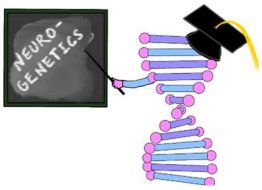


Teaching Guide

Module 9: IEM and Complex Molecule - Leukodystrophies

Slide 1: Title.

Slide 2: Review the learning objectives for this module.

Slide 3: Define newborn screening (NBS).

Slide 4: Chief complaint. The index patient is a healthy baby girl whose NBS indicated a risk of X-ALD due to abnormal VLCFA profile. Ask participants to think of disorders that are commonly on the NBS panel that would be relevant to a neurologist to know about.

- X-ALD: X-linked adrenoleukodystrophy
- VLCFA: very-long-chain fatty acid

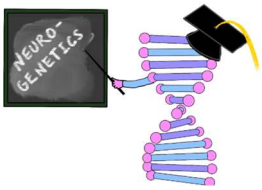
Slide 5: Briefly review the conditions and timing of disorders on the Recommended Uniform Screening Panel (RUSP). The RUSP is a list of disorders that the US federal government recommends to states to screen for in the newborn period.

Slide 6: Remind participants that conditions are decided on a state-by-state basis. Doctors in each state should be aware of what is on their state's NSB panel. **Also, it's important to remember that screening is not a diagnostic test.** If a given condition is in the differential diagnosis for a patient, it should be tested for rather than relying that it was screened for and not detected on NBS.

Slide 7: The slide starts with the specific biochemical screening paradigm for X-ALD, which can also pick up other peroxisomal disorders. Because learners often confuse peroxisomal and lysosomal disorders, there is brief discussion of lysosomal newborn screening disorders, one of which (Krabbe) is another leukodystrophy.

- **Additional explanations if necessary**: Peroxisomes are the recycling centers of cells. They are filled with enzymes that can break down larger molecules so that the body can use them. X-ALD occurs when ALDP (a transport protein on peroxisomes) is missing or not working properly. In this case, VLCFA from body fat and diet are not able to be broken down within the peroxisomes.

Slide 8: Discussion of the differential diagnosis of a positive X-ALD NBS. Because it tests for elevated VLCFA, other conditions causing peroxisomal dysfunction can result in a positive NBS. **Because several conditions can flag the NBS, genetic testing is needed to determine which condition a patient has.**



Slide 9: Text on slide.

Slide 10: Lab evaluation of the index patient to determine the diagnosis leading to positive NBS. **Reminder: a screening test is not diagnostic** and that is why we are clinically confirming elevated VLCFA. Note: ABCD1 is the protein that encodes the ALDP protein to be made so that is why this test is being performed.

Slide 11-12: Immediate next steps after confirming diagnosis depends on if it is a boy or a girl. You can use VLCFA to rule out X-ALD in boys but not in girls.

Slide 13: Maternal inheritance is most common.

Slide 14: Review X-linked inheritance. Females who carry pathogenic ABCD1 variants are likely to develop symptoms in adulthood.

Slide 15: The index patient's family medical history. *Who should be offered testing?*

Slide 16: The aqua-colored markings denote which family members should be tested.

Slide 17: *What should be done for the boys identified as having X-ALD?*

Slide 18: Text on slide.

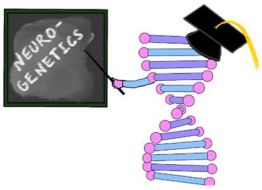
Slide 19: Typical MRI features of high yield leukodystrophies.

Slide 20: Three phenotypes associated with X-ALD and range in timing of onset**. Head trauma and probably vitamin D deficiency are two modifiable risk factors**, but we can't predict who will develop which phenotype or when. There must be a multitude of other factors that we don't yet understand.

Slide 21: Additional information to supplement the text on the slide: Adrenal insufficiency can be the sole expression of disease in 10% of boys. Adrenal onset can present years before neurological symptoms do. Childhood cerebral disease has the earliest age of onset 21 months. 60% of males will develop brain disease at some point. 10% of boys with cerebral ALD have chronic or arrested X-ALD.

Slide 22: Treatment options: patients presenting with advanced disease likely won't benefit from treatment. Disease severity is determined by MRI scoring (Loes score) and functional score (neurologic function scale or NFS).

Slide 23: This graph shows a survival curve after treatment with stem cell transplant. **Treatment early in symptoms results in better survival** (black line) and **better functional**



outcomes (gray line). On the right, survival is improved with treatment in advanced disease but functional outcomes are very poor.

Slide 24: Guidelines for monitoring individuals with NBS-identified X-ALD. These recommend life-long surveillance for symptoms.

Slide 25: There are challenging ethical considerations in newborn screening for X-ALD.

- In a clinical context, we generally do not offer carrier testing to minor females because it would not result in information that would impact their health in childhood. They should have the option to choose for themselves if they want to know their genotype once they are adults. However, for population-level newborn screening, female samples cannot easily be separated from males, so all infants are screened. This situation results in diagnosis based on screening that would not be offered on an individual clinical context outside of a screening program.
- Identifying an index patient (either female or male) can result in identifying multiple other at-risk family members.
    - *Whose responsibility is it for those at-risk to be informed?*
        - Genetic information is HIPPA-protected so it is up to the index family to notify the at-risk relatives.
- The case study resulted in diagnosis of two affected brothers, one of whom would not benefit from treatment while the other would. In some families, brothers with the same genotype may be affected very differently, with one brother severely symptomatic from childhood cerebral disease and while the other brother may never develop brain disease. **This can result in survivor's guilt and should be explored in the asymptomatic boys as they have ongoing follow up.**
- Carrier mothers can have a lot of guilt and feel like they caused the disease in their sons. This should be discussed with mothers and counseling should be offered, if needed.
- Newborn boys are recommended to enter a lifelong follow up pathway. There is no mechanism in place to ensure this follow up happens. It is a significant medical, financial, and psychological burden to receive a diagnosis in a baby who may never develop significant disease symptoms in childhood.

Slide 26: Suggested reading.

Slide 27: Acknowledgements.