home Reference, 2006; Dimmock et al, 2008; Haberle et al, 2009; Thoene, 2009
### Distinguishing biochemical findings of inborn errors of metabolism

<table>
<thead>
<tr>
<th>Findings</th>
<th>Maple syrup urine disease</th>
<th>Organic acidemias</th>
<th>Urea cycle defects</th>
<th>Disorders of carbohydrate metabolism</th>
<th>Fatty acid oxidation disorders</th>
<th>Mitochondrial disorders</th>
<th>Peroxisomal disorders</th>
<th>Lysosomal storage disorders</th>
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</tbody>
</table>

-: usually absent; ±: sometimes present; +: usually present; ++: always present; A: appropriate; H: inappropriately high; L: inappropriately low.
* Within disease categories, not all diseases have all findings; for disorders with episodic decompensation clinical and laboratory findings may be present only during acute crisis; for progressive disorders, findings may not be present early in the course of disease.

Triggers

- Infection is most frequent
- Diet
- Menstruation
- Pregnancy/Delivery
- Stress
- Other/unknown

Seminara, et al, 2010
Treatment

- **Hydration**
  - Rehydrate and maintain good urine output
  - Over-hydration may worsen cerebral edema

- **Limit Protein**
  - Stop protein intake for 24-48 hours
  - Provide calories from glucose and lipids to prevent catabolism

- **Avoid contraindicated drugs**

- **Limit sodium**

- **Hemodialysis or ECMO hemofiltration**

Ammonul®

• Sodium benzoate and sodium phenylacetate
  – Nitrogen scavenging
  – Forms water soluble metabolites that are excreted in urine
• Administer via dedicated central line
  – Extravasation may cause skin necrosis

Lee, 2011
Buphenyl®

- Sodium phenylbutyrate
- Converts to phenylacetate to promote urinary excretion of nitrogen waste
- Bitter taste can result in feeding avoidance
- Glycerol phenylbutyrate is a more palatable option

TCH Formulary, 2010; Quinonez et al, 2016
Arginine Replacement

• Enzyme deficiencies in the urea cycle prevent the formation of arginine; becomes an essential amino acid
• Deficiency results in a catabolic state leading to increased nitrogen levels
• Needed to generate water soluble urea cycle intermediates that increase ammonia excretion in the urine

Lee, 2011
Branched-chain Amino Acids (BCAAs)

- Promotes protein synthesis
  - Leucine, Isoleucine, Valine
- May be catabolized to serve as an energy source by skeletal muscle
  - Other amino acids require hepatic gluconeogenesis
  - Supplementation decreases protein catabolism under stress

TCH Formulary, 2010
Liver Transplantation

• Only known cure
• No need for dietary restrictions post transplant
• Does not reverse existing neurologic sequelae
• Ideal timing between 3 months and 2 years

Morioka et al, 2005; Haberle et al, 2012
Ongoing Treatment

• Restricted protein intake
• Change IV Ammonul ® to oral Buphenyl ® when possible
• Supplements
  – Essential amino acids (BCAAs)
  – Vitamins
  – Minerals
• Monitor ammonia and plasma amino acids
• Gastrostomy tube

Lee, 2011; Singh, 2007
Available Commercial Formulas

• Protein free
  – Mead Johnson 80056
  – Ross Formula ProPhree

• EAA formulas
  – Abbott Cyclinex – 1
  – SHS UCD - 1
Follow-up

• Biochemical geneticist
• Metabolic disease specialist
  – Risk for metabolic crisis in catabolic state
• Metabolic nutritionist
  – Early onset have complex nutrition needs
  – Mild/late onset may benefit from protein restriction
• Developmental follow-up

Parent Education

• Signs of impending hyperammonemia
  – Headache, mood changes, lethargy, vomiting, poor feeding, nausea, ankle clonus

• Diet restrictions

• Medications

• Triggers for metabolic crisis

Thoene, 2009
Case 2

History and Presentation

Diagnostic Work-UP

Outcome
Outcomes

• Mortality and morbidity is high in the newborn period
  – Improved with introduction of nitrogen scavenging drugs
  – 25 year study found 88% survival rate among citrullinemia patients diagnosed < 1 month of age
• Neurologic morbidity increases with duration of hyperammononemia
• Poor growth and liver dysfunction

Outcomes

• According to the Urea Cycle Disorders Consortium (UCDC) longitudinal study
  – In ASSD (n=75) cognitive impairment may be evident in the absence of recurrent hyperammonemia.

• Citrulline or its metabolic products may be neurotoxic
  – Leading to cerebral edema and cell death

Neuropsychological Deficits as Adults

- Developmental delay/learning disability
- Seizure disorder
- Vision problems
- Hearing impairment
- ADHD
- Psychiatric disorder
  - Including postpartum psychosis (case reports)

Liver Transplant

• For patients that are unresponsive to medical management
• 100% 5 year survival for citrullinemia patients
  – Data from 113 UCD patients from 1988-2004 United Network for Organ Sharing (UNOS)
• High rate of complications in infants
• Can permanently normalize elevated ammonia levels
• Living donor liver transplants
• Alternative options under investigation
  – Gene Therapy, Liver Cell and Stem Cell Transplant
Case Outcome

• Ammonul® and arginine rapidly reduced ammonia levels (<200 by ~36 hours after admission)
• Extubated 2 days after starting treatment
Case Outcome

• EEG
  – Seizures resolved and Phenobarbital stopped
  – EEG improved
  – MRI at 40 weeks gestation
    • Cerebral edema resolved
    • Prominent CSF spaces surround brain
    • Prominent ventricular system
    • Cystic encephalomalacia
    • Myelination less than expected for age
Case Outcome

• G-tube placed
• Discharged on continuous feedings of cyclinex-1
  – Feedings were prescribed by metabolic dietitian
    • Total protein intake 2.5 gm/kg/day
  – Phenylbutyrate
  – Arginine
  – BCAA
Case 2

History and Presentation

Diagnostic Work UP

Outcome

Resources
Patient education: Wolff-Parkinson-White syndrome (The Basics)

Written by the doctors and editors at UpToDate

What is Wolff-Parkinson-White syndrome? — Wolff-Parkinson-White (WPW) syndrome is a condition that can cause fast heartbeats that in turn cause episodes of dizziness or fainting.

People with WPW syndrome can have episodes when their heart beats much faster than normal. This can cause symptoms. The fast heartbeat can come and go suddenly. Sometimes, a fast heartbeat goes back to normal on its own. Other times, treatment is needed.

How do normal heartbeats happen? — A normal heartbeat happens when an electrical signal starts in one spot near the top of the heart. This electrical signal follows a path to spread across the heart. As it spreads, the signal causes the heart muscle to squeeze. Each time the heart squeezes, blood is sent all over the body. Normally, the heart beats in a regular way 60 to 80 times a minute.

People can have abnormal heartbeats if:

- The electrical signal does not start in the right place
- The electrical signal does not follow the right path as it spreads across the heart

Why is the heartbeat abnormal in WPW syndrome? — The heartbeat can be abnormal in WPW syndrome, because people with WPW syndrome have an abnormal extra path in the heart. When the electrical signal follows the abnormal extra path, the heart can beat at a rate that is much faster than normal.

Some people have an abnormal extra path in their heart, but they do not have a fast heartbeat. These people do not have any symptoms and do not have WPW syndrome. Instead, they have a “WPW pattern.” These people usually do not need treatment.

What are the symptoms of WPW syndrome? — People with WPW syndrome can have symptoms that include:

- Feeling their heart beating too fast
- Feeling dizzy or light-headed
- Fainting

Most people with WPW syndrome do not have any other heart problems, but some do. People with WPW syndrome who have other heart problems can have more serious symptoms. These include:

- Chest pain
- Trouble breathing

WPW syndrome can be life-threatening, because it can cause sudden death. But this is rare.

Is there a test for WPW syndrome? — Yes. Doctors can diagnose WPW syndrome by doing a test called an “electrocardiogram” (also called an “ECG” or “EKG”) (figure 1). An ECG measures the electrical activity in the heart. It can show if a person has an abnormal heart rhythm or rate.

Sometimes, a doctor will do another procedure to figure out where the extra path is and if it needs to be treated.

How is WPW syndrome treated? — WPW syndrome is treated in different ways. Some treatments can stop episodes of fast heartbeats. Other treatments can prevent episodes of fast heartbeats from happening in the future.
Wolff-Parkinson-White syndrome (WPW)

Wolff-Parkinson-White (WPW) syndrome is a condition in which there is an extra electrical pathway in the heart. The condition can lead to periods of rapid heart rate (tachycardia).

WPW syndrome is one of the most common causes of fast heart rate problems in infants and children.

Causes

Normally, electrical signals follow a certain pathway through the heart. This helps the heart beat regularly. This prevents the heart from having extra beats or beats happening too soon.

In people with WPW syndrome, some of the heart’s electrical signals go down an extra pathway. This may cause a very rapid heart rate called supraventricular tachycardia.

Most people with WPW syndrome do not have any other heart problems. However, this condition has been linked with other cardiac conditions, such as Ebstein anomaly. A form of the condition also runs in families.

Related MedlinePlus Health Topics

Arrhythmia

Images

Ebstein’s anomaly

Holtz heart monitor

Conduction system of the heart

Read More

Cardiac ablation procedures

Heart pacemaker

Pulse

Pulse - bounding
Citrullinemia is an inherited disorder that causes ammonia and other toxic substances to accumulate in the blood. Two forms of citrullinemia have been described; they have different signs and symptoms and are caused by mutations in different genes.

Type I citrullinemia (also known as classic citrullinemia) usually becomes evident in the first few days of life. Affected infants typically appear normal at birth, but as ammonia builds up in the body they experience a progressive lack of energy (lethargy), poor feeding, vomiting, seizures, and loss of consciousness. These medical problems are life-threatening in many cases. Less commonly, a milder form of type I citrullinemia can develop later in childhood or adulthood. This later-onset form is associated with intense headaches, partial loss of vision, problems with balance and muscle
Newborn Screening ACT Sheet
[Increased Citrulline]
Amino Aciduria/Urea Cycle Disorder

Differential Diagnosis: Citrullinemia I, argininosuccinic acidemia, citrullinemia II (citrin deficiency), pyruvate carboxylase deficiency.

Condition Description: The urea cycle is the enzyme cycle whereby ammonia is converted to urea. In citrullinemia and in argininosuccinic acidemia, defects in argininosuccinic acid (ASA) synthetase and lyase, respectively, in the urea cycle result in hyperammonemia and elevated citrulline.

You should take the following actions:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- Immediate consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, vomiting, lethargy, hypotonia, tachypnea, seizures, and signs of liver disease). Measure blood ammonia. If any sign is present or infant is ill initiate emergency treatment for hyperammonemia in consultation with metabolic specialist.
- Transport to hospital for further treatment in consultation with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- Provide family with basic information about hyperammonemia.
- Report findings to newborn screening program.
Citrullinemia Type 1

NORD gratefully acknowledges Jess G. Thoene, MD, Director, Biochemical Genetics Laboratory, Active Professor Emeritus of Pediatrics, University of Michigan, for assistance in the preparation of this report.

Synonyms of Citrullinemia Type 1

- argininosuccinate synthetase deficiency
- argininosuccinic acid synthetase deficiency
- ASS deficiency
- citrullinemia, classic
- CTLN1

General Discussion
Disorder Definitions

There can be an overlap in the symptoms of the different urea cycle disorders because they affect the body in the similar ways. Hence, descriptions of an individual disorder and the methods used to diagnose a particular disorder may be similar to other urea cycle disorders. The figure of the urea cycle illustrated here shows the role of the enzymes (depicted in blue) and transporters (depicted in red) in conversion of ammonia nitrogen into urea. The nitrogen from ammonia and aspartate is "handed over" to a number of intermediate compounds (depicted in green) before finally being converted into urea. A deficiency of any of the enzymes or transporters of the urea cycle leads to an inability or reduced ability to dispose of nitrogen and accumulation of ammonia.

- **N-acetylglutamate Synthase (NAGS) Deficiency**
- **Carbamoyl-phosphate Synthase 1 (CPS1) deficiency**
- **Ornithine Transcarbamylase (OTC) Deficiency**
- **Argininosuccinate Synthase (ASS1) Deficiency (Citrullinemia type I)**
- **Citrin Deficiency (Citrullinemia type II)**
- **Argininosuccinate Lyase (ASL) Deficiency (Argininosuccinic Aciduria)**
- **Arginase (ARG) Deficiency (Hyperargininemia)**

**Argininosuccinate Synthase (ASS) Deficiency (also known as Citrullinemia type I)**

The enzyme ASS1 (or ASS) uses the citrulline produced by OTC and combines it with the amino acid aspartate to make a compound called argininosuccinate. Patients with complete deficiency of ASS (most severe type of this disorder) present with high levels of ammonia soon after birth. The blood level of citrulline in these patients is typically many times higher than the normal. The specific diagnosis can be made by plasma amino acid analysis based on extremely elevated citrulline levels and/or by enzyme analysis of cultured skin cells obtained from a skin biopsy, or by genetic testing.
Disease Name: Citrullinemia
Alternate name(s): Argininosuccinic acid synthetase deficiency
Acronym: ASAS
Disease Classification: Amino Acid Disorder
Variants: Yes
Variant name: Citrullinemia type II (adult and neonatal onset forms) – caused by SLC25A13 mutations
Symptom onset: Neonatal with some variability
Symptoms: Potential lethal coma, seizures, anorexia, vomiting, lethargy, apnea and hypertonia. Possible enlarged liver.
INITIAL POSITIVE SCREENS

FAQS

DISORDER DESCRIPTIONS

SCID BROCHURES

CITRULLINEMIA (CIT)
An inherited disorder of the Urea Cycle in which the body cannot process proteins which causes ammonia to accumulate in the blood. Ammonia is toxic especially to the brain and liver if the levels become too high.
Website

CITRULLINEMIA TYPE II (CIT II)
An inherited disorder of the Urea Cycle in which the body cannot process proteins which causes ammonia to accumulate in the blood. Ammonia is toxic especially to the brain and liver if the levels become too high. This disorder also has a late-onset type not seen until adulthood.
Website

DISORDERS OF VITAMINS & COFACTORS

BIOTINIDASE DEFICIENCY (BIOT)
An inherited disorder in which the body is unable to use biotin, which is important for the metabolism of fatty acids and in production of blood cells.
Website
Take home messages…

– Abnormal HR should be followed up even if short
– ECG if unmonitored arrest
– Ammonia level if change in LOC

Parent teaching is essential!