The Essentials

National Urea Cycle Disorders Foundation

Project ECHO®

Welcome

Session 2

Diagnosis and Treatment

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Session 3: The Importance of Diet
Tuesday, September 16, 5-6:30 pm ET
Nicholas Ah Mew, MD and Erin MacLeod, PhD, RD, LD, Children's National Hospital

Session 4: Long-term Management
Tuesday, November 11, 5-6:30 pm ET
Laura Konczal, MD, University Hospitals Cleveland Medical Center

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Session 2: Diagnosis and Treatment

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Session 2 : Diagnosis and Treatment

Time	Content
5 minutes	Introductions and housekeeping
50 minutes	Didactic presentations: Sandesh CS Nagmani, MD, Baylor College of Medicine and Andrea Gropman, MD, St. Jude Research Hospital
20 minutes	Case studies
15 minutes	Group discussion

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

The Essentials

- If possible, please make sure to keep your camera turned on
- ECHO is intended for educational purposes only
- Presenters cannot and will not provide medical advice
- To receive CME credit, please remain in the session and complete the evaluation form using the link that will be provided after the presentation

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Welcome

Introduce yourself in the chat

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Urea Cycle Disorders:
Diagnosis and Treatment

Sandesh CS Nagamani, MD
Professor, Vice Chair for Clinical Research
Department of Molecular and Human Genetics
Professor, Department of Medicine
Baylor College of Medicine
Texas Children's Hospital
Houston, TX, USA

Andrea Gropman, MD
Director, Neurometabolic Translational Research
Mark F. Tamer Endowed Chair in Pediatric Neurology
St. Jude Children's Research Hospital
Memphis TN, USA

Financial Disclosures (SN)

Active/recent research funding or collaborations	Sanofi*, Innovations in Data Exploration and Analysis* (Sanofi)
Advisory Committee	Sanofi (2021), NextCure (2024)

Financial Disclosures (AG)

Speaker	Baylor Miraca

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Objectives

- **Diagnosis of UCDs**
  - ✓Overview of UCDs
  - ✓Review clinical presentations of UCDs (clinical diagnosis)
  - ✓Review biochemical features (biochemical diagnosis)
  - ✓Review practical aspects of genetic testing (molecular diagnosis)

- **Treatment of UCDs**
  - ✓ General principles of acute hyperammonemia
  - ✓ General principles of long-term treatment
  - ✓ Emerging therapies

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Objectives

- **Diagnosis of UCDs**
  - ✓Overview of UCDs
  - ✓Review clinical presentations of UCDs (clinical diagnosis)
  - ✓Review biochemical features (biochemical diagnosis)
  - ✓Review practical aspects of genetic testing (molecular diagnosis)

- **Treatment of UCDs**
  - ✓ General principles of acute hyperammonemia
  - ✓ General principles of long-term treatment
  - ✓ Emerging therapies

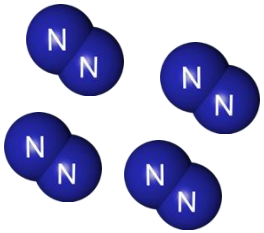
Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

All living things need nitrogen

National Urea Cycle Disorders Foundation

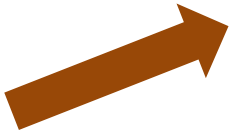
Project ECHO

Atmosphere



Proteins of all tissues

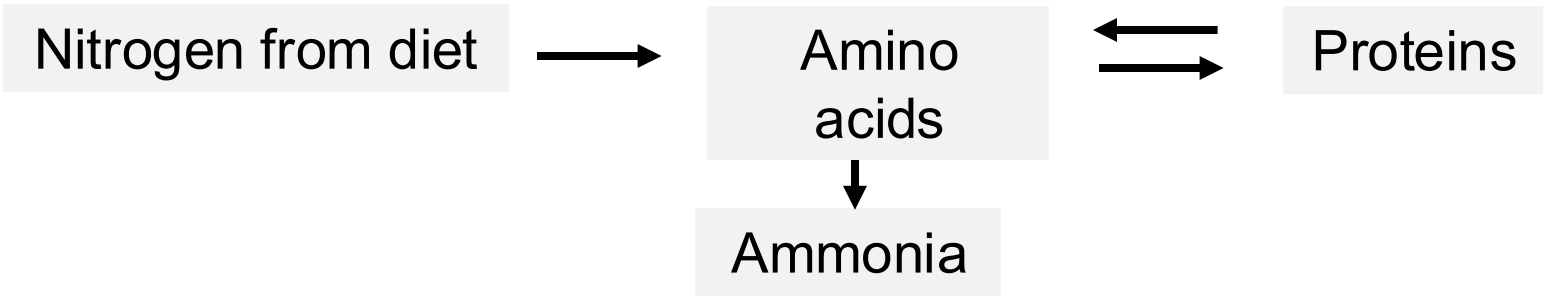
Food



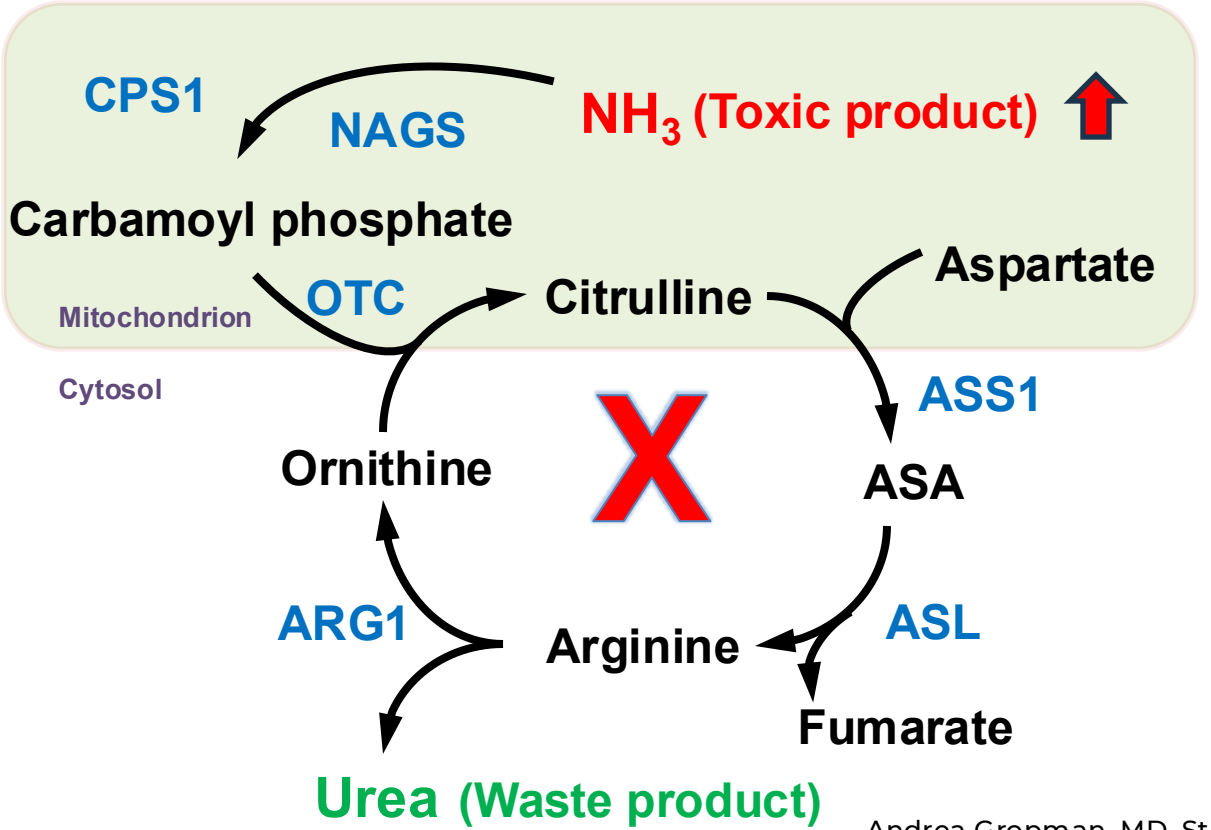
Nucleic acids

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

How is excess nitrogen excreted in animals?



Urea Cycle



Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

UCDs: subtypes and prevalence

UCDs	Estimated prevalence
Enzyme deficiencies	
NAGS deficiency	< 1 per 2,000,000
CPS1 deficiency	1 per 62,000
OTC deficiency	1 per 14,000-70,000
ASS1 deficiency (Citrullinemia type 1)	1 per 60,000
ASL deficiency (Argininosuccinic aciduria)	1 per 60,000
ARG1 deficiency (Argininemia)	1 per 353,000
Transporter defects	
Citrin deficiency (Citrullinemia type 2)	1 per 20,000 in Japan
HHH syndrome	Prevalence unknown
Secondary Urea Cycle Disorders	
Lysinuric protein intolerance, Carbonic anhydrase VA deficiency	Prevalence unknown

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Objectives

- **Diagnosis of UCDs**
  - ✓Overview of UCDs
  - ✓**Review clinical presentations of UCDs (clinical diagnosis)**
  - ✓Review biochemical features (biochemical diagnosis)
  - ✓Review practical aspects of genetic testing (molecular diagnosis)

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Clinical diagnosis of UCDs

Severe defects in urea cycle

- Catastrophic presentation in first week of life with hyperammonemia
- May mimic “sepsis”
- Poor suck, vomiting, refusal of feeds, altered consciousness
- Rapid progression to encephalopathy and coma, fatal when untreated

Partial defects in urea cycle

- May present later, i.e., in infancy, childhood, or even adulthood
- Protein aversion, behavioral abnormalities, mental status changes, encephalopathy

Some UCDs may have unique features

- Acute liver failure in OTCD
- Chronic liver disease, hypertension in ASLD
- Spasticity and motor problems in ARG1D

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Clinical features that should raise the possibility of UCDs in older children and adults

- Chronic, intermittent vomiting
- Headaches
- Lethargy
- Altered mental status
- Dietary protein avoidance
- Behavior change
- Nausea
- Confusion/Disorientation
- Anxiety
- Seizures
- Coma

Symptoms of hyperammonemia may mimic psychiatric illness (e.g., Bipolar Disorder or Schizophrenia) or drug/alcohol intoxication!

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Neurological Presentations Across the Age Spectrum

Neonatal: Poor feeding, lethargy, hypotonia, seizures, coma

Infant/Toddler: Developmental delay, irritability

Child: Episodic vomiting, behavioral issues, migraines

Adolescent: Encephalopathy, mood changes

Adult: Psychosis, catatonia, confusion

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Where are we in the talk?

- **Diagnosis of UCDs**
  - ✓Overview of UCDs
  - ✓Review clinical presentations of UCDs (clinical diagnosis)
  - ✓**Review biochemical features (biochemical diagnosis)**
  - ✓Review practical aspects of genetic testing (molecular diagnosis)

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Hyperammonemia is a hallmark of most UCDs

- **Normal ammonia levels in plasma vary by age and laboratory**
  - ✓Ammonia above ULN, especially when associated with clinical features is abnormal

- **Abnormal ammonia levels can be seen in:**
  - ✓ Erroneous sample draw or processing
  - ✓ UCDs
  - ✓ Liver failure and portosystemic shunts
  - ✓ Treatment with certain chemotherapeutic agents
  - ✓ Other IEM (e.g., organic acidemias, mitochondrial disorders)

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

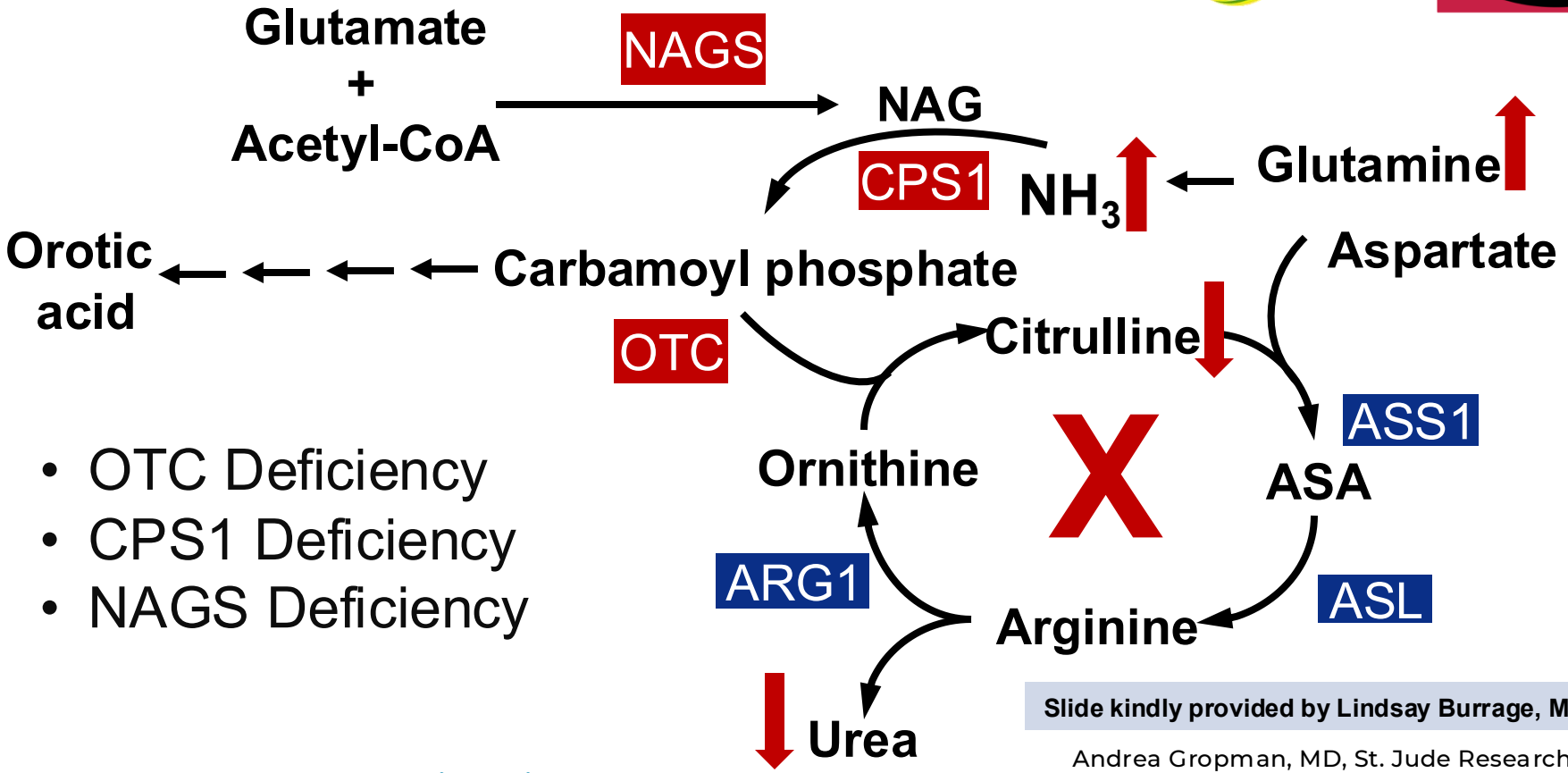
What further biochemical work up is necessary

- **To confirm hyperammonemia**
  - ✓Assess whether lab draw and analyses were done properly
  - ✓Consult metabolic genetics (others as indicated and available)
  - ✓Consider repeat testing as indicated for diagnosis and monitoring

- **To determine cause for hyperammonemia, consider:**
  - ✓ Routine comprehensive metabolic panel – liver functions, acid-base disturbances, hypoglycemia
  - ✓ Plasma amino acids – glutamine, citrulline, arginine, others
  - ✓ Acylcarnitine profile and urine organic acids
  - ✓ Others as indicated

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Proximal Urea Cycle Disorders

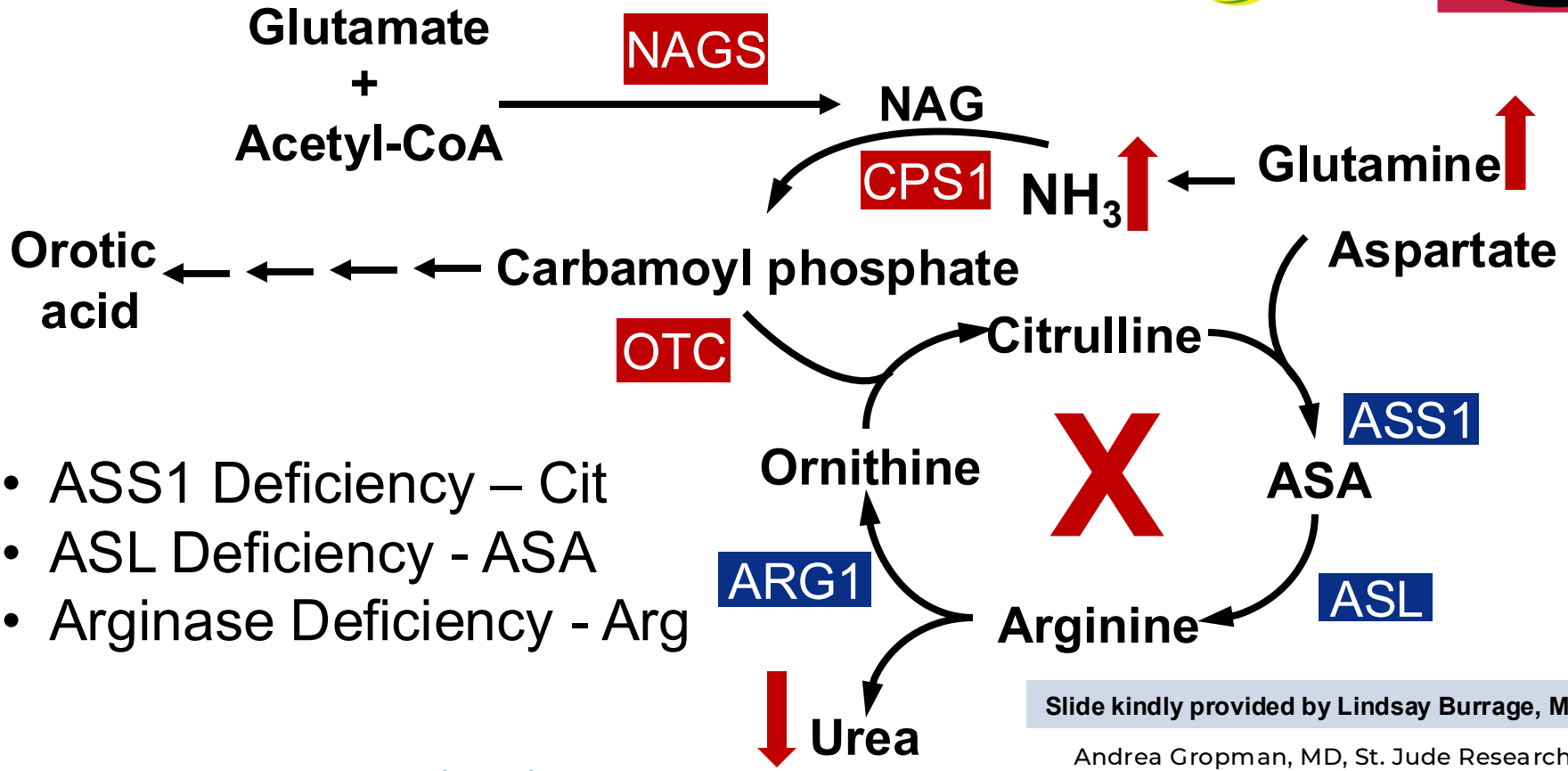


- OTC Deficiency
- CPS1 Deficiency
- NAGS Deficiency

Slide kindly provided by Lindsay Burrage, MD, PhD

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Distal Urea Cycle Disorders

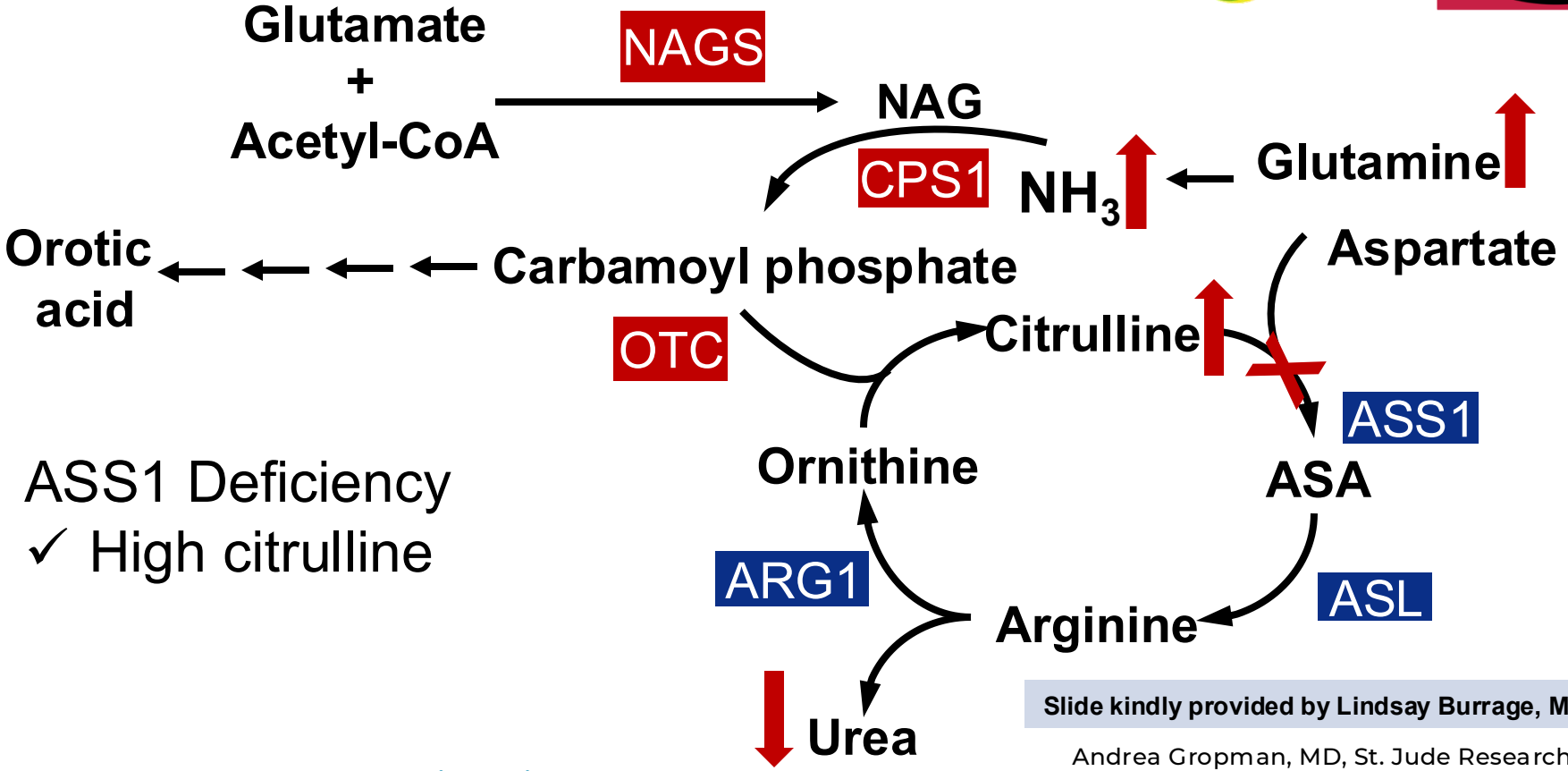


- ASS1 Deficiency – Cit
- ASL Deficiency - ASA
- Arginase Deficiency - Arg

Slide kindly provided by Lindsay Burrage, MD, PhD

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Distal Urea Cycle Disorders



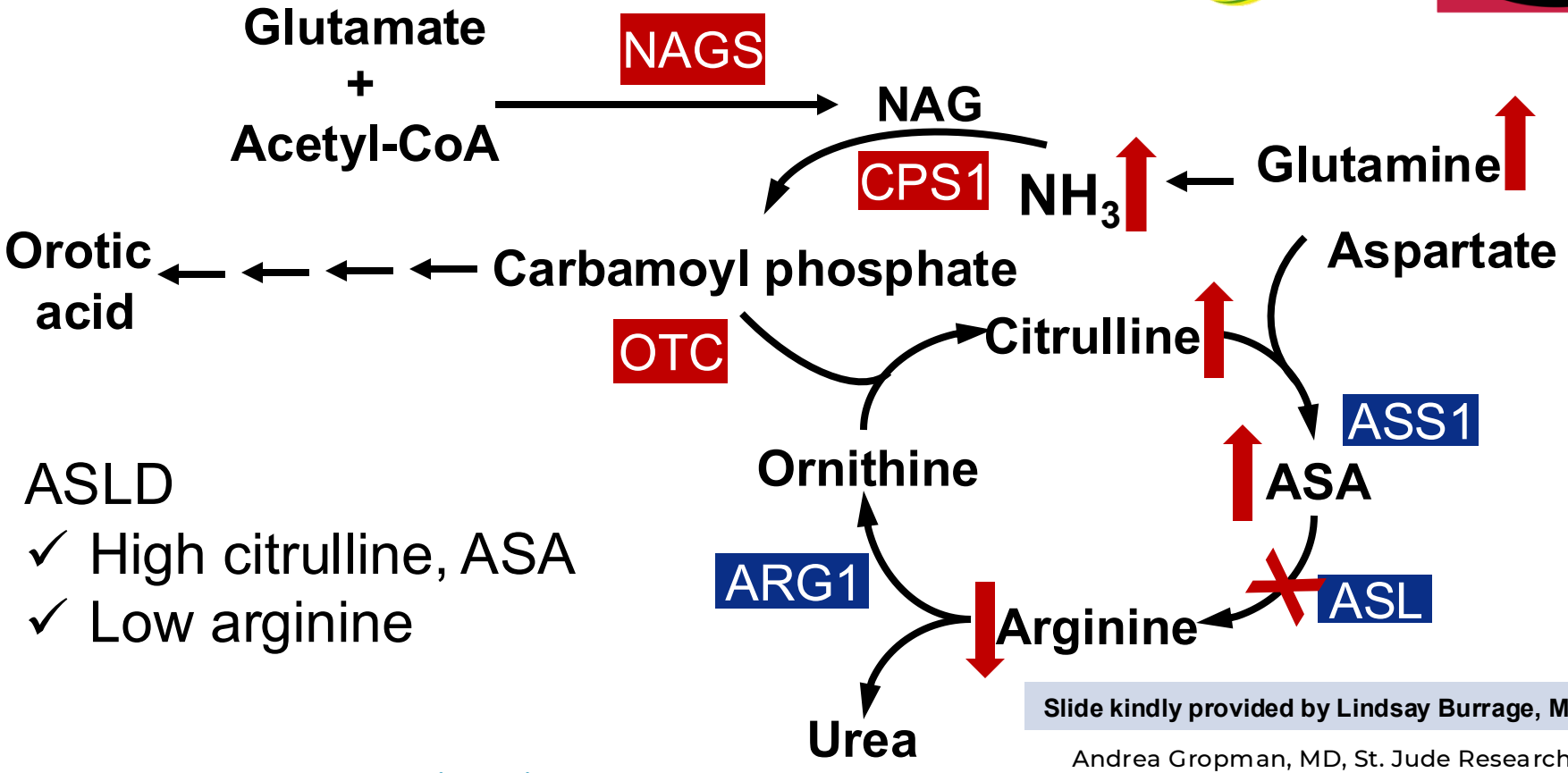
ASS1 Deficiency

✓ High citrulline

Slide kindly provided by Lindsay Burrage, MD, PhD

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Distal Urea Cycle Disorders



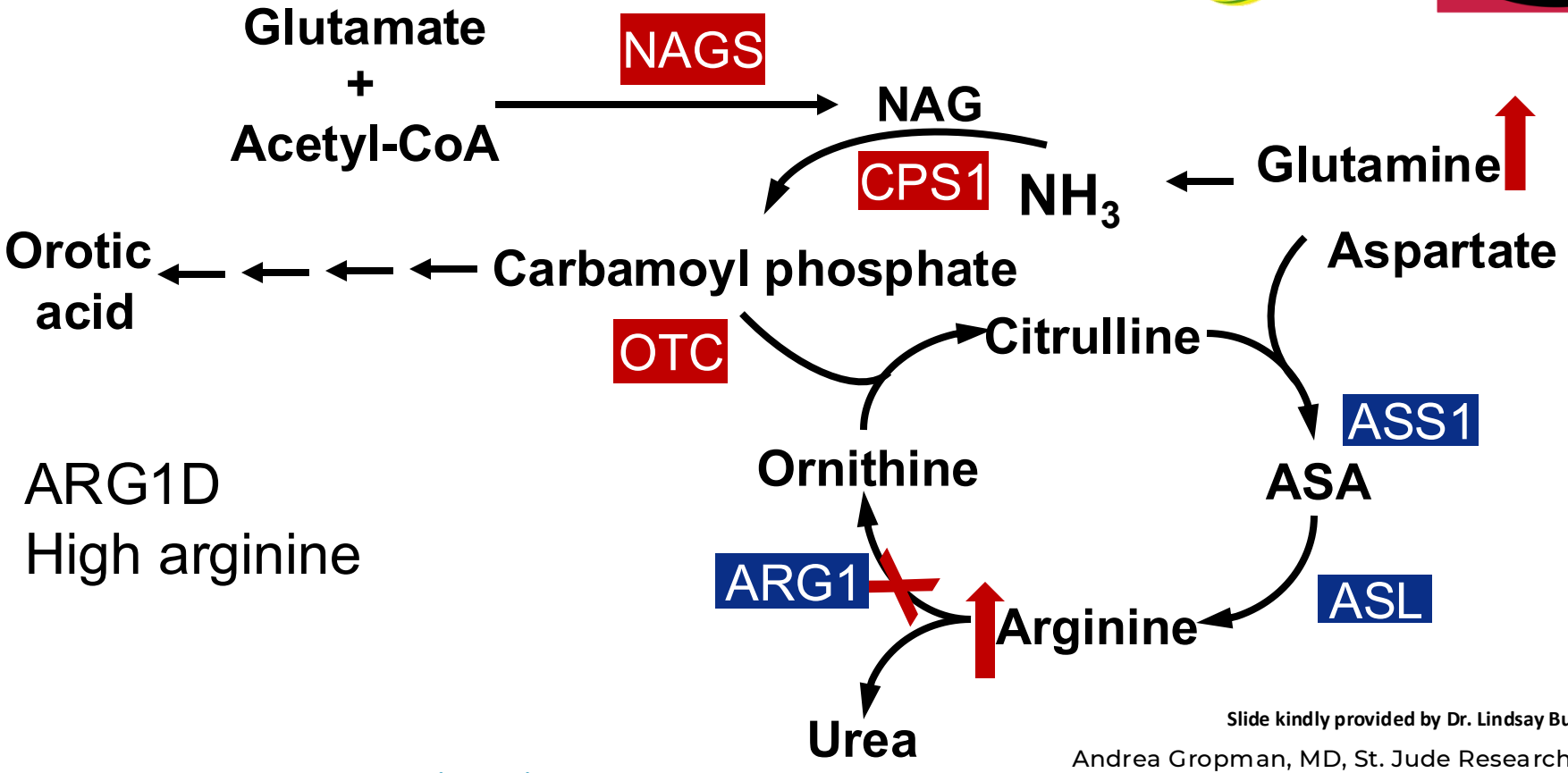
ASLD

- ✓ High citrulline, ASA
- ✓ Low arginine

Slide kindly provided by Lindsay Burrage, MD, PhD

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Distal Urea Cycle Disorders



ARG1D
High arginine

Slide kindly provided by Dr. Lindsay Burrage

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Typical biochemical features that may help in biochemical diagnosis of UCDs

Disorder	Ammonia	Glutamine	Citrulline	Arginine	Other classic biochemical features
NAGSD	↑	↑	↓		
CPS1D	↑	↑	↓		
OTCD	↑	↑	↓		↑ orotic acid
ASS1D	↑	↑	↑↑↑	↓	
ASLD	↑	↑	↑		↑ ASA
ARG1D		↑		↑↑↑	
HHH	↑				↑ ornithine and homocitrulline
Citrin deficiency	↑	↑	↑	↑	↑ methionine, threonine-serine ratio
Organic acidemia	↑	↑			Acidosis, abnormal acyl carnitine profile

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Confirmation of diagnosis of UCDs

- **For distal UCDs, typical biochemical features many be sufficient to make the diagnosis**

- **Confirmatory testing is often required for proximal UCDs and often performed for distal UCDs**
  - ✓Enzymatic testing – NOT widely available
  - ✓Molecular genetic testing

Treatment of hyperammonemia is NOT to be delayed while further testing is underway to confirm a diagnosis

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Where are we in the talk?

- **Diagnosis of UCDs**
  - ✓Overview of UCDs
  - ✓Review clinical presentations of UCDs (clinical diagnosis)
  - ✓Review biochemical features (biochemical diagnosis)
  - ✓**Review practical aspects of genetic testing (molecular diagnosis)**

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Practical Aspects of Genetic Testing & Genetic Counseling

National Urea Cycle Disorders Foundation

Project ECHO®

Slides for this section of the talk were kindly provided by Darwin Argueta, MS, CGC, BCM

- What types of genetic tests are available?
- What test does one choose?
- What genetic testing laboratories offers testing for UCDs?

- What is the importance of pre-test counseling?
- What samples can be used for diagnostic clinical genetic testing?

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

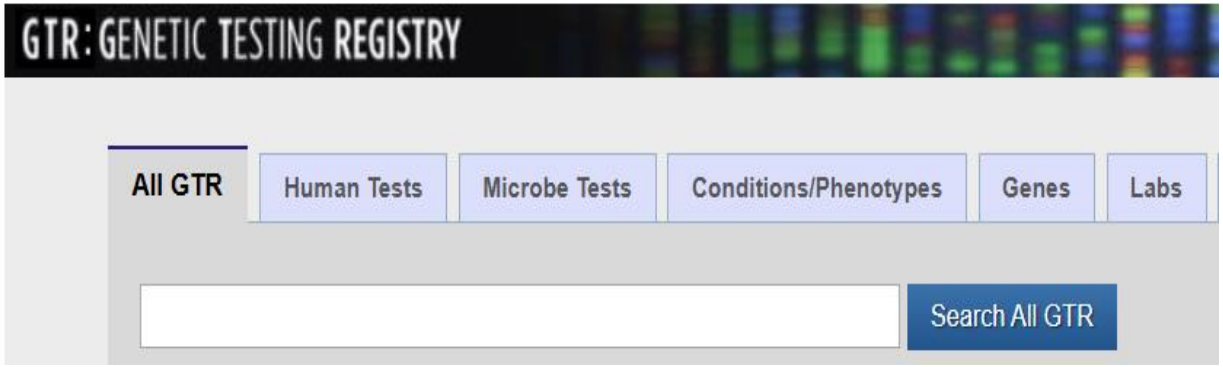
Types of genetic testing

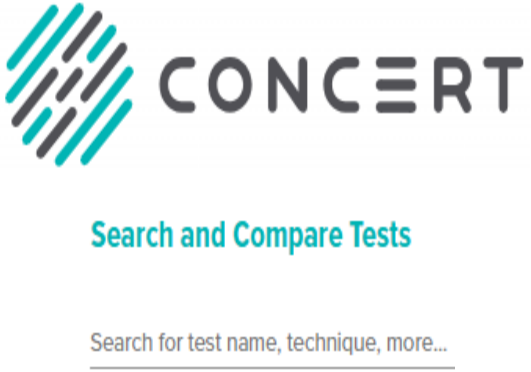
Methodology		Variations Detected	Utility in UCDs
Cytogenetic Testing	*Karyotype*	Extra/missing chromosomes, large chromosomal loss, gains, rearrangements	CMA might be useful in OTCD
	Chromosomal Microarray	CNVs -Submicroscopic chromosomal chromosomal loss, gains, rearrangements	
DNA Sequencing	*Sanger Sequencing*	Known single nucleotide variants in gene(s) of interest	Usually offered for a single genes, may be of help if familial mutation is known
	Massively Parallel Sequencing-Based Panel Tests	single nucleotide variants and copy number variants in gene(s) of interest	Most commonly used test
	Exome Sequencing	SNVs in exons, primarily, for all genes associated with Mendelian phenotype	For multisystem complex disorders
	Genome Sequencing	SNVs in exons and introns for all genes associated with Mendelians phenotype; CNVs	

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Finding an appropriate genetic test

- The Genetic Testing Registry (GTR) aims to enhance access to information about the availability, validity, and usefulness of genetic tests. https://www.ncbi.nlm.nih.gov/gtr/
- Concert Genetics allows you to search for and compare genetic tests from various labs: https://app.concertgenetics.com/apps/search/#/





Slide provided by Darwin Argueta, MS, CGC, BCM

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

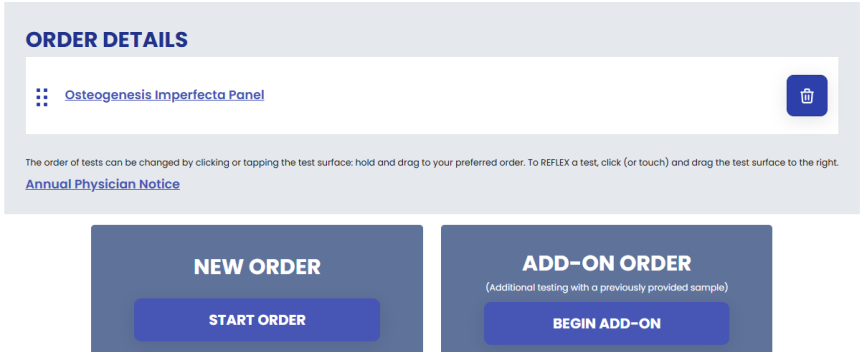
Finding an appropriate genetic test

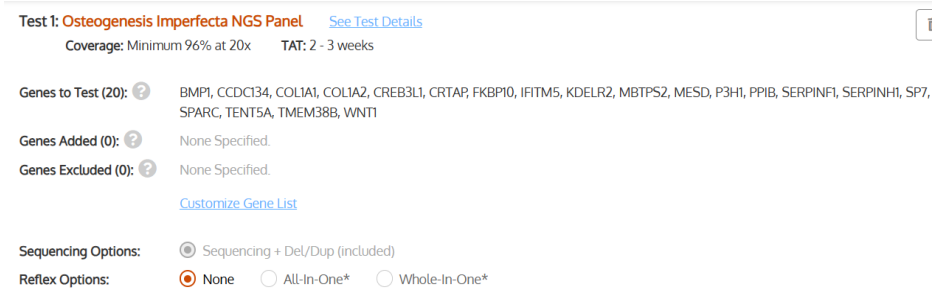
Hyperammonemia Panel Tests Products 14

Product	GTU	Lab's Test Code
PUCD Comprehensive - NGS & Deletion/Duplication Analysis *Baylor Genetics, LLC*	2BU2G	5274
UCD and Hyperammonemia Panel by Massively Parallel Sequencing *Baylor Genetics, LLC*	2AVDG	2110
Hyperammonemia and Urea Cycle Disorder NGS Panel (Deletion/Duplication Only) *Fulgent Genetics*	3QP3G	-
Hyperammonemia and Urea Cycle Disorder NGS Panel (Sequencing & Deletion/Duplication) *Fulgent Genetics*	77DRG	-
Hyperammonemia and Urea Cycle Disorder NGS Panel (Sequencing Only) *Fulgent Genetics*	77DHG	-
Invitae Hyperammonemia Panel *Invitae Corporation*	76SFG	06230
Invitae Urea Cycle Disorders Panel *Invitae Corporation*	4J6BG	06212
Invitae Urea Cycle Disorders Panel-Add-on Hereditary Orotic Aciduria Gene *Invitae Corporation*	5QJDG	06212-2
Invitae Urea Cycle Disorders Panel-Add-on Hyperammonemia Genes *Invitae Corporation*	4J7PG	06212-1
Urea Cycle Disorders *Knight Molecular Diagnostic*	5R22G	UREA-CYCLE-DISORDERS
Urea Cycle Disorders (NGS Panel and Copy Number Analysis) *MNG Laboratories*	76UUG	NGS321
Hyperammonemia Panel *PreventionGenetics, part of Exact Sciences*	77HWG	10407
Urea Cycle Disorders Panel *PreventionGenetics, part of Exact Sciences*	6JFPG	10273
Hyperammonemia Gene Sequencing *University of Minnesota Physicians Outreach Laboratory*	7WWEG	1202598

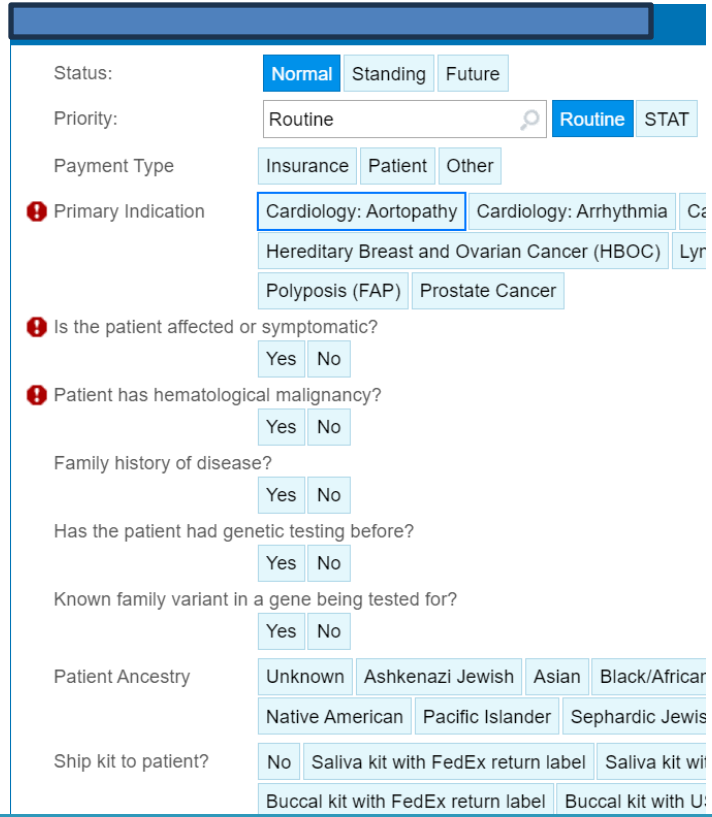
Ordering a genetic test

Genetic Testing Laboratory Portals





EMR-Integrated Order



On which Samples can genetic testing be ordered?

Buccal

Saliva

Blood

Pretest counseling

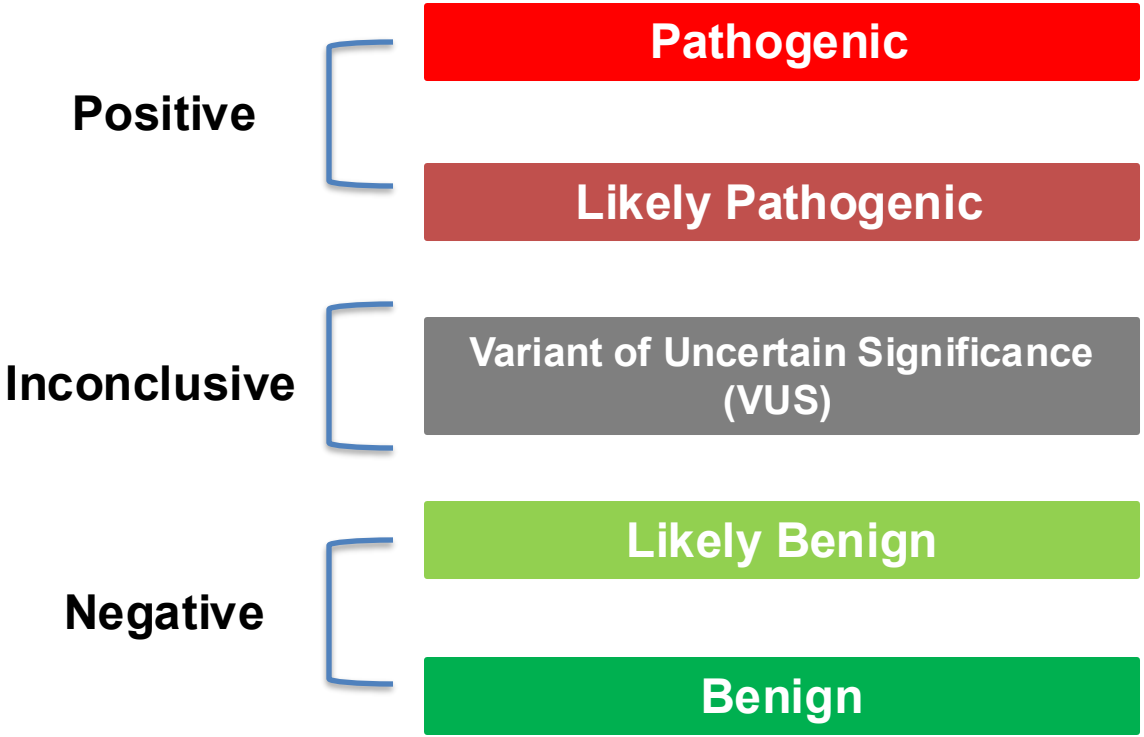
- What will the test inform us?
  - ✓Confirm a diagnosis
  - ✓Mode of transmission and recurrence likelihood
  - ✓Potentially inform clinical course and severity
  - ✓Potentially inform about clinical trial opportunities

- Genetic Information Nondiscrimination Act (GINA)
- Dispel myths about the disorder
- The patient and family members are not at fault
- Types of results (positive, negative, variant of uncertain significance)

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Types of results

- Several factors are considered for variant interpretation:
  - Population Frequency
  - Computational & Predictive Data
  - Functional Data
  - Segregation Data
  - *De novo* Data



Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Where are we in the talk?

- Diagnosis of UCDs
  - ✓Overview of UCDs
  - ✓Review clinical presentations of UCDs (clinical diagnosis)
  - ✓Review biochemical features (biochemical diagnosis)
  - ✓Review practical aspects of genetic testing (molecular diagnosis)

- **Treatment of UCDs**
  - ✓ General principles of acute hyperammonemia
  - ✓ General principles of long-term treatment
  - ✓ Emerging therapies

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

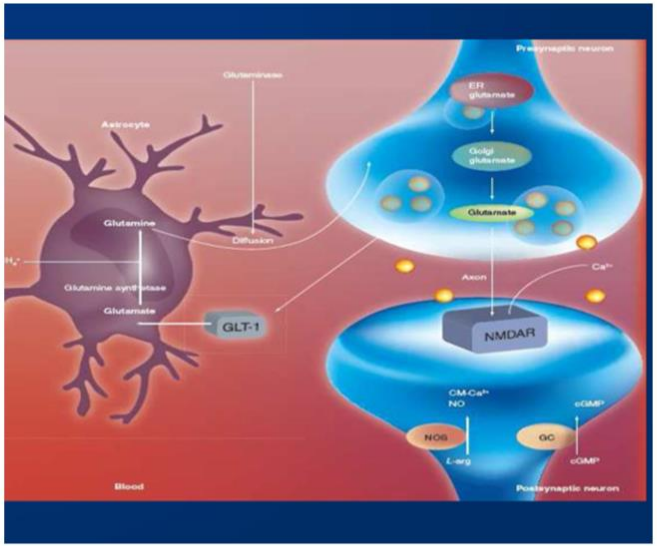
Diagnosis and Treatment of UCD: Don’t miss these neurological clues or atypical presentations

Andrea Gropman, M.D., FAAP, FAMG, FANA, FAAN, FCNS
St Jude Children’s Research Hospital

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Ammonia regulation in CNS

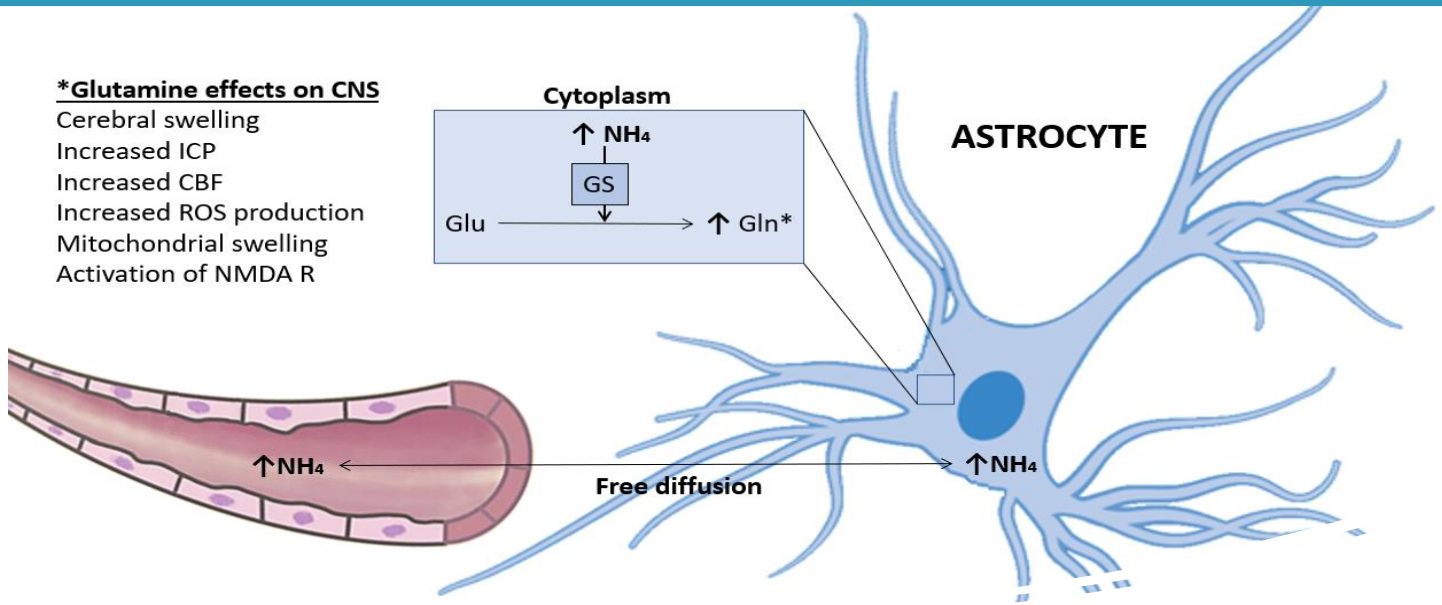
- Almost all the ammonia from the blood is converted instantly to glutamine
- The brain relies almost exclusively on astrocytic glutamine synthetase for the removal of excess ammonia
  - Brain lacks a urea cycle
  - Cerebral ammonia removal relies on formation of glutamine
  - Glutamine synthetase catalyzes glutamate and ammonia into glutamine an intracellular osmole
    - implicated in the astrocytic swelling



UCDs and the Brain — Why Neurology Matters

- Ammonia crosses the BBB → astrocyte swelling, cerebral edema
  - Glutamine accumulation causes osmotic stress
  - Neuronal dysfunction even without coma
  - "The brain is the first organ to suffer and the last to recover in UCDs."

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine



Etiology of neural injury in the proximal UCDs

- Hyperammonemic encephalopathy is associated with neural injury in UCDs
- Mechanism remains unclear
  - Energy deficit
  - Glial cell dysfunction with osmotic disturbances
  - Metabolic disturbances: gln, glu, NAA
- Is all the injury due to HA and associated metabolites?
- What markers are predictive of treatment response and cognitive outcome?

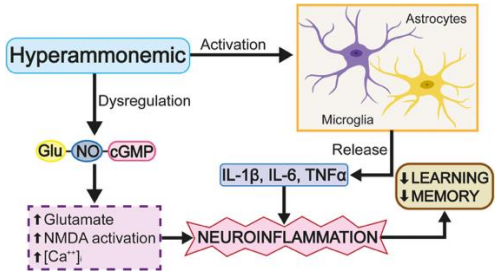
Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Hyperammonemia (HA)

Newborns have different diagnostic levels than older children and generally higher levels are tolerated

As a general rule,

- < 500µmol/L = liver failure
- > 1000µmol/L = urea cycle defects



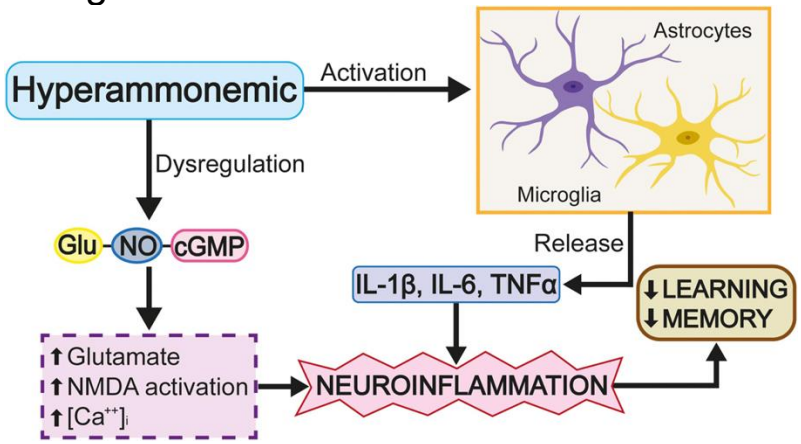
- Adults

  –>100 also consider late onset metabolic disease

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Hyperammonia

- Ammonia concentrations tend to be highest in urea cycle disorders
  - 300 to 1000 micromol/L [5.1 to 17 mcg/mL]
  - can be normal in urea cycle disorders when the patient is not acutely ill
  - Sometimes >1000 micromol/L (17 mcg/mL) in organic acidemias



Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Neurological Presentations Across the Age Spectrum

Neonatal: Poor feeding, lethargy, hypotonia, seizures, coma

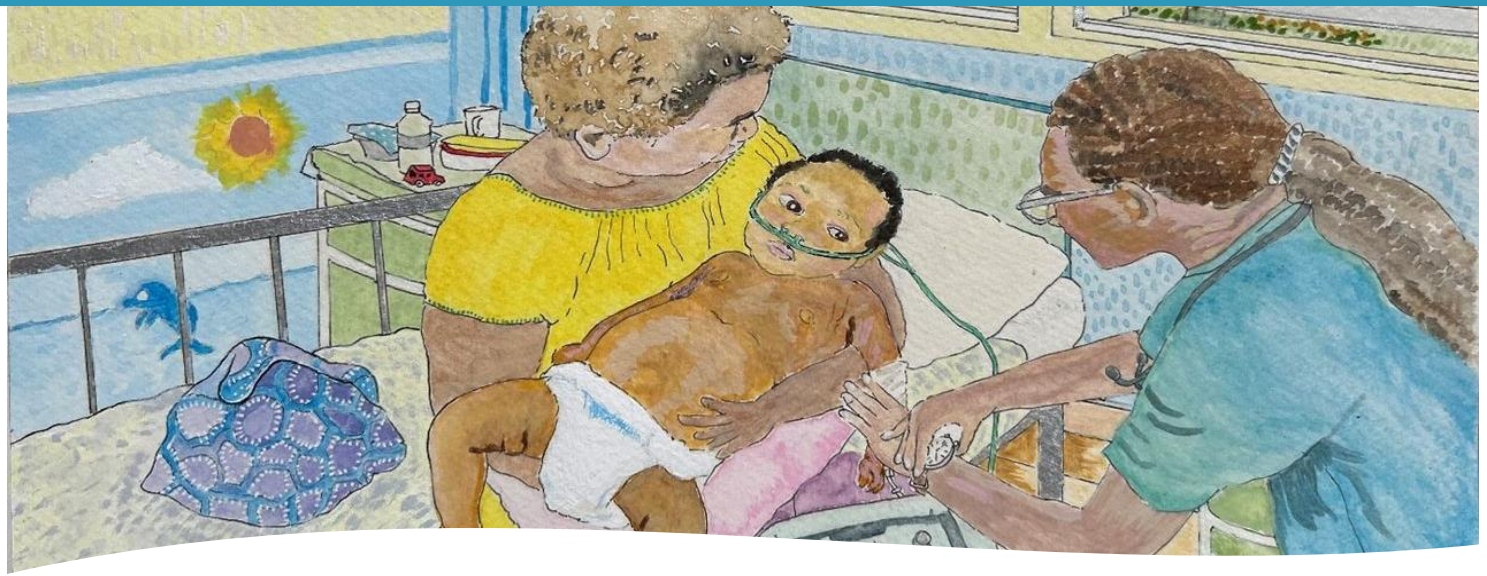
Infant/Toddler: Developmental delay, irritability

Child: Episodic vomiting, behavioral issues, migraines

Adolescent: Encephalopathy, mood changes

Adult: Psychosis, catatonia, confusion

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine



Clinical Vignette — Neonatal

- Baby A: Day 3 poor feeding, vomiting, lethargy
  - –Ammonia 540 µmol/L, EEG burst suppression
  - –Plasma amino acids
  - –OTC deficiency (male)

  Key Point: Ammonia >200 µmol/L in neonates is a red flag

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Day 3: poor feeding, vomiting, lethargy in a neonate

Presentation:

- Poor feeding
- Vomiting
- Lethargy

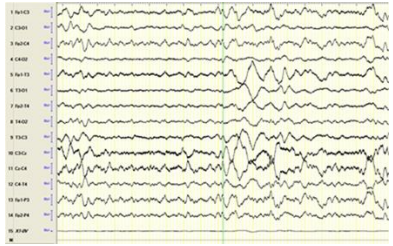
Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Initial laboratory values

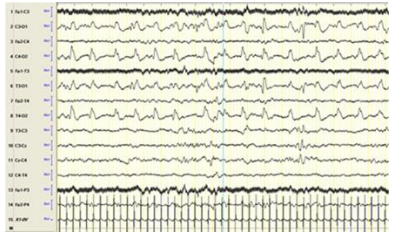
- Ammonia: 540 µmol/L (Normal <100 µmol/L)
- EEG: Burst suppression pattern

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

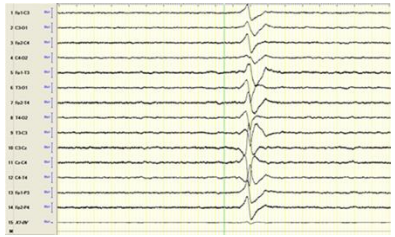
Long term EEG in neonates



Blood ammonia level 97micromole/l



Blood ammonia level 575 micromole/l and electrographic seizure



Blood ammonia level 807 micromole/L

Interburst interval duration

–Appeared to correlate with degree of hyperammonemia

- High plasma ammonia level associated with a shorter burst and longer background suppression

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Metabolic work up

- Plasma Amino Acids:
  - –Elevated glutamine
  - –low citrulline
- Urine Organic Acids: Unremarkable
- Orotic Acid: Elevated
- Diagnosis: Ornithine Transcarbamylase (OTC) Deficiency – X-linked, affecting males

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Clinical Vignette — Teenager

Emma, 14: Vomiting misdiagnosed as migraine

Mood swings, hallucinations, NH_3 = 220 µmol/L

Female heterozygous OTC

Key Point: Females can be symptomatic, crises often hormonal or infectious

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Migraine or something else?

- 14-year-old girl with no significant medical history presented to the emergency department with recurrent vomiting, severe frontal headache, and confusion.
- These episodes had occurred intermittently over the past year, each time diagnosed as abdominal migraine or cyclic vomiting syndrome.
  - She had been treated with antiemetics and sumatriptan, with partial symptom relief

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Migraine or something else

- On this presentation, her family noted increasing lethargy and word-finding difficulties
- There was no fever, diarrhea, or signs of infection
- Her vital signs were normal, but she appeared combative and psychotic, then drowsy and disoriented
- Neurological examination showed mild asterixis and slowed speech

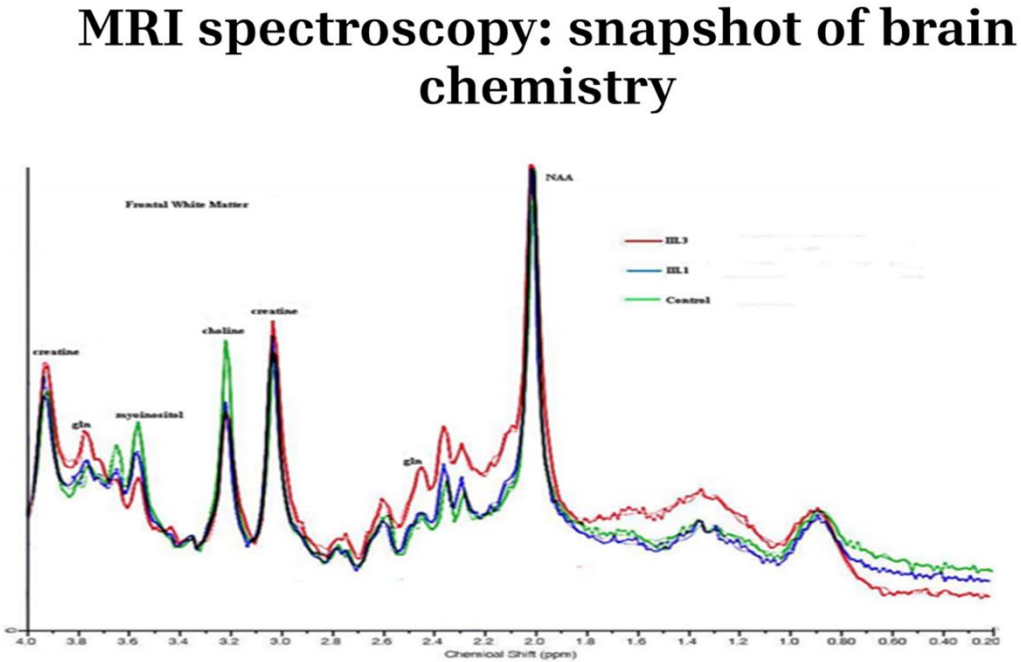
Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Initial labs

- Ammonia: 238 µmol/L (normal < 40 µmol/L)
- LFTs: normal
- Electrolytes and glucose: within normal limits
- CT head: normal
- CSF studies: unremarkable
- Plasma amino acids showed elevated glutamine and low citrulline
- Urine orotic acid was elevated
- These findings prompted suspicion for a urea cycle disorder.
  - heterozygous pathogenic variant in the *OTC* gene: **c.622G>A (p.Arg208Gln)**

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Brain imaging



Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Brain Imaging in UCDs

- MRI: Cortical swelling, insular/cingulate injury
- MRS: Elevated glutamine/glutamate peaks
- Chronic: Cerebral atrophy, white matter loss

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Clinical Vignette — Adult Onset

- Mr. R, 28: Sudden confusion, hallucinations, disinhibition
  - Initially misdiagnosed as psychosis
- NH_3 = 180 µmol/L, CPS1 deficiency
- Key Point: Family history may be silent in late-onset UCDs

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Cerebral palsy or something else?

A 7-year-old male was referred for evaluation of progressive lower extremity stiffness, toe walking, and frequent falls

He had been diagnosed with spastic diplegic CP at age 3, based on hypertonia and motor delay

There was no history of prematurity, perinatal hypoxic events, or brain injury

He had met early developmental milestones but began to show progressive motor decline between ages 3 and 5, including increased tone, scissoring gait, and difficulty with toileting and ambulation

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Cerebral palsy or something else?

- MRI of the brain demonstrated symmetric T2 hyperintensities in the corticospinal tracts, particularly involving the periventricular white matter and posterior limbs of the internal capsule
  - magnetic resonance spectroscopy (MRS) revealed a unique elevation of a peak at 3.8 ppm, consistent with elevated guanidino compounds
- plasma amino acid panel was obtained, showing significantly elevated arginine levels

- Molecular genetic testing confirmed biallelic pathogenic variants in the **ARG1** gene, confirming the diagnosis of **arginase deficiency (ARG1-related disorder)**.

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Psychiatric Manifestations of UCDs

- Acute psychosis, catatonia, mania
- Often misdiagnosed as schizophrenia, bipolar disorder
- Always check ammonia in new-onset psychiatric illness with encephalopathy

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Treatment Overview

- Acute: Dialysis, scavengers (Na benzoate, phenylacetate), arginine
- Long-term: Protein restriction, essential AA formula, carglumic acid
- Gene-based: Liver transplant, AAV/mRNA therapy (in trials)
- Adjunct: Cognitive rehabilitation, cautious psychiatric medications

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Management of Urea Cycle Disorders (UCDs) Acute vs. Chronic

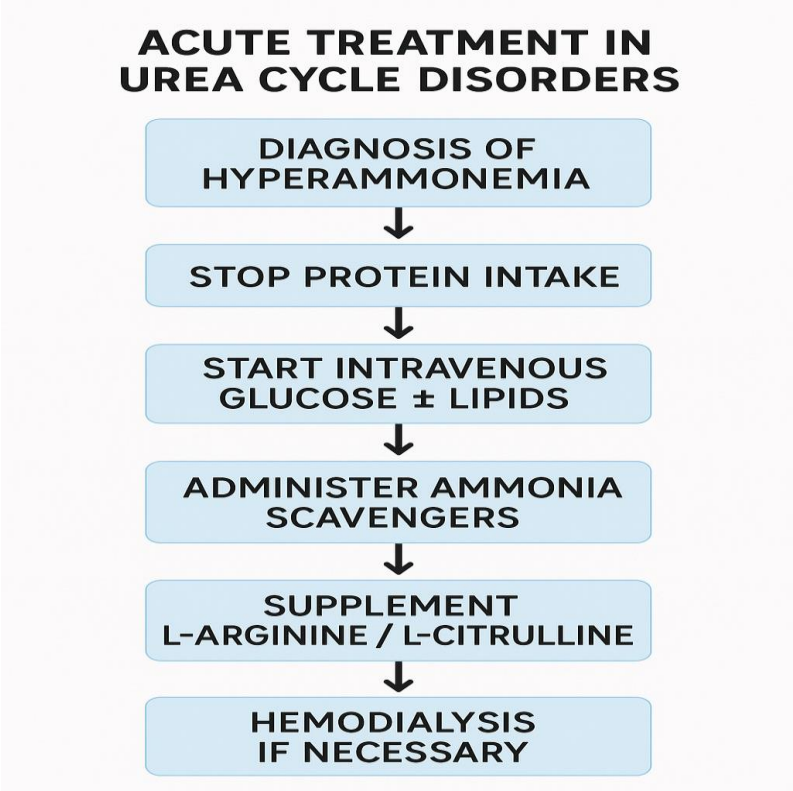
Acute Hyperammonemic Crisis

Goals: Rapidly lower ammonia, prevent brain injury

- **Hospital Admission (ICU if needed)**
- **Stop protein intake** immediately
- **Provide high-calorie glucose infusion** (10%–20% dextrose ± lipids) to prevent catabolism
- **Nitrogen scavenger therapy:**
  - IV sodium benzoate
  - IV sodium phenylacetate
- **L-Arginine or L-Citrulline** (depending on enzyme defect)
- **Hemodialysis or CRRT** if:
  - Ammonia > 500 µmol/L
  - Rapid deterioration, encephalopathy
- **Monitor labs:** Ammonia, electrolytes, liver/kidney function, plasma amino acids
- **Neuroprotection:** EEG, seizure monitoring, cooling if needed

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Acute Treatment in Urea Cycle Disorders



Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Management of Urea Cycle Disorders (UCDs) Acute vs. Chronic

Chronic Long-Term Management

Goals: Prevent catabolism, control ammonia, optimize development

- **Protein-restricted diet** (customized to tolerance; guided by metabolic dietitian)
- **Essential amino acid supplementation**
- **Chronic nitrogen scavengers (oral):**
  - Sodium phenylbutyrate or glycerol phenylbutyrate (Ravicti®)
- **L-Arginine or L-Citrulline** supplementation
- **Frequent monitoring:**
  - Plasma ammonia
  - Amino acids
  - Growth, neurodevelopment
- **Family education & emergency protocol**
- **Liver transplantation** (curative in severe/recurrent cases)

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Summary — Pearls for Neurologists & Psychiatrists

- Always check ammonia in encephalopathy or psychiatric crisis
- Neurologic injury is cumulative and preventable
- Neuroimaging + metabolic profiling = essential
- Early diagnosis = better outcomes

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine

Case Presentation

The Essentials

Upcoming UCD Event

Links in the chat

6th INTERNATIONAL SYMPOSIUM ON UREA CYCLE DISORDERS

ADVANCEMENTS IN UNDERSTANDING:
Global Perspective and Innovations In Urea Cycle Disorders

SEPTEMBER 1 - 2, 2025, KYOTO, JAPAN

Thank You

Session 3: The Importance of Diet

Tuesday, September 16, 5-6:30 pm ET

Nicholas Ah Mew, MD Children's National Hospital
Erin MacLeod, PhD, RD, LD, Children's National Hospital

Evaluation link / QR code

Andrea Gropman, MD, St. Jude Research Hospital
Sandesh CS Nagamani, MD, Baylor College of Medicine