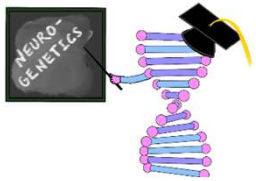
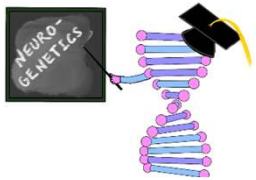
Movement 2: Cerebral Palsy

MODULE 6



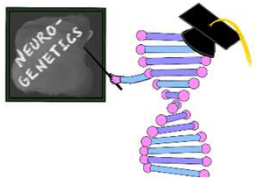
Learning Objectives

- Review genetic mimics of cerebral palsy and red flags to consider alternate diagnosis
- Interpret results of genetic testing using OMIM. Discuss concepts of founder variants.
- Review results of metabolic testing in diagnosing inborn error of metabolism.



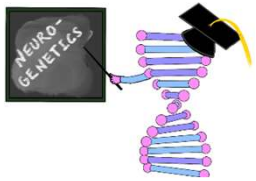
Chief Complaint

- 10-year-old boy with h/o spastic quadriplegia (CP) and failure to thrive presenting with status epilepticus and hyperammonemia



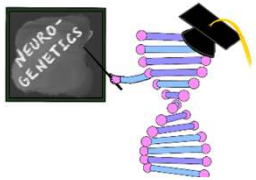
Differential Diagnosis - Interactive

Name of condition	Gene and mode of inheritance	Clinical features and Treatment



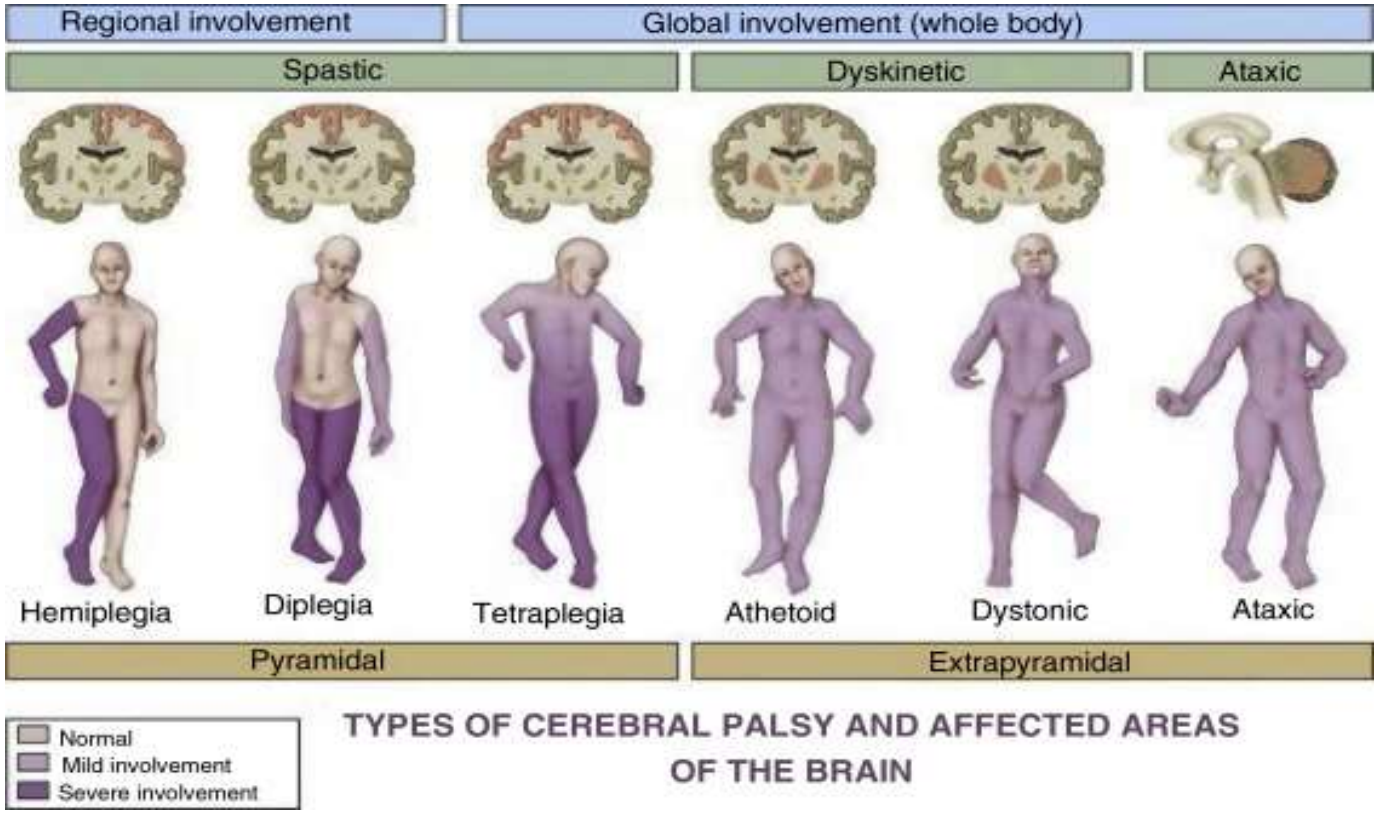
What is Cerebral Palsy?

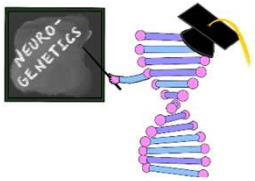
- Physical disability that's an umbrella term referring to a group of disorders affecting a person's ability to move
- Due to damage of the developing brain during pregnancy, birth, or shortly after birth
- It is a non-progressive condition
  - While the brain injury that causes it doesn't change over time, the wear and tear of living with CP often means that people experience age-related changes



ce•re•bral / of the brain

pal•sy / lack of muscle control

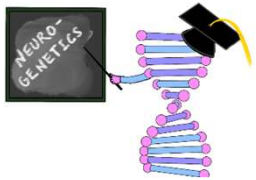




Padmakar, P., Kumar, K., & S Parveen, P. (2018).

Red Flags to Consider Alternate Diagnosis

- No clear history of birth injury
- Birth injury not sufficient to explain pattern and severity of motor symptoms
- Progressive symptoms (cognitive regression, refractory epilepsy, movement disorder)

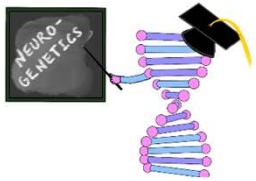


Red Flags (Continued)

Episodes of metabolic decompensation (metabolic acidosis, hyperammonemia, hypoglycemia)

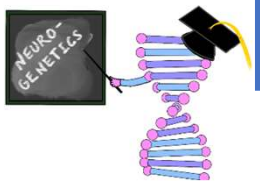
Failure to thrive, hepatic dysfunction, history of protein restriction or cyclical vomiting

Family history of similarly affected individuals in multiple (dominant, X-linked) or same generation (recessive), consanguinity



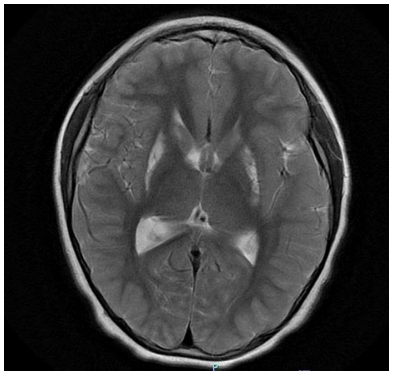
Genetic Mimics of "CP"

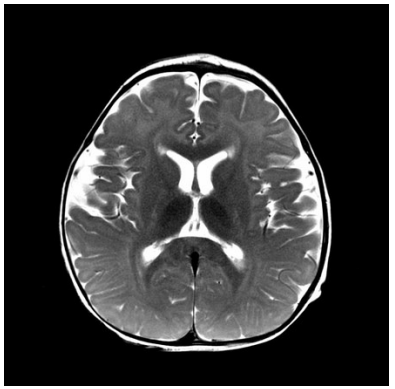
Type of CP	Classically associated birth Injury	Genetic Mimics
Spastic Diplegia	IVH/ prematurity	Hereditary Spastic Paraplegia Arginase deficiency
Spastic Quadriplegia	HIE	Urea Cycle Disorders Organic Acidemia MoCD, Sulfite Oxidase deficiency Non ketotic hyperglycinemia Cerebral Creatine Deficiency syndrome Leukodystrophies (Krabbe, Aicardi Goutierres)
Spastic Hemiplegia	Perinatal stroke	COL4A1 Mitochondrial disorders
Dystonic/ Choreoathetoid CP	Kernicterus	Glutaric aciduria type 1 Monoamine metabolism disorders PKAN
Ataxic CP	Cerebellar injury	Pontocerebellar hypoplasia Joubert syndrome Spinocerebellar ataxia

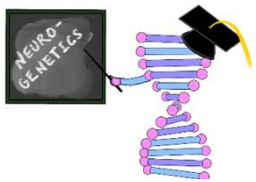


Workup for CP Mimics

- Neuroimaging
- Metabolic testing
- Genetic testing (multi-gene panels versus exome sequencing)

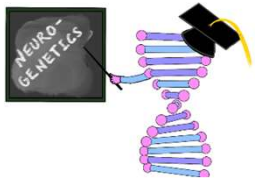






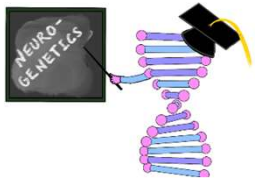
HPI and Exam

- Patient was born full term and attained early milestones on time. No h/o HIE or NICU stay
- At 8 months, he was hospitalized for a seizure in the setting of reported sepsis and anemia
- At 2 years of age, he began walking.
  - But after a couple of months, he exhibited regression and was no longer able to walk.
  - His legs became ‘stiff’ and he was given a diagnosis of “CP”



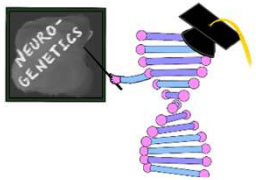
Other Pertinent History

- Nutrition and Growth:
  - As an infant, the patient refused food and preferred breast milk.
  - His mother described him as difficult to feed and picky eater who favored simple carbohydrates (corn tortilla), fruits (banana and avocado), and minimal proteins (beans and occasional seafood)
- Over time, he avoided protein rich foods and never had an interest in eating meat



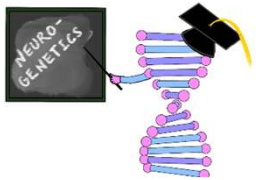
HPI (Continued)

- At 8 years of age, he developed worsening stiffness and weakness.
- At 10 years of age, he developed multiple unprovoked seizures and was admitted in PICU. Serum ammonia was elevated at 350.
- No family history of epilepsy, CP or neurodevelopmental disorders. Parents denied consanguinity but were from a small village.
- Patient was born outside the US where Newborn screening is not performed and additionally was born in the home.



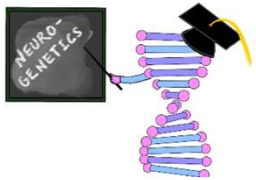
Exercise 1

- Team 1: Discuss consanguinity versus founder effect.
- Team 2: Does he have any risk factor for CP?
- Team 3: Are symptoms progressive or non-progressive?
- Team 4: What clues do sudden neurological symptoms and hyperammonemia provide?



Investigations

- **EEG:** slow background, irregular 2.5-3 Hz generalized epileptiform
- **MRI Brain:** mild cerebral volume loss and moderate volume loss involving the brainstem and cerebellum with enlarged sulci/fissures and commensurate ventriculomegaly



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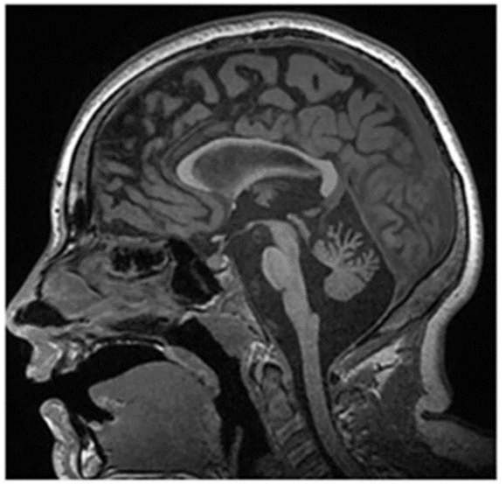
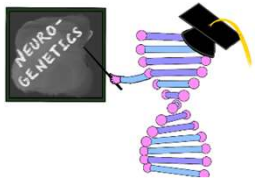


Investigations (Metabolic)

- Ammonia: 265
- CMP
  - AST: 397 (8-33 U/L)
  - ALT: 668 (4-36 U/L)
  - PT: 18.5 (11-14.5 sec)
  - INR: 1.58 (0.87-1.13)

Key metabolite derangements during illness in this patient

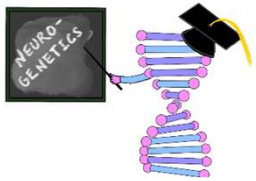
Date	Plasma Arginine	Plasma Glutamine	Plasma Ammonia
Admission at 00:35	907	57	441
Day of admission at 06:50	846	665	285
At discharge	341	582	
2 Mo later in setting of illness	462	821	
	[12-133 mmol/L]	[372-876 mmol/L]	[11-32 mmol/L]



Investigations (Genomic)

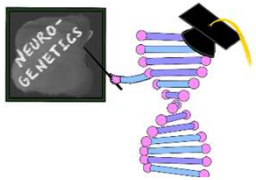
- Urea cycle panel

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Classification
ARG1	Arginemia	Autosomal Recessive	c.871C>T p.R291*	Homozygous	Pathogenic

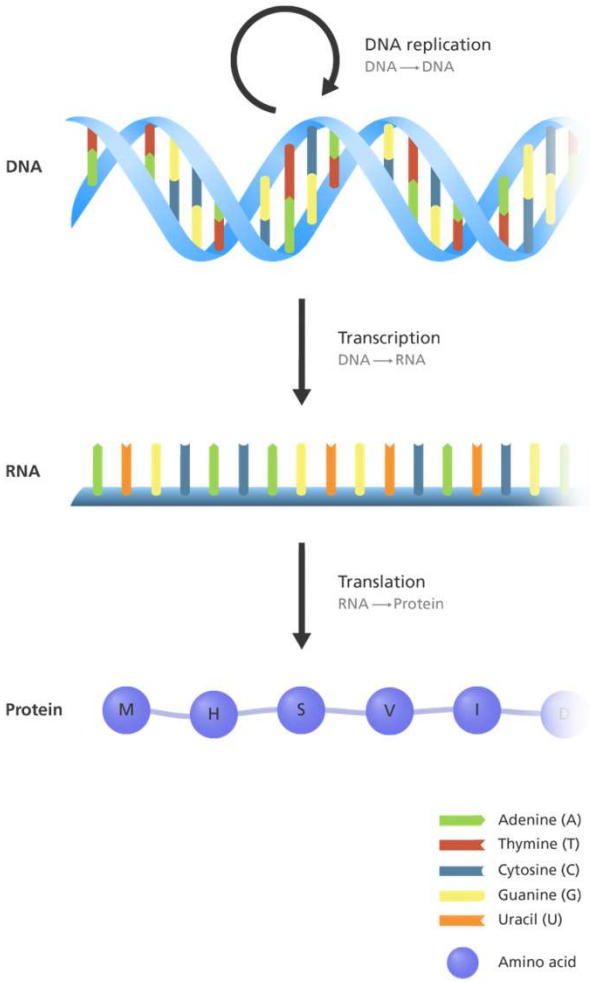


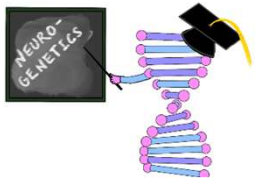
Exercise 2

- Team 1 – Please review metabolic labs and using PubMed, GeneReviews (for Urea Cycle Disorder) and other resources, discuss if PAA are concerning for any specific disorder.
- Team 2 – What is the difference in PAA for this disorder versus other disorders in the category?
- Team 3 – Comment on the gene and variant shown in the report. What is the disorder associated and mode of inheritance?
- Team 4 – What is the typical clinical presentation and management of this condition? What drugs should you avoid?

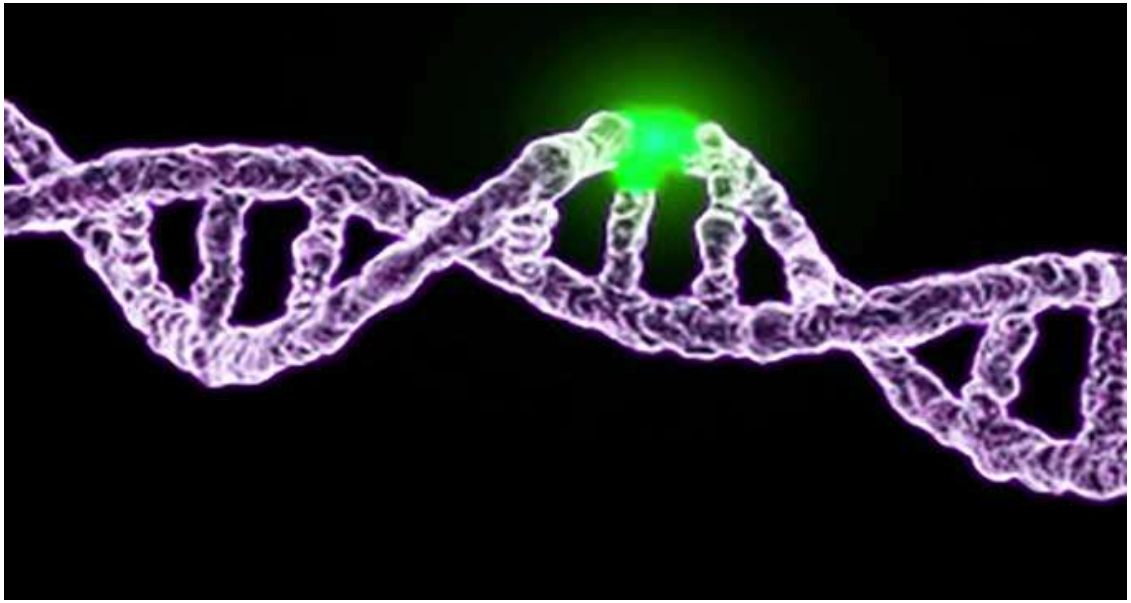


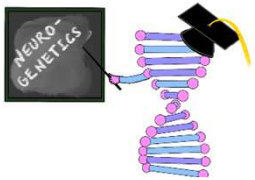
Central Dogma



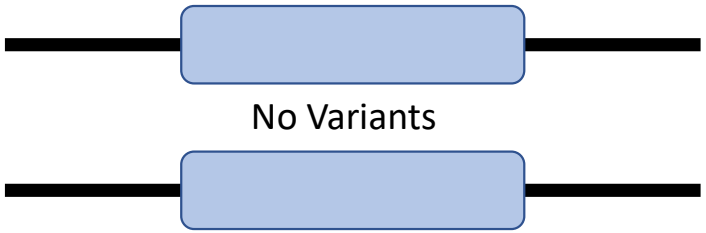


Mutation/Pathogenic Variant



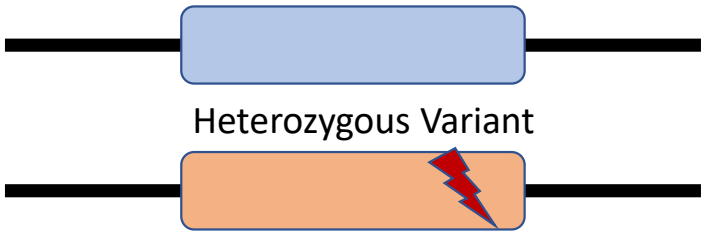


NO DISEASE



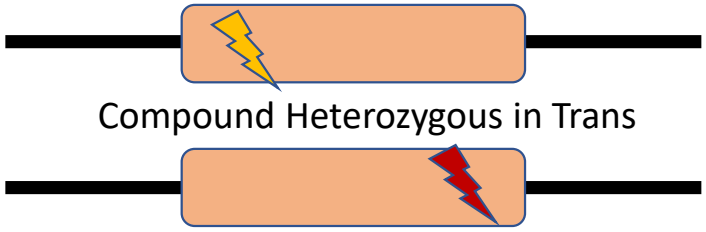
No Variants

Monoallelic/AD



Heterozygous Variant

Biallelic/AR



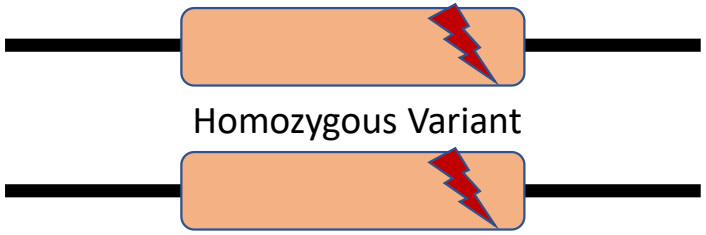
Compound Heterozygous in Trans

Unaffected Allele

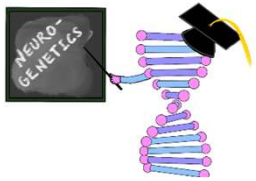
Affected Allele

AD Autosomal Dominant

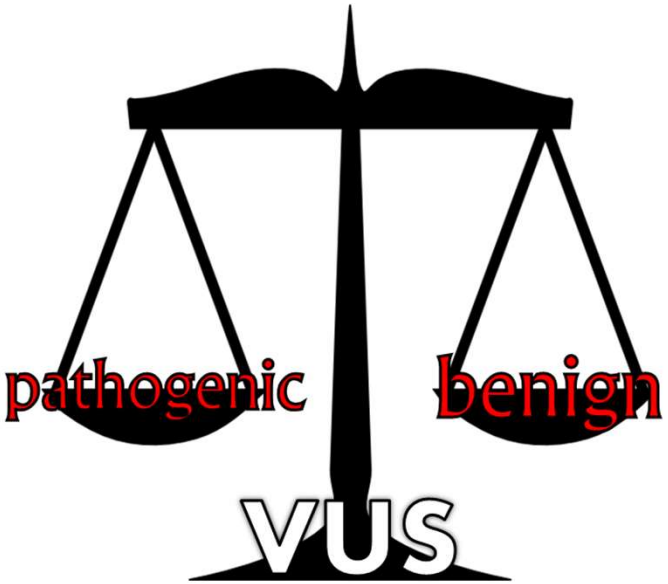
AR Autosomal Recessive



Homozygous Variant



Variant of Uncertain Significance



THEATER

THEATRE

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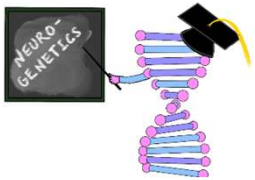
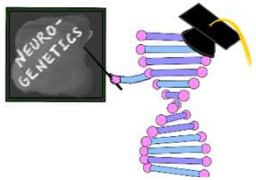


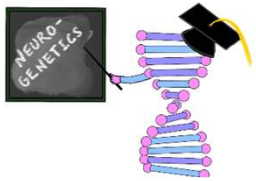
Approach for VUS resolution

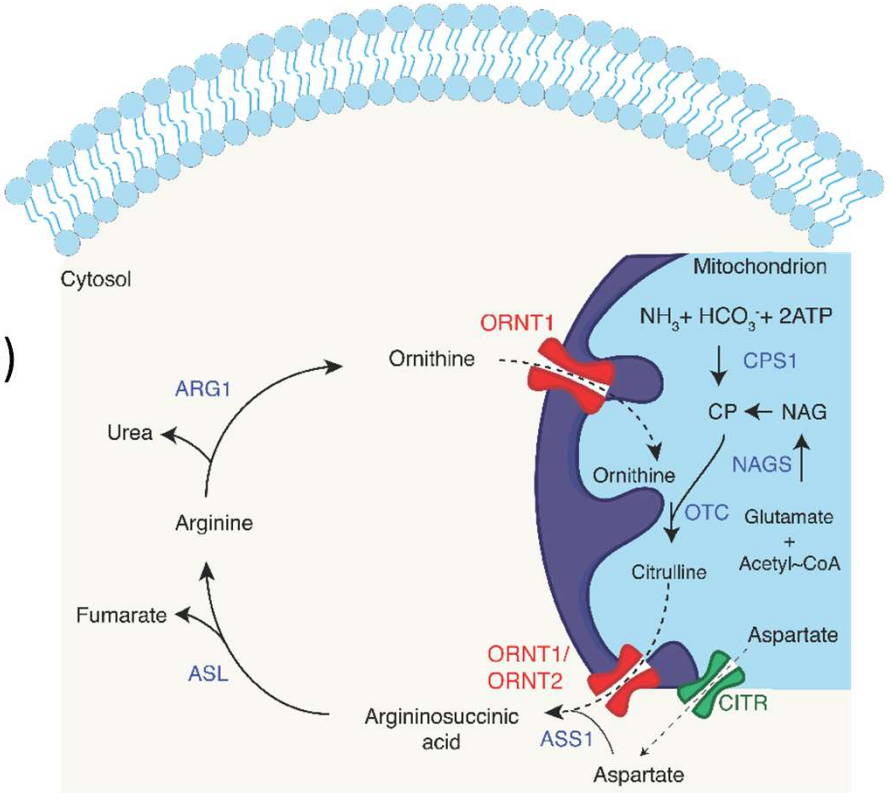
- **Look at inheritance pattern**
- **Look at phenotypic match**
- Look at variant – present in population? Effect on Protein?
- Familial Segregation Studies
- Functional studies – measure enzyme or transporter activity



Urea Cycle Disorders

- **Deficiency of cofactor synthesis**
  - NAGS deficiency
- **Deficiency of catalytic enzymes**
  - CPS1 deficiency
  - OTC deficiency
  - ASS1 deficiency (citrullinemia type 1)
  - ASL deficiency (argininosuccinic aciduria)
  - ARG1 deficiency (hyperargininemia)
- **Deficiency of transporters**
  - Citrin deficiency (citrullinemia type 2)
  - Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome

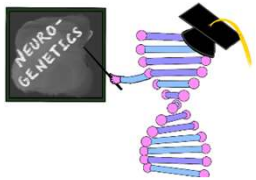




Swaiman Pediatric Neurology, Sen et al

Clinical Presentation of Urea Cycle Disorders

- **Complete defect in urea cycle**
  - Presentation in first week of life with hyperammonemia
  - Encephalopathy and coma, death if untreated
  - Poor suck, vomiting, refusal of feeds, altered consciousness
- **Partial defect in urea cycle**
  - May present later, i.e., in infancy, childhood, or even adulthood
  - Protein aversion, behavioral abnormalities, mental status changes, ADHD, cyclical vomiting
- **Some UCDs may have unique features**
  - Acute liver failure in OTCD
  - Chronic liver disease, hypertension in ASLD
  - Spasticity and motor problems in ARG1D



Neuroimaging and MR Spectroscopy

- In neonates with coma, generalized brain edema
- "Central pattern" with involvement of insular and periinsular regions, perirolandic areas, cingulate gyrus, and basal ganglia
- Atypical findings –
  - ✓ asymmetric cortical edema
  - ✓ lesions in occipital lobes

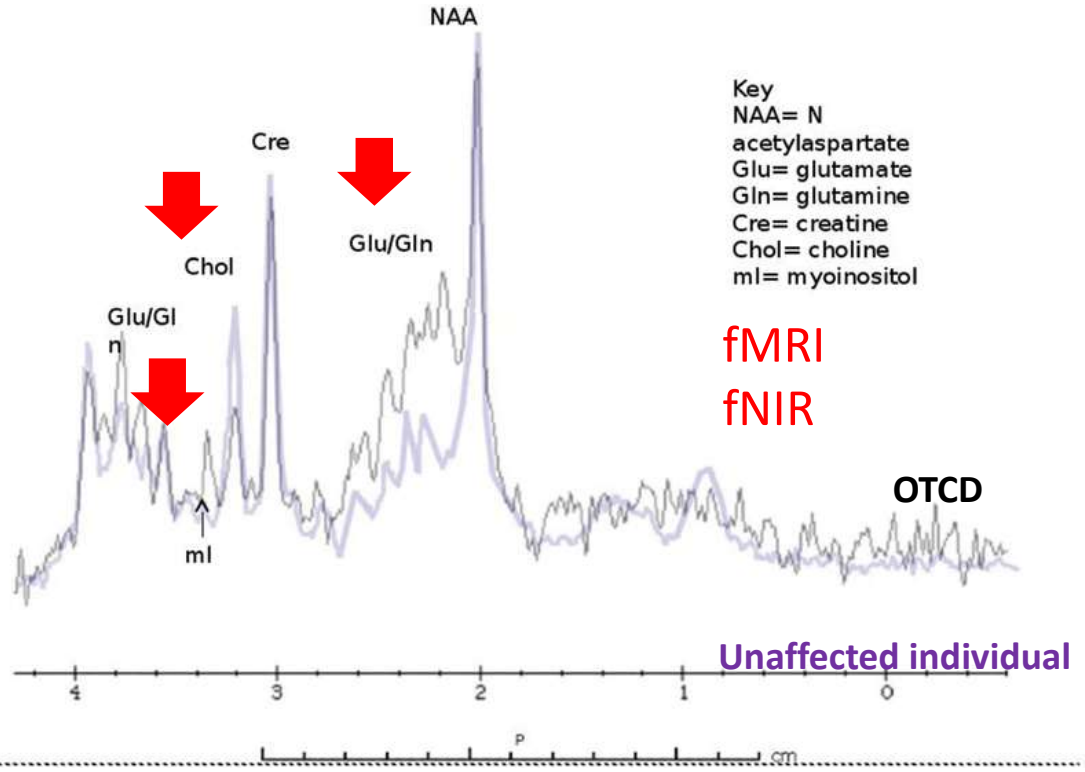
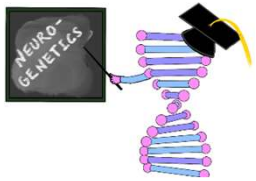


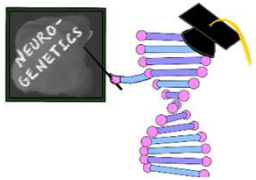
Figure 60-2



Gropman & Anderson, 2021

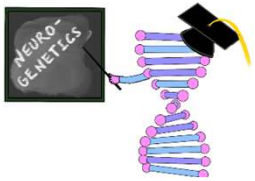
Treatment of Hyperammonemia

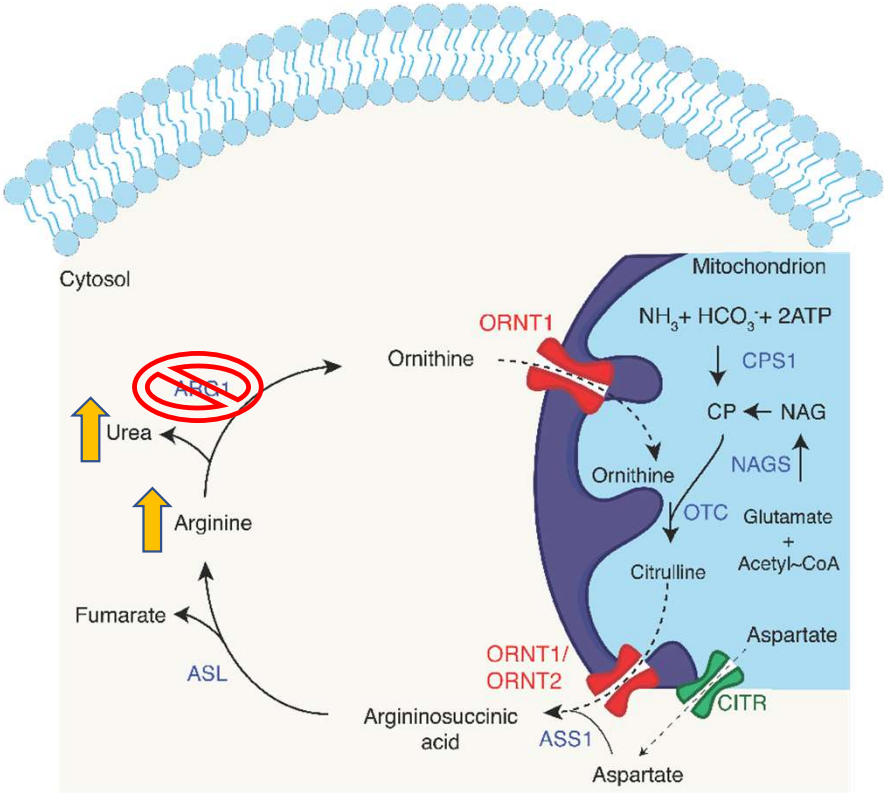
- Rehydrate and maintain good urine output without overhydration
- Remove nitrogen (ammonia) from the body using medications and/or hemodialysis
- Stop protein intake and minimize catabolism
- Stimulate anabolism and uptake of nitrogen precursors by muscle
- Initial IV administration of a combination preparation of sodium phenylacetate-sodium benzoate (Ammonul) followed by maintenance with oral sodium phenylbutyrate (Buphenyl) or glycerol phenylbutyrate (Ravicti)
- Pegzilarginase - ERT
- Some patients may require liver transplantation



Arginase Deficiency (Arg1)

- Arginase deficiency is a rare genetic disorder that affects the metabolism of the amino acid **arginine**
  - Caused by a gene variant in the arginase1 gene, which leads to a deficiency in the arginase enzyme
  - Without this enzyme, the body is unable to properly break down arginine, which can lead to a buildup of toxic byproducts

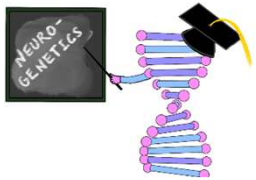




Swaiman Pediatric Neurology, Sen et al

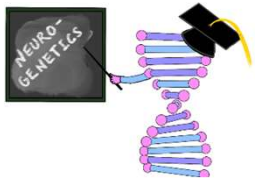
Arginase Deficiency (Arg1)

- Symptoms of arginase deficiency can include:
  - Intellectual disability
  - Seizures
  - Delayed growth
  - Progressive spastic diplegia/quadriplegia
  - Liver damage.
- NUCDF is patient advocacy for urea cycle disorders.
- UCDC is the major multinational research consortium for these conditions



Take Home Points

- There are many genetic mimics of “CP”, some of which have specific treatments.
- Red flags to consider alternate diagnoses are absence of birth injury, progressive symptoms or family history.
- A founder effect can also explain why certain inherited diseases are found more frequently in some limited population groups.
- Some common causes of hyperammonemia are proximal UCD, organic acidemia, liver failure, and valproate toxicity.
- Plasma amino acid and urine orotic acid can help to distinguish between different types of UCD.
- Neurologists should be familiar with different clinical presentations of UCD.



Suggested Reading

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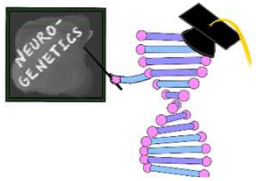

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