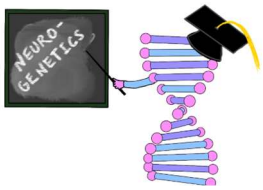


Teaching Guide

Module 6: Movement 2 - Cerebral Palsy

Slide 1: Title

Slide 2: Learning Objectives

Slide 3: Chief complaint, **at first glance appears nonspecific for a child neurologist**

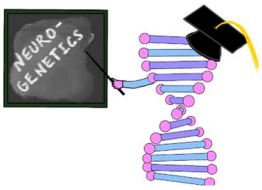
Slide 4: Spend a few minutes having participants share genetic mimics of CP based on their previous knowledge. If they say HSP, encourage them to share what additional information they know about the condition including gene, inheritance pattern, MRI pattern, treatment etc. So on and so forth. Encourage them to discuss why is it important to identify these genetic mimics of CP (because it can lead to change in treatment, surveillance of medical complications and recurrence risks for future pregnancies).

Slide 5: *So what is cerebral palsy?* Cerebral palsy is an umbrella term referring to a group of disorders affecting a person's ability to move. Cerebral palsy is due to damage to the developing brain during pregnancy, birth, or shortly after birth. By definition, **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 cerebral palsy often means that people with CP will experience age-related changes. Patients may have developmental delay, epilepsy, and other medical complications but the **motor symptoms are defining to the condition**.

Slide 6: In this slide, let us learn about the different causes and types of CP.

- In this first image, we see **spastic hemiplegia** which results from perinatal stroke. So similar to adult stroke, the contralateral side of the body is affected with weakness and spasticity.
- In the second image, we see **spastic diplegia** which is most associated with intraventricular hemorrhage seen in premature babies. And the reason is that the motor fibers of legs are represented in the area around germinal matrix.
- In the third image, we see **spastic quadriplegia** which results from a global injury to the cerebral cortex, with the most common etiology being hypoxic ischemic encephalopathy (HIE).
- The next 2 categories are **athetoid** and **dystonic** CP which is from injury to basal ganglia. In the past, the most common etiology was kernicterus but that is rare now due to phototherapy. There are several genetic mimics for this category.
- The last image shows **ataxic** CP which results from injury to cerebellum.

Slide 7: *What are some of the red flags that should make you consider an alternate or genetic diagnosis instead of "CP"?* So, if you are seeing a patient with CP in clinic or on the floor, **always inquire if they had a history of birth injury such as IVH or HIE** and if not, it is always prudent to question the diagnosis. Also, if they had some minor birth injury but it is not significant to explain the severity and pattern of motor deficits. We learnt CP is a non-progressive condition so it should not cause progressive symptoms, such as cognitive regression or refractory seizures.



Slide 8: Episodes of metabolic crisis such as **hyperammonemia, hypoglycemia, or acidosis should always make you think of an inborn error of metabolism**. Another red flag is hepatic dysfunction or history of protein aversion with cyclical vomiting. And everyone knows**, family history is very important**. So, if there are similarly affected individuals in multiple generations, you should consider a dominant or X linked condition. If there are similarly affected individuals in same generation or if there is consanguinity, that points to a recessive condition.

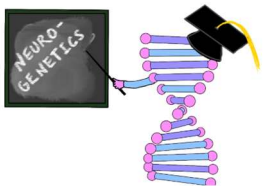
Slide 9: Let us review some of the genetic disorders which can mimic each of these categories. This slide looks a little busy and participants are not expected to memorize this.

- Spastic diplegia is IVH and some of the genetic mimics for this category are hereditary spastic paraplegia and arginase deficiency.
- Spastic quadriplegia can be caused by any inborn error of metabolism which causes global injury to the brain in newborn period. Common examples are urea cycle disorders, organic acidemia and some leukodystrophies like Krabbe disease and some of the rarer causes include non-ketotic hyperglycinemia and molybdenum cofactor deficiency.
- Spastic hemiplegia may include COL4A1-related disorder which affects the collagen in cerebral blood vessels and also mitochondrial disorders, which can cause stroke like episodes.
- Dystonic/Choreoathetoid CP may be misdiagnosed as glutaric aciduria type 1, disorders of dopamine metabolism, and PKAN, in which there is iron deposition in the brain.
- Ataxic CP mimics are genetic conditions that affect the structure or function of cerebellum. Some of the examples are spinocerebellar ataxia and Joubert syndrome, which is associated with molar tooth sign on MRI.

Slide 10: *Very briefly, how do we go about the work up for genetic causes of CP?*

1. Neuroimaging can give very important clues.
    a. In the first image, which is an axial T2 of the Brain, we see **bilateral hyperintensities in the basal ganglia**. This is known as Leigh syndrome and should make you think of mitochondrial etiology.
    b. In the second image, we see high signal in the **periventricular white matter** sparing U fibers which is classic for Krabbe disease.
2. **The next step is metabolic testing**. Our first-tier screen consists of ammonia, lactate, plasma amino acids, and urine organic acids which can help to evaluate for several different disorders of small molecules.
3. Lastly there is molecular, or DNA, testing and we tend to choose either a **multi gene panel or exome sequencing.** It is important to recognize that each genetic testing method has some limitations. For example, the multi gene panel may not include newly described conditions or trinucleotide repeat disorders.

Slide 11- 13: Text from slide. **Note: the red flag of normal development and then regression**. The neurologist often does not focus on diet history but remind the learners that in many inborn errors, especially small molecule and urea cycle, there may be FTT due to food refusal. Pay attention to the types of foods that are refused and rule out allergy, sensory/textural and cultural diets as well to arrive at possible IEM. This is important in patients of all ages with unexplained neurological syndromes. For



suspected X linked conditions in males, ask about maternal diet (i.e., OTC moms who are vegetarians or vegan or eat very little protein).

Slide 14:

Team 1: In clinical genetics, a consanguineous marriage is defined as a union between two individuals who are related as second cousins or closer. **A founder effect, as related to genetics, refers to the reduction in genomic variability that occurs when a small group of individuals becomes separated from a larger population.** A founder effect can also explain why certain inherited diseases are found more frequently in some limited population groups. Here, the family is from a small town.

Team 2: Patient does not have history of any major perinatal event or injury such as HIE, prematurity, stroke, meningitis etc.

Team 3: Patient's symptoms appear progressive given worsening stiffness and explosive onset of seizures with metabolic decompensation.

Team 4: **Hyperammonemia is suggestive of an inborn error of metabolism**. Typically, it is seen in proximal UCD but can also be seen in organic acidemias, such as methylmalonic acidemia (MMA) and propionic acidemia (PA). It can also be seen in hepatic failure or toxicity of some medications, such as valproate.

Slide 15: Discuss MRI and EEG findings of patient from slide.

Slide 16- 18: Share the metabolic labs and genetic testing report and start the second interactive exercise.

Team 1: The first thing participants should identify is **liver dysfunction and hyperammonemia**. When thinking of metabolic decompensation, the main categories of abnormalities are – hypoglycemia, rhabdomyolysis, liver dysfunction, metabolic acidosis, hyperammonemia, and lactic acidosis. If one or more of these findings are noted and IEM is suspected, the following labs are typically sent as first tier – plasma amino acids, acylcarnitine profile, free and total carnitine, and urine organic acid. **Many IEMs have signature findings which can help to confirm a diagnosis biochemically before DNA testing.** Elevated glutamine and arginine in the setting of HA, is highly suggestive of arginase deficiency which is the most distal urea cycle disorder.

Team 2: Review the following slides to help distinguish biochemical profile in different UCDs.

1. Low citrulline is seen in CPS1 and OTC and elevated citrulline is seen in ASS-1 and ASL.
2. Low orotic acid is classic for CPS1.
3. Elevated arginine is classic for arginase deficiency.

	CPS-1 deficiency	OTC deficiency	ASS-1 deficiency	ASL deficiency
Citrulline	Absent	Low	Elevated (tenfold)	Elevated (twofold)
Arginine	Reduced	Reduced	Reduced	Reduced
Orotic acid	Low	Elevated	Elevated	Elevated

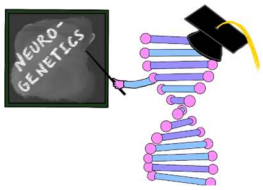
Type of UCD	Amino acid*	
	Citrulline (µmol/L) (NV: 26 ± 8)	Arginine (µmol/L) (NV: 64 ± 24)
NAGSD, CPS1D, OTCD	10 (7-16)	39 (20-59)
ASSD	1654 (984-2400)	31 (17-41)
ASLD	173 (103-256)	36 (24-81)
ARG1D	21 (20.5- 21.5)	351 (231-470)

Team 3: The *ARG1* gene provides instructions for producing the enzyme arginase. This enzyme participates in the urea cycle, a series of reactions that occurs in liver cells. **The variant is a nonsense variant, as denoted by * which stops the translation.** Inherited autosomal recessive. Phenotype associated: arginemia.

Team 4: Untreated individuals have **slowing of linear growth** at age one to three years, followed by development of **spasticity, plateauing of cognitive development**, and subsequent **loss of developmental milestones**. Some patients, but not, all can have hyperammonemia. Treatment should involve a team coordinated by a metabolic specialist. Routine outpatient management includes **restriction of dietary protein** and **consideration of oral nitrogen-scavenging drugs** (in those who have chronic or recurrent hyperammonemia). **Avoid Valproic acid** (exacerbates hyperammonemia).

Slide 19-23: Recurring slides from the curriculum. Okay to skip through given focus of this module is biochemical testing rather than VUS interpretation.

Slide 24: Text from slide. Enumerate the different entities in UCD. Note: OTC is X-linked, most common, rest are autosomal recessive.



Slide 25: Text from slide. Discuss typical clinical presentation in complete versus partial UCD.

Slide 26: Review classic MR and MRS findings in UCD. Additional references included at the end.

Slide 27-29: Text on slide.

Slide 30: Emphasize take home points.

Slide 31: Additional references.

Slide 32: Acknowledgements.